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Original Article

Effects of percutaneous coronary intervention on viable myocardium and heart function of diabetic patients with chronic total occlusion

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Abstract: Objective: We aim to compare the effects of percutaneous coronary intervention (PCI) on coronary chronic total occlusion (CTO) patients with or without diabetes mellitus (DM). Background: CTO is common in coronary heart disease (CHD) patients with DM. There was no study to compare clinical outcomes of PCI between CHD patients with and without DM. Methods: A total of 78 patients were divided into DM group and NDM group according to whether the patient has DM. The results of PCI were analyzed using quantitative coronary analysis (QCA). In addition, all the patients underwent 99mTc-MIBI Single-photon emission computed tomography (SPECT) and ultrasonic cardiogram (UCG) in the 1st week and the 6th month after PCI to evaluate PCI results. During the 6-month follow-up, MACE was recorded and analyzed as well. Results: The 1st and 2nd class of collateral circulation between the 2 groups have significant differences ($P<0.05$). Left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) were decreased at the 6th month compared with those at the 1st week. Left ventricular ejection fraction (LVEF) was significantly increased. In both groups, the defect size significantly reduced and percentage of radionuclide scintigraphic count significantly increased between rest and nitroglycerin interventional SPECT. There were no significant differences in defect sizes and percentage of radionuclide scintigraphic count between the two groups. After 6 months, both groups repeated nitroglycerin interventional SPECT, which showed that defect size was significantly reduced and the percentage of radionuclide scintigraphic count was significantly increased compared with those of the 1st week. During the 6-month follow-up, the incidence of MACE between the two groups had no significant difference. Conclusion: PCI has beneficial effects on heart functions and MACE when performed on CTO patients with and without DM.

Keywords: Chronic total occlusions (CTO), diabetes mellitus (DM), percutaneous coronary interventions (PCI), heart function, viable myocardial, major adverse cardiac event (MACE)

Introduction

Coronary chronic total occlusion (CTO) is common in patients with coronary heart disease (CHD), accounting for 20% to 40% of the patients with CHD who were finally diagnosed by coronary angiography (CAG) [1, 2]. CHD patients with diabetes often present with multivessel coronary artery disease and more severe symptoms than non-diabetic patients. In addition, compared with non-diabetic patients, diabetic patients respond less favorably to percutaneous coronary interventions (PCI) and have higher rates of restenosis and repeat revascularization after PCI. Therefore, their prognoses are worse [3]. Epidemiology data indicated that currently there are more than 220 million diabetic patients worldwide and this number will reach 360 million by 2030 [4]. Cardiovascular disease remains the leading cause of mortality and account for 80% of diabetes-related deaths [5, 6].

The clinical trials have shown that there was higher mortality and repeat revascularization in diabetic patients in the long-term. However, the comparison regarding short-term clinical outcomes of successful PCI on CTO patients with and without diabetes remains obscure. This study was designed to compare the effects of successful PCI on viable myocardium, global cardiac function, and prognoses in CTO patients

with or without diabetic mellitus (DM) by using 99mTc-methoxy isobutyl isonitrile (99mTc-MIBI) single-photon emission computed tomography (SPECT) myocardial perfusion imaging and ultrasonic cardiogram (UCG) to compare the changes of myocardium ischemic area (MIA) before and after PCI between the two groups.

Material and methods

Patient population

A total of 78 patients (57 males and 21 females, aged 62.34±7.1 years) with CTO undergoing successful percutaneous transluminal coronary angioplasty (PTCA) and stent implantation were screened and recruited between May 2005 and October 2006. Recruitment criteria were as follows. ① Had angina symptoms or myocardial ischemia confirmed by 99mTcMIBI myocardial perfusion imaging, treadmill exercise test (TET), and dynamic electrocardiography (DCG), etc; ② CAG demonstrated total occlusion of coronary arteries and distal blood flow reached Thrombolysis In Myocardial Infarction (TIMI) grade 0 or coronary artery stenosis reached 99% and distal blood flow TIMI flow grade 1; ③ The CTO was defined as obstruction of a native coronary artery with no luminal continuity and with TIMI flow grade 0 or 1. The duration of the occlusion had to be more than 30 days, which was estimated from clinical events such as MI, sudden onset or worsening of the symptoms, or proven by previous angiography. If the duration of the occlusion was uncertain, but the investigators had no clear reason to think the occlusion was less than 30 days, the patient was recruited. Exclusion criteria were as follows. ① Acute myocardial infarction (AMI) within 1 month after the onset; ② Critical valvular heart disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy; ③ Cardiogenic shock; ④ Severe hepatic and renal dysfunctions.

Data collection and methodology

Clinical data collection and grouping: We recorded patients' medical history, physical and laboratory examination results, electrocardiogram (ECG) results, treatment regimens, and clinical outcomes, *etc*. All the patients underwent 18-synchronous-lead ECG and chest 12-lead anchor soon after admission. Routine laboratory tests including hepatic and renal functions, blood lipid, blood glucose, and platelet aggregation were performed within 24 hours after admission. To compare the effects of PCI on viable myocardium, cardiac function, and prognosis of patients with CTO with or without DM, 78 CTO patients were divided into two groups including DM group (27 males, 8 females, aged 62.43±7.58 years) and NDM group (30 males, 13 females, aged 61.05±7.20 years). The coronary angiographic and interventional data were collected and compared. Having been diagnosed with diabetes or been treated with medications were used as a basis for diagnosis of DM. If a patient had the history of DM whose duration was longer than one year, he/she was assigned into DM group. All patients were treated with aspirin, clopidogrel, statins, β blockers, ACEI, nitrates, and digitalis. All patients with DM had their blood glucose level well controlled. UCG and 99mTc-MIBI-SPECT myocardial perfusion imaging, which can objectively reflect the changes of viable myocardium, were done 1 week and 6 months after the procedure to assess the myocardial viability.

Coronary angiography and intervention: All the patients were treated with aspirin 300 mg/d and clopidogrel 75 mg/d 1-3 days before PCI. And they were given heparin 10000 U before the operation, and an additional 2000 U per hour during the operation. We chose to use GE INNOVA-4100 digital subtraction angiography system and Ultravist 370 non-ionic contrast agent to obtain CAG image. By using Seldinger technique, CAG was conducted by puncturing radial, ulnar, or femoral arteries percutaneously with 6 F catheter in the supine position. By using Judkins' method, left and right coronary angiographies were carried out alternatively with conventional multi-posture projection to obtain clear images of coronary artery, the main bifurcations, and the orifice of side branches. The record time must be no less than 6-8 cardiac cycles. Computer-assisted quantitative coronary analysis (QCA) system was applied to measure diameters of the occlusive artery and degree and length of stenosis of the non-occlusive artery. Coronary lesion and distal blood flow were recorded. The selection of the type of balloon and stent should be in accordance with the CAG findings. Successful PCI were defined as: ① The residual stenosis was reduced to 20% or below; ② TIMI flow has reached grade 3; ③ No severe complications occurred.

Table 1. Baseline Characteristics of CTO patients underwent successful PCI with or without DM

	DM Group	NDM Group	*P* value
Number of patients	35	43	
Age, y	62.43±7.58	61.05±7.20	0.587
Male, n (%)	27 (77.14%)	30 (69.77%)	0.746
Hypertension	19 (52.86%)	23 (53.49%)	0.685
Smoking history	17 (48.57%)	21 (48.84%)	0.874
Familial history of CTO	9 (25.71%)	14 (32.56%)	0.462
Hypercholesterolemia	4.83±0.71	4.83±0.94	0.975
Hypertriglyceridemia	2.57±1.73	2.14±0.89	0.324
Time from CTO onset to PCI, minutes	20.83±19.8	17.38±17.87	0.153
NYHA Grade 1, n (%)	9 (25.71)	13 (30.23)	0.246

SPECT image acquisition and quantitative analysis: Rest and nitroglycerin interventional 99mTc-MIBI SPECT were performed 1 week after PCI. And all the patients underwent nitroglycerin interventional 99mTc-MIBI SPECT again at 6 months after PCI. Approximately 3-7 days after PCI, as the patients were in stable conditions, we discontinued all the drugs except aspirin, clopidogrel, low molecular weight heparin (LMWH), and Lipitor. And then, all the patients received rest 99mTc-MIBI SPECT at the first 24 hours and nitroglycerin interventional 99mTc-MIBI SPECT which allowed repeated sublingual nitroglycerin in order to collect images when the systolic blood pressure dropped for 10 mmHg at the next 24 hours. Images were obtained 1 hour after administration of the radiopharmaceutical 740 MBq 99mTc-MIBI by using INFINIA II SPECT with double large-field-of-view gamma cameras, which showed high radiochemical purity of 95%. Images were collected from right anterior oblique (RAO) 45° to left posterior oblique (LPO) 60° per frame and 30 s for each frame. We acquired matrix 64 × 64 by Hann filtration and then performed image reconstruction which were analyzed by quantified polar bull's eye plot. The equality of maximum pixel count was obtained by normalized processing of the bull's eye map before and after nitroglycerin interventional 99mTc-MIBI SPECT in both groups. Generated by the machine software, we defined the rest image as bull's eye map A1 and the nitroglycerin one as A2 in the DM group, corresponding B1 and B2 in the NDM group. We drew the region of interest (ROI) based on the sparse or defect area of radioactive nuclide in the bull's eye map. The technique of drawing ROI was then used to obtain the pixels of the area and radioactivity count. Radioactivity count ratio = radioactivity total count of ROI/pixels of ROI × 100%.

UCG image acquisition and quantitative analysis: All the patients underwent UCG 1 week and 6 months after CAG. A color Doppler ultrasonic system (GE Vivid 7) and 2-5 MHz transducer were used. We tested the repeatability and reliability for measurement results obtained by the same and different operators respectively. The difference was less than 5%. Left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were evaluated by biplane Simpson's method. LVEDV and LVESV were converted into the left ventricular end-diastolic volume index (LVEDVI) and left ventricular end systolic volume index (LVESVI) respectively based on body surface area (BSA). The formulas were given as: ① BSA = 0.0061 × height (cm) + 0.0128 × body weight (kg)-0.1529; ② LVEDVI = LVEDV/BSA; ③ LVESVI = LVESV/BSA.

Follow-up: All the patients were followed for 6 months after PCI and then underwent UCG and SPECT again. The parameters of heart function, changes of the viable myocardium, and incidence of major adverse cardiac events (MACE) including recurrent angina, myocardial infarction, coronary artery bypass grafting, and cardiogenic death were collected and compared.

Statistical analysis

SAS 6.12 statistics software was adopted to carry out the data processing and analyses. The measurement data were expressed as x±s. The variable data were expressed as ratio or percentage. Differences of measurement data were analyzed by paired t test. The variable data were analyzed by χ^2 test. Values of $P<0.05$ were considered statistically significant.

Results

Baseline characteristics

There were no significant differences in the age, gender, smoking or drinking history, hyper-

Table 2. Angiographic Characteristics of CTO patients underwent successful PCI with CTO with or without DM

Group	Numbers of Pathological Coronary Arteries			Artery occlusion				Coronary collateral circulation				Glycoprotein IIB/IIIA inhibitor, n (%)
	1	2	3	Total	LAD	LCX	RCA	Grade 3	Grade 2	Grade 1	Grade 0	
DM group (n = 35)	5 (14.26%)	13 (37.14%)	17 (48.57%)	44	29 (65.91%)	8 (18.18%)	7 (15.91%)	8 (22.86%)	12 (34.29%)	5 (14.29%)	4 (11.43%)	9 (25.71%)
NDM (n = 43)	3 (6.98%)	15 (34.88%)	25 (58.14%)	54	36 (66.67%)	8 (14.81%)	10 (18.52%)	11 (25.58%)	7 (16.28%)	10 (23.26%)	6 (13.95%)	13 (30.23%)
P	0.527	0.348	0.251	0.264	0.922	0.42	0.464	0.944	0.028	0.017	0.721	0.45

LDA = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Table 3. Outcome measures of the left ventricular function of CTO patients underwent successful PCI with or without DM

Group		LVEF (%)	LVESVI (ml/m^2)	LVEDVI (ml/m^2)
DM group	1st week after PCI	53.57±13.5	37.42±35.34	79.54±39.49
	6th month after PCI	58.42±9.75##	27.75±13.75#	65.27±15.31#
NDM group	1st week after PCI	50.32±11.3	42.74±22.81*	81.48±30.54
	6th month after PCI	61.80±10.4##	30.12±11.85*	67.61±28.58**

Comparison of parameters of the two groups in the same phase *P<0.05; **P<0.01. Comparison of parameters of 1st and 6th month after PCI in the same group #P<0.05; ##P<0.01.

Table 4. Outcome measures of rest and nitroglycerin interventional 99mTc-MIBI SPECT of CTO patients underwent successful PCI with or without DM

Group			Size of cardiac defects	Radionuclide scintigraphic count (%)
NDM group	6th month after PCI	Nitroglycerin	148.52±34.0**	36.76±9.0*
	1st week after PCI	Nitroglycerin	180.43±35.9**	31.64±8.1**
		Rest	240.46±49.41**	26.42±8.0**
DM group	6th month after PCI	Nitroglycerin	143.75±30.8##	33.75±9.4
	1st week after PCI	Nitroglycerin	176.54±32.7##	28.51±8.3#
		Rest	230.51±46.4	23.74±7.4

Comparison of parameters of the two groups in the same phase *P<0.05; **P<0.01. Comparison of parameters of 1st and 6th month after PCI in the same group #P<0.05; ##P<0.01.

tension, hyperlipidemia, time from CTO onset to PCI, history of AMI, and NYHA classification between the DM and NDM groups (P>0.05) (**Table 1**).

Angiographic characteristics

There were no statistical differences in coronary artery occlusion, single-vessel, double-vessel and triple-vessel diseases, as well as collateral circulation grade 0 between the two groups (P>0.05) except collateral circulation grade 1 and 2 (P<0.05). For the DM group, collateral circulation grade 1 and 2 were 5 (14.29%) and 12 (34.29%) respectively; For the non-DM group, they were 10 (23.26%) and 7 (16.28%) respectively. The *p* values were 0.017 and 0.028 respectively (**Table 2**).

Outcome measures of the left ventricular function

There were no statistical differences in parameters of LVEF, LVESVI, and LVEDVI between the two groups 1 week after PCI. After following up for 6 months, the values of LVESVI and LVEDVI in the two groups were significantly decreased while LVEF were significantly increased compared with those of 1 week after PCI (P<0.01). But there still was no significant difference between the two groups (**Table 3**).

Viable myocardium

1 week after PCI, the size of cardiac defects after nitroglycerin interventional 99mTc-MIBI SPECT was significantly lower than that of the rest in the DM group (P<0.01), but the percentage of the radionuclide scintigraphic count was higher (P<0.05). And so were those in the NDM group. There were no significant differences regarding the size of cardiac defects after rest or nitroglycerin interventional 99mTc-MIBI SPECT and the percentage of the radionuclide scintigraphic count between the two groups. Compared to the size of cardiac defects after nitroglycerin interventional 99mTc-MIBI SPECT 1 week after PCI, the defects at 6 months after PCI was significantly decreased (P<0.01), while the percentage of the radionuclide scintigraphic count was significantly increased (P<0.05) (**Table 4**).

Incidence of major adverse cardiac event

There were no significant differences in the total incidence of MACE between the two groups (14.26% vs 10.60%, P>0.05). In the DM group, one patient died of cardiac death (2.86%) and one patient underwent coronary artery bypass grafting (CABG) (2.86%), while in the NDM group, two patients died of cardiac death (4.65%) and no patient underwent CABG (0%). However, there were no significant differences between the two groups (**Table 5**).

Discussion

Coronary artery CTO is often found in patients with CHD. The efficacy of regular cardiac medi-

Table 5. Incidence of MACE of CTO patients underwent successful PCI with or without DM

	Cardiac death	CABG	Angina	MI	MACE
DM-PCI group	1 (2.86%)	1 (2.86%)	2 (5.71%)	1 (2.86%)	5 (14.26%)
NDM-PCI group	2 (4.65%)	0	4 (9.30%)	2 (4.65%)	8 (18.60%)
P	0.763	1.000	0.583	0.565	0.654

MACE: major adverse cardiac event; CABG: coronary artery bypass grafting; MI: myocardial infarction.

cine therapy to lower the risks of total occlusion is limited. And the MACE incidence remains relatively high [7-9]. Many clinical studies have shown that successful myocardial revascularization and long-term recanalization can significantly improve the left ventricular function and reduce long-term mortality as well as the need for CABG [10-12].

CHD in patients with diabetes often present as diffuse lesions, small vessel disease, excessive intimal hyperplasia, and pathological remodeling. Blood vessels often show enhanced proliferative reaction as response to local injury by PCI. Diabetic patients often exist an increased level of fibrinogen, thrombin as well as coagulation factor VII and a decreased level of fibrinolysis system as well as anti-thrombin III activity. The previous studies have shown that platelets collected from patients with DM have a larger volume and are more easily activated. Therefore, they have stronger adhesion ability and express more thromboxane A_2 as well as platelet glycoprotein II_b/III_a. That is why CHD patients with type 2 diabetes are more likely to form thrombus. Therefore, diabetic patients should receive appropriate and adequate antiplatelet therapy before PCI. In the present study, patients in the DM group had an increased platelet aggregation rate when admitted to hospital. So they all received proper antiplatelet and anticoagulant therapy before and after PCI to keep the platelet aggregation rate less than 50%.

Although there are different views on the long-term outcome of PCI for CTO patients with type 2 diabetes [13-17], recent studies have shown that patients with and without diabetes underwent CTO resolution and stent implantation do not differ during long-term follow-up regarding death, myocardial infarction, and target lesion revascularizations [18, 19]. This finding confirms that cardiologists should always attempt to perform coronary angioplasty stent implantation (CASI) and try their best to use the minimum stent to reach the maximum lumen diameter as long as the angiographic characteristics of patients with CTO are suitable for interventional therapy.

In the present study, we found that the prevalence of collateral circulation in patients with DM is much lower than that in patients without DM. This may be explained by the effects of DM on endothelial functions. The previous studies have shown that neovascularization is dependent on vascular endothelial growth factor (VEGF) which induces capillary-like angiogenesis by binding and phosphorylating its receptors. Neovascularization is accompanied by migration and proliferation of endothelial cells. The increased blood glucose level in patient with DM prevents endothelial cells from migrating and VEGF from binding its receptors therefore inhibits angiogenesis in patients with DM [20-25]. It has been shown in the present study that ratio of coronary collateral circulation grade 1 and 2 in the DM group was significantly lower than that in the NDM group, which might be able to explain why there were no significant differences regarding clinical outcomes including viable myocardium and heart function between the two groups. From the above results, we could also conclude that the effects of diabetes on microvasculation are persistent and chronic.

In the present study, there were no significant differences regarding clinical prognosis between patients with and without diabetes, which was probably due to the similarity of the patients' characteristics at the baseline in both groups. However, there were several limitations of the present study. First of all, this was a small clinical study with limited number of subjects recruited. Secondly, the follow-up duration was certainly not long enough. Therefore, the long-term prognosis of the two groups needs to be further explored.

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Disclosure of conflict of interest

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