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Full Length Research Paper

Effects of delayed recanalization on left ventricular function in diabetic and non-diabetic patients with acute anterior wall myocardial infarction

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To investigate the effects of delayed recanalization through percutaneous coronary intervention (PCI) on the left ventricular function after acute anterior wall myocardial infarction in diabetes (DM) and non-DM patients, a total of 125 consecutive subjects with acute anterior wall myocardial infarction were recruited and divided into DM group (n=43) and non-DM group (n=82) based on the presence of DM. All patients received successful PCI at about 2 weeks after symptom onset. Ischemic viable myocardium was detected with low-dose dobutamine stress echocardiogram test, and left ventricular function and wall motion were also assessed before PCI. Clinical manifestations and angiograms before and after PCI were analyzed. Levels of creatinine kinase-MB (CK-MB) and troponin T (TnT) before PCI, 6 and 24 h after PCI were determined. All patients received clinical and echocardiographic follow-up 6 months after PCI. Higher rate of TIMI flow grade 2 and lower rate of TIMI flow grade 3 were observed immediately after PCI, and the elevation of serum CK-MB and/or TnT levels were higher in DM group when compared with non-DM group ($P<0.05$). In addition, 63% of DM patients and 56% of non-DM patients had viable myocardium before PCI ($P>0.05$). There were no significant differences in the LVEF, LVEDVI, LVESVI or wall motion score (WMS) between two groups before PCI ($P>0.05$). But, 6 months after PCI, WMS and LVEF were decreased and increased, respectively, in non-DM group, and the WMS and LVEF in DM group were not changed and the LVEDVI increased, when compared with before PCI. The LVEDVI, LVESVI, LVEF, and WMS differed significantly between two groups 6 months after PCI. Compared with non-diabetics, delayed revascularization with PCI in diabetics with acute myocardial infarction has less benefit on the improvement of left ventricular function, and it may be the insufficient reperfusion or reperfusion injury to myocardium but not the viable myocardium contribute to the poor result.

Key words: Diabetes, myocardial infarction, left ventricular function, percutaneous coronary intervention, delayed recanalization.

INTRODUCTION

Diabetes mellitus (DM) remains an important independent predictor of poor prognosis in acute myocardial infarction patients (Norhammer et al., 2003; Katayama et al., 2005). As we known, early revascularization of coronary artery is of vital importance for the preservation of cardiac function and improvement of prognosis after acute myocardial infarction (Brodie et al., 2003). Numerous clinical studies have demonstrated that even though early recanalization of infarct-related arteries (IRA) have been achieved, diabetic patients still have an unfavorable short and long-term outcome as compared to non-diabetic patients (Harjai et al., 2003; Bolognese et al., 2003).

The 'open artery hypothesis' suggests late recanalization of IRA is also beneficial in selected patients especially with considerable amounts of viable myocardium (Piscinoe et al., 2005; Sadanandan and Hochman, 2000; Schomig et al., 2006; Nijland et al., 2002). Recent studies reveal the beneficial effects of delayed recanalization on left ventricular (LV) dilatation

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and myocardial function in a well defined group of patients with occlusion of the left anterior descending coronary artery (Yousef et al., 2002). The present study aimed to investigate the effects of delayed recanalization with percutaneous coronary intervention (PCI) on LV function in diabetics and non-diabetics with acute anterior wall myocardial infarction.

PATIENTS AND METHODS

Patient selection

A total of 125 consecutive patients with acute anterior wall myocardial infarction were admitted 24 h after symptom onset and did not receive any early recanalization therapies from January 2004 to August 2008. All patients had wall motion abnormalities confirmed by echocardiography at baseline and exclusion criteria included: (1) a history of myocardial infarction (MI) or revascularization; (2) concomitant cardiomyopathy, severe valvular disease, chronic renal failure or other severe diseases; (3) bundle branch block or permanent pacemaker; (4) <70% stenosis of IRA in angiography; (5) severe complications (no re-flow, MI, resuscitation, or emergency coronary artery bypass graft) during PCI; (6) age >80 years; (7) technically inadequate acoustic window and inability to receive low dose dobutamine stress echocardiography (DSE); and (8) without 6 months of follow-up.

The study protocol was approved by the ethics committee of our hospital, and informed consent was obtained from each patient. There were 43 DM patients and 82 non-DM patients. DM was diagnosed, if one or more of the following criteria occurred: (1) treatment with insulin or oral hypoglycemic agent or both; (2) fasting blood glucose level ≧126 mg/dl and casual blood glucose level ≧200 mg/dL; and (3) either a fasting or casual blood glucose level higher than the upper limit and a hemoglobin A1C level of 6.5% or higher.

Echocardiographic study

Two-dimensional echocardiography was performed with commercially available imaging systems (HP-1500, frequency: 2.5 MHz). Left ventricular remodeling and function at baseline and 6 months after PCI were analyzed by two experienced echocardiographers blind to the study. LV end-systolic volume (ESV), end-diastolic volume (EDV), and ejection fraction (EF) were obtained from three consecutive cardiac cycles in the apical 4 chamber views with the modified Simpson's rule (Shiller et al., 1989). ESV and EDV were corrected by body surface area and expressed as ESV index (ESVI) and EDV index (EDVI). The left ventricle was examined in standard views, and divided according to the 16-segment model. For each segment, wall motion was graded as follows: normal, 1; hypokinesia, 2; akinesia, 3; dyskinesia, 4 (Shiller et al., 1989). A wall motion score (WMS) represented the sum of the number of visualized segments.

DSE was performed at 12±8 days (range: 9~18 days) after MI before PCI in 3 min stages of 5, 10, 20, 30, and 40 μg/kg/min. Atropine up to 1 mg was administered if required, to achieve 85% of age-predicted maximum heart rate. During each stage, the blood pressure and 12-lead electrocardiogram were recorded. Tests were discontinued once new wall motion abnormalities occurred in >2 segments. Other end points of the test were significant ventricular or supraventricular arrhythmia, significant bradyarrhythmia, elevated blood pressure of more than 240/120 mmHg or >20 mmHg systolic blood pressure decrease compared with baseline, ≧2 mm ST-segment depression, and severe angina. At each step, images during DSE and recovery were recorded with a super-VHS videotape for subsequent analysis. Myocardial viability was considered; when the improvement involved at least two segments or at least one segment and only two basally asynergic segments (Previtali et al., 1998). Once myocardial viability was present, the patient was defined as viable patient, otherwise nonviable patient.

Coronary angiographic analysis

All coronary angiograms were recorded in more than 2 angulation projections and analyzed in a random sequence by 2 experienced cardiographers blind to the study. The IRA was analyzed before and after PCI to assess the vessel diameter and residual stenosis. Anterior flow of IRA was evaluated according to TIMI criteria (Chesebro et al., 1987). TIMI grade 0 or 1 flow was defined as total occlusion. Collaterals to the IRA were recorded according to the definition of Rentrop et al. (1988). The presence of TIMI grade 2 or 3 collateral flow was considered significant. Multivessel disease was defined as >70% stenosis in ≧2 major epicardial arteries or >50% stenosis of the left main coronary artery.

PCI was performed in the IRA immediately after angiography. In all patients, rapamycin-eluting stent was implanted in the target vessel. Revascularization was performed simutaneously in another coronary artery if necessary. PCI procedural success was defined as restoration of TIMI grade 3 flow, residual stenosis <30% and without severe complications after angioplasty. If significant stenotic diseases confirmed by symptom, electrocardiogram, or echocardiogram at rest or during stress test were successful revascularization, it was defined complete revascularization.

Detection of cardiac markers

Blood samples were taken from all subjects before PCI and at 6 and 24 h after PCI, and levels of serum creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) were determined. The elevation of serum cardiac markers was defined as more than two times elevation in CK-MB and/or cTnI levels at any point in time after PCI was compared with before PCI.

Follow-up

Aspirin 100 mg and clopidogrel sulfate 75 mg were orally administered once daily in all patients after PCI. Other cardioactive agents including nitrates, β-blockers, ACE inhibitors and lipid-lowering agents were administered according to the disease condition. Follow-up was carried out by same investigators through medical record reviewing and telephone. Major adverse cardiac events (MACEs) were defined as cardiac death, non-fatal re-acute myocardial infarction, and unstable angina requiring hospitalization and/or target vessel revascularization (coronary artery bypass graft surgery or repeat PCI).

Statistical analysis

Qualitative data were expressed as means ± standard deviation (SD) and compared by the unpaired t test. The 95% confidence interval (CI) and quartiles were calculated if necessary. Proportions were analyzed by chi-square test. A value of $P<0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

Clinical characteristics of DM patients and non-DM

Table 1. Clinical characteristics of DM patients and non-DM patients.

	DM (n=43)	non-DM (n= 82)	P
Age, y	62±12	65±14	NS
Gender, M/F	37/6	69/13	NS
Hypertension, n (%)	18 (42)	28 (34)	NS
Hyperlipidemia, n (%)	16 (3)	22 (27)	NS
Smoking, n (%)	22 (51)	46 (56)	NS
History of angina, n (%)	7 (16)	11 (13)	NS
Medical therapy			
Nitrates, n (%)	37 (86)	66 (80)	NS
ß-blockers, n (%)	15 (35)	32 (39)	NS
ACE-Inhibitors, n (%)	29 (67)	61 (74)	NS
Statins, n (%)	38 (88)	69 (84)	NS
Anticoagulation, n (%)	41 (95)	79 (96)	NS
Classification of NYHA	2.1±0.7	2.3±0.8	NS
Times from onset to PCI, d	13±6	12±7	NS

NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; NS: No significance.

Table 2. Angiography and PCI.

	DM (n =43)	non-DM (n = 82)	P value
Single vessel disease, n (%)	17 (40)	47 (57)	NS
Multivessel disease, n (%)	26 (60)	35 (43)	NS
Stenosis of IRA before PCI (%)	94.6±5.9	96.3±6.2	NS
Collaterals (≧2 grade) to IRA, n (%)	4 (9)	15 (18)	NS
Reference diameter pre-PCI (mm)	2.93±0.51	3.29±0.63	P<0.05
MLD post-PCI (mm)	3.01±0.42	3.18±0.37	NS
IRA flow before PCI			
TIMI0/1 grade, n (%)	31 (72)	55 (67)	NS
TIMI2 grade, n (%)	8 (19)	14 (17)	NS
TIMI3 grade, n (%)	4 (9)	13 (16)	NS
IRA flow post PCI			
TIMI grade 0/1, n (%)	1 (2)	1 (1)	NS
TIMI grade 2, n (%)	10 (23)	6 (7)	P<0.05
TIMI grade 3, n (%)	32 (75)	75 (92)	P<0.01
Complete revascularization, n (%)	38 (88)	67 (82)	NS

PCI: Percutaneous Coronary Intervention; IRA: reperfusion to Infarct-Related Arteries; MLD: Minimal Lumen Diameter.

patients are summarized in Table 1. There were no significant differences in ages, gender, coronary risk factors, history of angina, and medications between the two groups. No marked differences were observed in baseline classification of NYHA and the interval between symptom onset and PCI.

Angiography and PCI

Table 2 shows the findings in angiography and PCI. DM patients had a trend of higher incidence of multiple vessel disease compared with non-DM patients, but without significant difference (P=NS). In addition, the residual stenosis of IRA and the established sufficient collateral flow to the diastolic part of IRA before PCI were comparable between the two groups.

In DM group, the diameter of target vessel before PCI was smaller than in non-DM group (P<0.05). The ratio of complete revascularization was achieved in 88% of DM patients and 82% of non-DM patients (P = NS). Even

Table 3. Changes in serum levels of cardiac markers.

	DM (n=43)	non-DM (n= 82)	P
Baseline before PCI			
CK-MB (U/L)	16.42±11.48	15.69±10.62	NS
cTnI (μg/L)	0.031±0.042	0.029±0.032	NS
6 h after PCI			
CK-MB (U/L)	31.12±18.49	18.23±14.56	P<0.05
cTnI (μg/L)	0.143±0.091	0.053±0.048	P<0.01
24 h after PCI			
CK-MB (U/L)	17.12±10.43	16.89±12.76	NS
cTnI (μg/L)	0.132±0.113	0.048±0.073	P<0.05

PCI: Percutaneous Coronary Intervention; CK-MB: Creatine Kinase-MB; cTnI: cardiac Tropnin I.

though there was no difference in TIMI flow grade in the IRA before PCI in two groups, the rate of TIMI flow grade 3 in DM group was significantly lower than in the non-DM group after PCI (75% vs 92%, P<0.01).

Changes in levels of cardiac markers

There were no significant differences in the serum CK-MB and cTnI levels between the two groups before PCI. At 6 h after PCI, CK-MB and cTnI levels in the two groups were all elevated compared with baseline, especially in DM group, and there were significant differences between the two groups (Table 3). At 24 h after PCI, the serum cTnI level in DM group was still higher than in the non-DM group (P<0.05). In DM group, there were 25% (11/43) of cases having elevated levels of cardiac markers, compared with 10% (8/82) of cases in non-DM group at 6 and 24 h after PCI, (P<0.05).

Viable myocardium and left ventricular function

In DM group, 27/43 (63%) patients were identified as viable patients compared with 46/82 (56%) patients in the non-DM group (P=NS). There were no significant differences between the two groups with respect to the LVEF, LVEDVI, LVDSVI, or WMS scores before PCI (P=NS). Six months after PCI, in DM group, the LVESVI, LVEF and WMS were not improved (P=NS), and the LVEDVI was markedly elevated (P<0.05) compared with baseline. However, in non-DM group, the LVEF was increased (P<0.05) and WMS decreased (P<0.01) at 6 months after PCI when compared with baseline. There were significant differences in the LVEF, LVEDVI, LVDSVI and WMS between the two groups six months after PCI (P<0.01 or P<0.05) (Table 4).

Cardiac events during follow-up

There were 8 patients with MACEs during 6 months follow-up in DM group, including 1 cardiac death, 2 unstable anginas and 5 re-hospitalizations due to heart failure. However, in non-DM group, 9 patients had MACEs including 2 cardiac deaths, 3 unstable anginas and 4 re-hospitalizations due to heart failure. There was no significant difference in MACEs between the two groups (19 vs 11%, P=NS).

DISCUSSION

Despite successful delayed recanalization of IRA and complete revascularization with PCI after acute anterior wall myocardial infarction, LVEF was not improved and LV remodeling still ongoing in diabetics when compared with non-diabetic patients. The presence of viable myocardium before PCI cannot completely explain these discrepancies, due to comparable ratio of viable patients between two groups. It is conceivable that other factors may influence the post-procedural improvement of left ventricular function and prognosis.

Delayed recanalization and viable myocardium in diabetes: Recently, a variety of studies have shown that delayed recanalization (days to weeks after symptom onset) of IRA may also confer a long-term protective effect. This potential time-independent benefit of delayed recanalization leads to the ‘late open artery hypothesis’ (Yousef and Marber, 2002; Puma et al., 1999). Delayed recanalization of IRA may not only salvage the preconditioned, stunned or hibernating myocardium, but accelerate repair and scar formation by aggressive inflammatory reaction, stiffer and firmer infarct tissue that reduces expansion, all of which can attenuate LV remodeling and stable electricity (Yousef and Marber, 2002). The ‘open artery hypothesis’ suggests that late recanalization of IRA is especially beneficial in patients with considerable amounts of viable myocardium. As Piscinoe et al. demonstrated that delayed recanalization of the IRA may also improve LV function, provided viable myocardium is present within the zone supplied by the

Table 4. Echocardiographic findings before and 6 months after PCI.

	DM	non-DM	P
	(n= 43)	(n= 82)	
Baseline before PCI			
LVEDVI (ml/m^2)	53.5±11.3	51.5±13.2	NS
LVESVI (ml/m^2)	34.1±8.2	31.2±12.5	NS
LVEF (%)	36.4±10.6	39.6±13.7	NS
WMS	19.3±7.6	21.4±4.9	NS
Six months after PCI			
LVEDVI (ml/m^2)	62.6±21.3	58.1±13.6	P<0.05
LVESVI (ml/m^2)	38.3±17.2	28.3±11.2	P<0.05
LVEF (%)	38.3±12.1	52.7±14.8	P<0.01
WMS	17.6±8.7	13.7±3.1	P<0.05

LVEDVI: Left Ventricular End-Diastolic Volume Index; LVESVI: Left Ventricular End-Systolic Volume Index; LVEF: Left Ventricular Ejection Fraction; WMS: Wall Motion Score.

artery (Piscinoe et al., 2005). The present study is for the first time to analyze the prognosis of delayed recanalization of IRA in diabetic and non-diabetic patients with myocardial infarction. We found that despite with complete recanalization of IRA, diabetes patients had compromised improvement of LV function to which the amount of viable myocardium before PCI did not attribute due to comparable ratios of viable patients between DM and non-DM patients.

Actually, diabetes cannot influence the presence of viable myocardium. Previous studies in patients with ischemic LV dysfunction also demonstrated that patients with and without diabetes had a comparable number of dysfunctional but viable segments per patient. Also, the number of patients with a substantial amount of dysfunction was different between two groups but viable myocardium was comparable (Schinkel et al., 2006).

Diabetes and the late prognosis of AMI: Previous studies have shown that patients with DM have an increased risk for developing heart failure after myocardial infarction, and diabetic patients benefit less from coronary revascularization compared with non-DM patients (The BARI Investigators, 1997). In the thrombolytic era of acute myocardial infarction, a pooled analysis of several thrombolytic trials have demonstrated that the mortality is more than 60% higher among patients with DM than those without DM (Mak et al., 1997). Even though preliminary results suggest that mechanical reperfusion with primary coronary angioplasty may improve the outcome of acute myocardial infarction, DM is closely related to left ventricular systolic dysfunction and worse clinical outcomes (Bolognese et al., 2003). The mechanism is still uncertain. As we know, DM patients usually have more extensive vascular lesions, and progression of coronary artery disease and recurrence of ischemia are also frequently observed in DM patients (Rizzello et al., 2006). We also found that DM patients had a trend of higher incidence of multiple vessel disease and the diameter of target vessel before PCI was smaller than non-DM patients. It is conceivable that disease progression and restenosis cannot fully explain the poor prognosis (Bolognese et al., 2003).

Other factors may influence the post-procedural prognosis, such as increased myocardial injury secondary to ischemia/reperfusion, decreased rate of successful recanalization, a higher rate of revascularization (Woodfield et al., 1996), microvascular endothelial dysfunction and abnormalities relating to platelet function, coagulation and fibrinolysis (Piemontino et al., 1994). In EMERALD trial database, Marso et al. (2007) investigated the effectiveness of primary PCI in establishing myocardial perfusion patients with and without, and results showed that, even though diabetic patients had similar rates of epicardial flow after primary PCI, myocardial reperfusion demonstrated by incomplete ST-segment resolution and myocardial blush grade were decreased and associated with larger infarction, development of congestive heart failure and decreased survival (Matetzky et al., 1999). In our present study, we found that there was no difference in TIMI grades flow of IRA at baseline, but the rate of TIMI grade 3 flow was significantly lower in DM group than in non-DM group after PCI, and associated with more patients having elevated serum levels of cardiac markers. In some studies on early recanalization with primary PCI, results revealed DM patients were less likely to attain TIMI 3 coronary flow after angioplasty and more DM patients failed to show ST-segment resolution compared with non-DM patients and these patients were likely to have sustained greater microvascular injury and consequently have less salvageable myocardium (Katayama et al., 2005; Matetzky et al., 1999). Due to the close relationship between DM and microvascular disorder, patients with DM are less likely to achieve favorable reperfusion at

microcirculation level, despite an aggressive treatment strategy for recanalization.

Study limitations: There are still a number of limitations in the present study. First, this was not a randomized study having a relatively small sample size which means that our results require confirmation before any concrete conclusions can be drawn. Moreover, angiographic follow-up was not performed in follow up period to detect angina or re-MI. So far, there was no report about restenosis and reocclusion at 6 months after PCI, and which may influence the late prognosis. We only compared the MACEs including cardiac death, non-fatal re-AMI and unstable angina, which were not significantly different between the two groups.

Conclusions

Our results showed that despite the successful delayed recanalization of all IRA and the similar rates of complete revascularization with PCI, after acute anterior wall myocardial infarction, LVEF was not significantly improved and LV remodeling was still ongoing in DM patients compared with non-DM patients. The presence of viable myocardium before PCI cannot fully explain these discrepancies, due to comparable ratios of viable patients between the two groups. However, in DM patients, the rate of TIMI grade 3 flow immediately after PCI was significantly lower than in non-DM patients, and more patients had elevated serum levels of cardiac markers. These findings suggest that insufficient reperfusion or reperfusion injury to the myocardium may be a reasonable explanation for the poor prognosis, after late revascularization in patients with DM. However, this is required to be validated by randomized clinical trials with large sample size.

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