ORIGINAL RESEARCH

Cardiac Rehabilitation of Patients with Acute ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention in a Han Population in Northern China: A Prospective Cohort Study

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Background: Cardiac rehabilitation (CR) has been associated with improved cardiac function in cardiovascular diseases. Our aim was to explore the factors associated with cardiac function and CR.

Methods: This prospective cohort study had 473 STEMI patients admitted for primary percutaneous coronary intervention (PCI) who were divided into a CR group (group A, n = 104) and a non-CR group (group B, n = 369) based on whether they could complete CR. Patients' clinical features, such as age, hyperlipidemia, family history of premature coronary heart disease (FHPCHD), smoking history, body mass index (BMI, kg/m^2), number of diseased vessels, arrhythmia during PCI, N-terminal pro–B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF) and major adverse cardiac events (MACEs) at 6 months after PCI were compared. Then, the clinical characteristics of patients were further analyzed according to those with MACEs (n = 78) and those without MACEs (n = 395).

Results: After CR of 6 months, NT-proBNP levels (p = 0.027), 6-MWD (meter, P = 0.000), LVEF (P = 0.000) were significantly improved in group A compared to group B, but not for SMWA (P = 0.875). Multivariate analysis indicated that even though patients in group A (OR 3.06, 95% CI 1.132–8.274, p = 0.03) have a higher incidence of hyperlipidemia, their MACEs (OR 0.191, 95% CI 0.038–0.961, p = 0.05) at 6 months were significantly lower than in group B, mainly because the average patient low age (<65 years, OR 0.917, 95% CI 0.859–0.979, p = 0.01) and significant improvement of 6-MWD (OR 7.999, 95% CI 4.342–14.737, P = 0.00) and the LVEF at 6 months (OR 1.112, 95% CI 1.072–1.154, p = 0.00). Further analysis based on the MACES outcomes showed that there were 6 factors associated with the occurrence of MACEs, they were age >65 years (OR 1.032, 95% CI 1.009–1.009, p = 0.007), smoking history (OR 0.485, 95% CI 0.238–0.989, p = 0.046), education level (OR 2.646, 95% CI 1.370–5.108, p = 0.004), 6-MWD (OR 1.688, 95% CI 1.104–2.811, p = 0.044), LVEF (OR 0.958, 95% CI 0.926–0.991, p = 0.013) and CR (OR 6.271, 95% CI 2.236–17.590, p = 0.000).

Conclusion: CR, including exercise rehabilitation, is a beneficial option to reduce MACEs in STEMI patients treated with primary PCI.

Keywords: rehabilitation, ST-elevation myocardial infarction, percutaneous coronary intervention, major adverse cardiac events

Introduction

Diseases of the cardiovascular system, including acute myocardial infarction (AMI), can result in high rates of disability and death and place a significant burden on society.[1] Among them, acute ST-segment elevation myocardial infarction (STEMI) is a serious global critical illness and a challenge to human health. Percutaneous coronary intervention (PCI) has become the treatment strategy of choice for reperfusion in STEMI patients.[2] Among different reperfusion strategies for STEMI, primary PCI was associated with the lowest risk of mortality.[3] There are approximately 750,000 patients in China underwent PCI treatment in 2017.[4] In patients with STEMI, PCI technology may relieve atherosclerotic vascular narrowing or thromboembolization, but exercise tolerance may still decline after revascularization.[5,6] Recent evidence has demonstrated exercise-based cardiac rehabilitation is beneficial in improving clinical outcomes and secondary prevention of acute myocardial infarction.[7] Comprehensive rehabilitation treatment is related to improved cardiac function and exercise tolerance in cardiovascular diseases.

The values of cardiac rehabilitation (CR) for patients with heart diseases such as coronary artery bypass surgery, heart valve repair, PCI, myocardial infarction (MI), stable angina, stable chronic heart failure, heart transplantation, arrhythmias, and severe arterial hypertension have been demonstrated.[8] The goals of CR include improvement in exercise tolerance and optimization of coronary risk factors, including improvement in lipid and lipoprotein profiles, body weight, blood glucose levels, blood pressure levels, and smoking cessation.[9]

It has been reported that Asian patients are less involved in CR after PCI than in Western countries.[10] In a prospective study in Singapore, the participation rate in CR was only 12.3% among 414 eligible patients.[11] However, there is an increasing number of STEMI patients after primary PCI who receive CR including exercise rehabilitation in China. CR not only improves the quality of life of patients but also improves several important outcomes, such as control of cardiovascular disease-related risk factors, exercise ability, readmission rates, and mortality.[12]

Our objective was to investigate the relationship between CR and major adverse cardiac events (MACEs) in STEMI patients after PCI. Data from China may provide further insight into CR as well as explore factors related to cardiac function and CR.

Methods
Study Population and General Baseline Characteristics

Four hundred and seventy-three STEMI patients admitted to the Second Affiliated Hospital of Shenyang Medical College between January 2017 and December 2019 were used as study subjects. Inclusion criteria: Han Chinese diagnosed with STEMI and treated with primary PCI with drug-eluting stents who have been taking Dual antiplatelet therapy (DAPT, clopidogrel 75 mg and aspirin 100 mg daily) postoperatively. Exclusion criteria: (a) cerebrovascular diseases, severe valvular diseases, uncontrolled hypertension or uncontrolled arrhythmia, hypertrophic obstructive cardiomyopathy, aortic dissection, severe orthopedic or neurological disability to exercise, (b) advanced heart failure (functional class IV), (c) individuals with incomplete clinical information who did not undergo enrollment and withdrawal.

General baseline characteristics, blood biochemical indicators including creatine kinase myocardial band (CK-MB), Troponin T (TnT), N-terminal pro–B-type natriuretic peptide (NT-proBNP) and serum creatinine were obtained from peripheral venous blood within 24 hours of admission for all studied participants. Clinically relevant data included the pre-hospital delay time, door-to-balloon time, the number of diseased-vessels, and the color flow Doppler echocardiography data including left ventricular ejection fraction (LVEF), 6-minute walking distance (6-MWD) in meters, segmental wall motion abnormalities (SWMA) and complications.

Intervention

In the absence of medical contraindications, the basic medications, including DAPT (dual antiplatelet therapy), ARB (angiotensin receptor blockers), ACEI (angiotensin-converting enzyme inhibitors) ß-receptor blocker or statins, etc., were routinely given to patients with STEMI after PCI. The patients were divided into CR group (group A, n=104) and non-CR group (group B, n=369) according to their wishes and whether they could complete CR. Group A was given the CR + basic medication therapy. Group B was given the basic medication therapy.

CR was defined as a combination of cardiac rehabilitation in the acute phase (beginning in the hospital) and the

convalescence phase (6 months after discharge). CR including exercise rehabilitation was carried out after vital signs stabilized. Patients in group A started CR on the tenth day on average. Exercise rehabilitation was formulated according to the consensus of Chinese experts on exercise rehabilitation after PCI.[13] Step 1 consisted of low levels of aerobic exercise for 5–10 min. Step 2 consisted of aerobic, resistance, and flexibility exercise lasting 30–90 min. Step 3 was a relaxation exercise lasting 5–10 min.

The points to note during rehabilitation process were as follows: (a) patients need to be informed about the purpose, methods and warning symptoms of exercise prescription before exercise rehabilitation, (b) patients undergoing early rehabilitation should be evaluated pre-rehabilitation and post-rehabilitation, (c) cardiac first aid emergency plans, equipment and medicines need to be prepared for the patients with STEMI after PCI during hospitalization, (d) cardiac first aid training for CR doctors and nurses should be conducted regularly. In addition, we further analyzed the potential factors contributing to the occurrence of MACEs based on patients presenting with MACEs (n=78) and those without MACEs (n=395). The written informed consent for CR was given by all patients.

Follow-Up

At 6-month follow-up, patients were evaluated and recorded for post-PCI arrhythmia and complications, 6-MWD, NT-proBNP, LVEF, SWMA and MACEs (including death, recurrent myocardial infarction, stroke, and target-vessel revascularization).

Statistical Analysis

All data were analyzed by IBM SPSS 24.0 (IBM Co., Armonk, NY, USA). Continuous variables in accordance with the normal distribution were presented as mean ± standard deviation, and the *t*-tests were used to compare the between-group data. Categorical data were presented as percentage (%) and chi-square tests were used to compare the between-group data. ANCOVA (Analysis of Covariance), followed by Bonferroni test, was performed for NT-proBNP level, 6-MWD, LVEF and SWMA before and after CR. A multivariate logistic regression analysis, using CR or MACEs as the dependent variable (dichotomous for logistic regression) and using age, gender, hyperlipidemia, FHPCHD, smoking history, higher education, BMI (kg/m2), heart rate, number of diseased vessels, arrhythmia during PCI, NT-proBNP, 6-MWD (meter), LVEF (%), NT-proBNP at 6-month, 6-MWD (meter) at

6-month, LVEF (%), SWMA and MACEs at 6-month follow-up or CR as the independent variables, was performed. A p value <0.05 was considered to be statistically significant.

Results
Baseline Characteristics

The baseline characteristics of the two groups are shown in Table 1. Age, gender, hyperlipidemia rate, family history of premature coronary heart disease (FHPCHD), rate of smoking history, education levels, body mass index (BMI), heart rate, number of diseased vessels, arrhythmia during PCI, and MACEs at 6-month between the two groups were significantly different (Table 1, P < 0.05).

Among the 620 patients with STEMI, the overall in-hospital mortality rate was 3.87%. Among the 473 STEMI patients who underwent primary PCI, pre-hospital delay time and door-to-balloon time averaged 3.66 to 4.46 hours (P=0.16) and 91.26 to 95.27 minutes (P=0.645) in groups A and B, respectively. The overall proportion of comprehensive rehabilitation was 22.0%.

The median duration of follow up was 6 months. 473 (99.4%) completed 6-month follow-up. The rate of MACEs at 6-month follow-up was significantly lower in group A than in group B (3.8% vs 20.1%, P < 0.05). The proportion of recurrent angina at 6-month follow was significantly lower up in group A than in group B (0% vs 11.4%, P < 0.05). There was no significant difference in the proportion of recurrent myocardial infarction between the two groups at 6-month follow-up (1.9% vs 1.9%, P > 0.05).

Analysis of Covariance (ANCOVA) Between the Groups

After 6 months of CR, NT-proBNP levels (P=0.027), 6-MWD (P=0.000), and LVEF (P=0.000) were significantly improved in group A compared to group B, but not for SMWA (Table 2, P=0.875).

Multivariate Logistic Regression Analysis

Multivariate analysis for CR (Table 3) showed that although the incidence of hyperlipidemia in group A (OR 3.06, 95% CI 1.132–8.274, p=0.03) was higher than that in group B, their MACEs (OR 0.191, 95% CI 0.038–0.961, p=0.05) were significantly lower than that of group B at 6 months, mainly due to the lower average age of patients in group A (<65 years, OR 0.917, 95% CI 0.859–0.979,

Table 1 Baseline Characteristics Between the Two Groups

Variables	Group A (n = 104)	Group B (n = 369)	t/χ^2	P value
Age, y	50.39 ± 9.381	65.6 ± 10.752	13.086	0.000
Gender, n (%)				
Male	90 (86.5%)	274 (74.3%)	6.903	0.009
Female	14 (13.5%)	95 (25.7%)		
History of hypertension, n (%)	64 (61.5%)	250 (67.8%)	1.403	0.236
History of diabetes, n (%)	19 (18.3%)	97 (26.3%)	2.818	0.093
Hyperlipidemia, n (%)	59 (56.7%)	155 (42.0%)	7.101	0.008
FHPCHD, n (%)	13 (12.5%)	7 (1.9%)	19.982	0.000
HMD, n (%)	3 (2.9%)	12 (3.3%)	0.000	1.000
Smoking history, n (%)	35 (33.7%)	75 (20.3%)	8.076	0.004
Higher education, n (%)	95 (91.3%)	65 (17.6%)	197.041	0.000
BMI, kg/m2	27.41±2.31	25.77±2.38	−5.838	0.000
Heart rate, bpm	76.65±17.01	72.63±17.13	2.061	0.040
Serum creatinine, μmol/L	73.32±26.95	77.05±24.52	−1.339	0.181
[a]Pre-hospital delay time, hours	3.66±5.15	4.46±10.97	−1.618	0.106
Door-to-balloon time, min	91.26±137.56	95.27±50.50	−0.461	0.645
[b]Killip classification	1.27±0.74	1.44±0.83	−1.917	0.056
Number of diseased vessels	1.58±0.63	1.85±0.72	−3.465	0.001
Arrhythmia during PCI, n (%)	6 (5.8%)	73 (19.8%)	11.453	0.001
Complications during PCI, n (%)	3 (2.9%)	25 (6.8%)	2.205	0.138
CK-MB, mmol/L	109.13±127.16	113.16±128.25	−0.284	0.777
TnT, ng/L	4.07±3.96	4.42±3.77	−0.792	0.429
MACEs at 6-month, n (%)	4 (3.8%)	74 (20.1%)	25.495	0.000

Notes: [a]Pre-hospital delay time was defined as the time from pain onset to the chest pain center. Door-to-balloon (D2B) time was defined as the time from hospital entrance to guide wire passing; [b]Killip Class I was represented by 1, Killip Class II was represented by 2, Killip Class III was represented by 3, and Killip Class IV was represented by 4.
Abbreviations: FHPCHD, family history of premature coronary heart disease; HMD, History of myocardial infarction; BMI, body mass index; PCI, percutaneous coronary intervention; CK-MB, creatine kinase myocardial band; TnT, Troponin T; MACEs, major adverse cardiac events.

p=0.01) and significant improvement in 6-MWD (OR 7.999, 95% CI 4.342 −14.737, P=0.00) and LVEF (OR 1.112, 95% CI 1.072–1.154, p=0.00).

Multivariate analysis of MACEs (Table 4) showed that there were 6 factors were associated with the occurrence of MACEs, they were age >65 years (OR 1.032, 95% CI 1.009–1.009, p=0.007), smoking history (OR 0.485, 95% CI 0.238–0.989, p=0.046), education level (OR 2.646, 95% CI 1.370–5.108, p=0.004), 6-MWD (OR 1.688, 95% CI 1.104–2.811,

p=0.044), LVEF (OR 0.958, 95% CI 0.926–0.991, p=0.013) and CR (OR 6.271, 95% CI 2.236–17.590, p=0.000).

Discussion

There is an increasing number of STEMI patients after primary PCI who receive CR including exercise rehabilitation in China, the proportion group A in our study was 22.0%. Our study showed that comprehensive rehabilitation treatment significantly reduced the incidence of

Table 2 ANCOVA Analysis 4 Indicators Before and After CR

Indicators	Group A		Group B		F	P
	Within 24 Hours	6 Month Later	Within 24 Hours	6 Month Later		
NT-proBNP (pg/L)	1456.35±1071.28	155.01±162.05	2400.25±3254.32	931.45±1683.00	1.427	0.027
6-MWD (meter)	312.56±16.71	632.43±10.89	320.08±15.69	486.52±16.07	51.72	0.000
LVEF(%)	56.55±6.57	60.73±6.17	54.42±8.21	54.68±9.37	2.136	0.000
SWMA, n(%)	73 (70.2%)	69 (66.3%)	292 (79.1%)	262 (71.0%)	0.025	0.875

Abbreviations: NT-proBNP, N-terminal pro–B-type natriuretic peptide; 6-MWD, 6-minute walk distance; LVEF, Left ventricular ejection fraction; SWMA, Segmental wall motion abnormalities.

Table 3 Results of Multivariate Logistic Regression Analysis for CR (McFadden's Rho-Squared = 0.715)

Variables	OR	95% CI	P
Age>65	0.917	0.859–0.979	0.009
Gender	2.253	0.475–10.694	0.306
Hyperlipidemia	3.060	1.132–8.274	0.028
FHPCHD	2.436	0.225–26.389	0.464
Smoking history	0.508	0.171–1.512	0.224
Higher education	0.014	0.003–0.060	0.000
BMI (kg/m^2)	0.931	0.710–1.221	0.606
Heart rate, bpm	1.001	0.975–1.027	0.969
Number of diseased vessels	0.778	0.409–1.479	0.444
Arrhythmia during PCI	0.286	0.071–1.147	0.077
NT-proBNP	1.000	0.999–1.000	0.168
6-MWD (meter)	0.009	0.002–0.044	0.000
LVEF (%)	0.930	0.816–1.059	0.271
NT-proBNP at 6-month	0.998	0.997–1.000	0.000
6-MWD (meter) at 6-month	7.999	4.342–14.737	0.000
LVEF (%) <54.68±9.37	1.112	1.072–1.154	0.000
SWMA	1.278	0.802–2.036	0.302
MACEs at 6-month follow-up	0.191	0.038–0.961	0.045

Abbreviations: OR, odds ratio; CI, confidence interval; FHPCHD, family history of premature coronary heart disease; BMI, body mass index; PCI, percutaneous coronary intervention; NT-proBNP, N-terminal pro–B-type natriuretic peptide; 6-MWD, 6-minute walk distance; LVEF, Left ventricular ejection fraction; SWMA, Segmental wall motion abnormalities; MACEs, major adverse cardiac events.

Table 4 Results of Multivariate Logistic Regression Analysis for MACEs (McFadden's Rho-Squared = 0.083)

Variables	OR	95% CI	P
Age>65	1.032	1.009–1.005	0.007
Gender	0.922	0.475–10.694	0.794
Hyperlipidemia	1.233	0.745–2.007	0.426
FHPCHD	0.824	0.174–3.909	0.807
Smoking history	0.485	0.238–0.989	0.046
Higher education	2.646	1.370–5.108	0.004
BMI (kg/m^2)	0.944	0.849–1.049	0.282
Heart rate, bpm	0.997	0.983–1.012	0.726
Number of diseased vessels	1.167	0.829–1.644	0.377
Arrhythmia during PCI	1.315	0.709–2.439	0.384
NT-proBNP	1.000	1.000–1.000	0.199
6-MWD (meter)	1.688	1.014–2.811	0.044
LVEF (%)	0.958	0.926–0.991	0.013
NT-proBNP at 6-month	1.000	1.000–1.000	0.488
6-MWD (meter) at 6-month	0.596	0.343–1.037	0.067
LVEF (%) <54.68±9.37	1.009	0.968–1.052	0.669
SWMA	1.342	0766–2.351	0.304
CR	6.271	2.236–17.590	0.000

Abbreviations: OR, odds ratio; CI, confidence interval; FHPCHD, family history of premature coronary heart disease; BMI, body mass index; PCI, percutaneous coronary intervention; NT-proBNP, N-terminal pro–B-type natriuretic peptide; 6-MWD, 6-minute walk distance; LVEF, Left ventricular ejection fraction; SWMA, Segmental wall motion abnormalities; CR, Cardiac rehabilitation.

MACEs during 6-month follow-up in patients with STEMI after PCI. The rate of MACES of patients treated by CR was 5 times lower than the patients without CR even they had much higher rates of hyperlipidemia. Patients' low mean age and higher LVEF at 6 months may be the favorable factors contributing to the low MACEs. CR and education were associated with lower MACEs in patients with acute coronary syndrome.[14]

ANCOVA analysis showed that after CR, the NT-proBNP levels, 6-MWD and LVEF were significantly improved when compared group A to group B. Further analysis indicated that 6-MWD at 6-month was about 8 times better in group A than in group B.

The fact that CR reduces the incidence of MACEs and restenosis is due to improvements in blood rheology and endothelial function.[15] Vascular endothelium is the primary regulator of blood flow through its vasodilatory properties. This is primarily through the release of nitric oxide (NO), but also prostacyclin (PGI2) and endothelial-derived hyperpolarizing factor (EDHF), in response to various chemicals (eg, 5-hydroxytryptamine, bradykinin and acetylcholine), and physical stimuli (eg, shear stress).[16] Exercise training augments the expression of NO synthase in endothelial cells and induces the up-

regulation of copper-and-zinc–containing superoxide dis-mutase in the cytosol.[17,18] Exercise rehabilitation can increase cardiac blood flow, and increase myocardial con-tractility, and improve the heart pumping strength.[19] Exercise training has been shown to attenuate ST depres-sion during exercise and reduce hypoperfusion on thallium scanning, suggesting that myocardial perfusion may increase.[19]

In addition, exercise rehabilitation can enhance para-sympathetic tone,[20] alter the production of angiotensin II and reduce aldosterone production, thereby reducing sym-pathetic tone, and complementing the effects of other exercise-induced modulators of parasympathetic activity such as plasma adrenomedullin and atrio/brain-natriuretic-peptides.[21,22] These effects are related to aerobic capacity and work by inhibiting endothelin-1 and norepinephrine, leading to improved endothelial function and responsiveness.[23,24]

A recent retrospective analysis conducted in Korea found that CR treatment was accompanied by lower MACE, especially in patients with low pre-procedure TIMI blood flow in primary PCI for STEMI.[7] Our results on the relationship between CR and MACEs were consis-tent with those reported in Korea. In addition, several

studies investigated that early and regular CR may reduce the incidence of lumen loss, coronary restenosis, and vascular events after stenting after PCI in patients with AMI patients and promote early physical recovery and improve quality of life.[25,26] A meta-analysis of the CR effect on left ventricular remodeling after MI showed that the earlier and longer the exercise training, the more significant the reversal cardiac remodeling.[27]

According to our results, higher NT-proBNP, lower LVEF and the shorter 6-MWD had a statistically significant impact on MACEs in patients with STEMI after primary PCI. Patients with reduced LVEF have more potential risk factors and an increased incidence of thromboembolic events, which may contribute to the increased cardiovascular mortality.[28] Results from the Australian Capital Territory PCI Registry showed that the incidence of MACEs was strongly associated with door-to-balloon time, which was an independent predictor of MACEs.[29] The prolonged ischemia, increased oxidative stress, and increased MI size will increase the risk of MACEs.[29]

Our results from this study have valuable clinical implications for STEMI patients accepting primary PCI. CR significantly reduced the incidence of MACEs during 6-month follow-up in STEMI patients after PCI. Delayed CR after myocardial infarction may lead to a reduced quality of life after MI. In patients with AMI, an early home-based CR program can greatly improve ventricular function in the short term.[30] Long et al found that CR may have little effect or no difference on all-cause mortality in the short term.[31] In our study, the incidence of recurrent angina was significantly lower in group A than in group B and no patients died in either group, which may be related to the short duration of follow-up. Thus, it may be safe and effective to start CR on day 10 on average for STEMI patients after primary PCI.

Despite the well-known benefits of CR, adherence to CR remains low.[32] In the United States and Europe, CR is performed in less than 30% of patients with indications for CR.[13,33] And the percentage of Asian patients participating in CR after PCI was lower than that reported in western countries. We hope that our study can encourage more patients to participate in CR.

The limitations of this study are as follows: (1) only patients from one tertiary grade A hospital in China were included; and (2) some potential relative factors such as socioeconomic situation, basic medical insurance and social support were not collected. (3) Additional research is needed to improve our understanding of the relationship between CR and long-term clinical prognosis.

Conclusion
CR significantly reduces NT-proBNP levels and significantly improves 6-MWD and LVEF, thereby reducing MACEs in STEMI patients after PCI. CR including exercise rehabilitation is a useful option for reduced MACEs in STEMI patients after primary PCI.

Data Sharing Statement
The analyzed data sets generated during the study are available from the corresponding authors on reasonable request.

Ethics Approval and Consent to Participate
The study was proceeded conforming to the ethical guidelines of the Declarations of Helsinki. The study was approved by The Second Affiliated Hospital of Shenyang Medical College. All participants had signed the written consent forms.

Disclosure
The authors report no conflicts of interest in this work.

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