International Journal of Cardiology 167 (2013) 2617–2622

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Regular exercise training reduces coronary restenosis after percutaneous coronary intervention in patients with acute myocardial infarction

Hye Young Lee [a], Jeong Hoon Kim [b], Byung Ok Kim [b,*], Young-Sup Byun [b], Sungwoo Cho [b], Choong Won Goh [b], HyoSeung Ahn [b], Kun Joo Rhee [b], Chul Kim [c]

[a] Department of Cardiology, Severance Hospital, Yonsei University, Seoul, Republic of Korea
[b] Department of Cardiology, Sanggye Paik Hospital, Inje University, Seoul, Republic of Korea
[c] Department of Rehabilitation Medicine, Sanggye Paik Hospital, Inje University, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 19 September 2011
Received in revised form 18 June 2012
Accepted 23 June 2012
Available online 12 July 2012

Keywords:
Cardiac rehabilitation
Exercise training
Coronary restenosis

ABSTRACT

Background: It is well known that cardiac rehabilitation (CR) including regular exercise training (ET) is cardioprotective with respect to clinical events in patients with acute myocardial infarction (AMI). However, it is not known whether the regular ET may affect coronary restenosis after percutaneous coronary intervention (PCI) with stenting in AMI. The aim of this study was to evaluate the effect of regular ET on a stented coronary segment and its association with inflammatory markers in AMI.

Methods: Consecutively 74 AMI patients who underwent PCI with implantation of a drug-eluting stent and 9 month follow-up angiography were included. Thirty seven patients who received CR with ET were assigned to the ET group. Another 37 patients who did not participate in ET, of similar age to those of participants, were assigned to the control group. At 9 months, angiographic restenosis measured as in-segment late luminal loss of the stented coronary artery was analyzed via quantitative coronary angiography using CAAS 5.9.

Results: There were no significant differences in baseline characteristics including age, sex, body mass index, smoking, DM, hypertension, lipid profile, use of statin, and complete blood cell between two groups. On 9 month follow-up angiography, late luminal loss per stent was significantly smaller in the ET group compared to the control group (0.14 ± 0.57 vs. 0.54 ± 0.88 mm, $p = 0.02$). Maximal oxygen consumption (VO_2max) significantly improved in the ET group after 9 months (27.9 ± 6.4 vs. 30.8 ± 5.2 mL/kg/min, $p < 0.001$). Increment in high density lipoprotein-cholesterol (HDL-C) was significantly larger in the ET group at 9 months (0.15 ± 0.12 vs. 0.04 ± 0.24 mg/dL, $p = 0.03$).

Conclusion: Regular ET contributes to a significant reduction in late luminal loss in the stented coronary segment in AMI patients. This effect was associated with increased exercise capacity and increased HDL-C.

1. Introduction

Cardiovascular diseases are currently a major health problem with a large burden of chronic diseases, impairment and handicap. Percutaneous coronary intervention (PCI) with stent implantation has been the mainstay of treatment in most patients with symptomatic coronary artery disease (CAD) [1]. Although a decline in cardiovascular mortality has been observed over the last decade, the benefit of PCI still carries significant risks of restenosis and recurrent ischemia during follow up [2,3]. Therefore, additional strategies to improve cardiovascular mortality and morbidity are being investigated in terms of stent design and medical treatment [4–6].

Recently, the beneficial effects of cardiac rehabilitation (CR) with exercise training (ET) in primary and secondary prevention of cardiovascular disease have been investigated. Several studies have revealed that ET improved not only functional capacity, cardiac function and quality of life, but also mortality and morbidity in patients with PCI treatment, heart failure, and stable coronary artery diseases [7–10].

With regard to the basic science of atherothrombosis, recent advances have established a fundamental role of inflammation in all stages of atherothrombosis thoroughly from initiation, progression and thrombotic complication [11]. Several inflammatory markers including neutrophil have been found to be associated with cardiovascular risks in many studies [12–15]. And many studies have revealed the effect of ET on inflammatory risk factors of CAD [16–18].

However, very little research has been conducted to identify the impact of ET on coronary restenosis after PCI with stenting in AMI.

In the present study, our aims were to elucidate the effects of regular ET on coronary restenosis and its association with inflammatory

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Sanggye-dong, Nowon-gu, Seoul, 139-200, Republic of Korea. Tel.: +82 2 950 1266; fax: +82 2 950 1248.
E-mail address: byungokim@paik.ac.kr (B.O. Kim).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.06.122

markers following PCI for AMI. Our findings may serve as a basis to design a necessary systematic exercise program for secondary prevention of AMI patients.

2. Materials and methods

2.1. Subjects

Consecutively, a total of 121 patients who were referred for planned CR after successful PCI with drug-eluting stent (DES) for AMI were screened between Nov. 2007 and Mar. 2009. All patients aged from 50 to 75 were encouraged to participate in CR with ET. They were excluded in both groups if they had; a history of prior myocardial revascularization, third degree AV block, severe aortic stenosis, systolic blood pressure above 200 mm Hg at rest, diastolic blood pressure above 110 mm Hg at rest, left ventricular ejection fraction<40%, pericarditis, cardiomyopathy, ST segment depression of more than 2 mm at rest, uncontrolled tachycardia, exercise-induced malignant ventricular arrhythmia, acute systemic illness, skeletal vascular disease, and acute metabolic disorders. The patients who denied giving their informed consent to exercise program were exclude in both group.

Because our institute was the only location in Seoul that performed PCI and subsequent ET after AMI, the study sample very closely approximated a community based sample of people undergoing PCI and ET in Seoul, Korea.

2.2. Cardiac rehabilitation and exercise training

Participation in CR was defined as commencement of outpatient CR session starting within 4 weeks of the index PCI and completion of a 9-month ET program. CR with ET program comprised two stages; the first stage was supervised exercise under prescription for 6 weeks and the second stage was community-based and self-managed exercise over 9 months. Cardiorespiratory capacity was measured twice by a symptom-limited treadmill exercise test under the protocol of modified Bruce, before the commencement and at the end of the first 6 week supervised exercise training. The exercise test was supervised by experienced physicians and ECG monitoring was done throughout the test. Maximal oxygen uptake (VO_2max) was defined as the highest value or the plateau of directly measured oxygen consumption using a respiratory gas analyzer (QMC, Quinton Instrument Co., USA).

The exercise program included a 10 minute warm-up, a 40 minute aerobic exercise on a treadmill or bicycle ergometer, and a 10 minute cool-down phase. Exercise intensity in the first stage was gradually increased from 50 to 80% of VO_2max determined by exercise test. After the 6 week supervised exercise, community-based and self-managed exercise was performed according to the reassessed cardiorespiratory capacity. Patients were required to exercise at a local fitness center and maintain aerobic exercise on a treadmill or bicycle ergometer in a same manner. Every exercise training session should be composed of 1 h and patients were required to do three times a week. Adherence to exercise was monitored every month at the outpatient clinic.

2.3. Primary outcome and quantitative coronary angiography

The primary outcome was late luminal loss per stent of the culprit lesion which was defined as the minimal luminal diameter (MLD) immediately after the procedure minus the MLD at a 9-month follow-up. If there were more than 2 lesions in one patient and the culprit vessel was not discernible, both vessels were evaluated as a separate lesion. Binary angiographic restenosis was defined as the incidence of percent diameter stenosis of 50% or more at the qualifying angiographic follow-up. Two experienced cardiologists independently interpreted the images in a blinded manner. Disagreement was resolved by reanalysis and consensus. Standard image acquisition was performed using ≥2 angiographic projections of the stenosis. Intracoronary nitroglycerin was administered to provide maximum coronary vasodilation. At follow-up, repetition of identical angiographic projections of the lesion was performed. Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by 20%. Selected images for analysis were identified by use of angiographic projections that demonstrated the stenosis in an unforeshortened view, minimized the degree of vessel overlap, and displayed the stenosis in its "sharpest and tightest" view. The target lesion was defined as the stented segment plus a 5 mm segment proximal and distal to the stent. Angiographic follow-up was routinely performed at 9 months after the index procedure unless earlier angiography was required for clinical reasons. At 9 months, angiographic restenosis was measured as the in-segment late loss of the stented coronary artery via quantitative coronary angiography using CAAS 5.9. (Pie Medical Imaging B.V., Netherlands, Fig. 1).

2.4. Secondary outcome; laboratory evaluation

Laboratory evaluation was done to all patients at the commencement and completion of the 9 month exercise. All patients routinely had blood drawn for white blood cell (WBC) and differential counts, creatine kinase-myocardial band (CK-MB), troponin-T (Tn-T), and lipid profiles when they were admitted and at the time of 9 month angiography. All patients maintained an overnight fasting >12 h prior to follow up blood collection. An automated hematology analyzer (Sysmex SE-2100; Sysmex Corporation, Kobe, Japan) measured the total WBC and neutrophil counts. High density lipoprotein-cholesterol (HDL-C) and triglyceride levels were measured by the homogenous assay and enzymatic method, respectively (Sigma Co., St. Louis, MO, USA).

2.5. Clinical outcome evaluation

Clinical outcome was the major adverse cardiac event (MACE), defined as cardiac death, re-infarction, and target lesion revascularization (TLR) at 9 months after the index procedure. TLR was defined as ischemia-driven revascularization of the infarct-related artery by PCI or bypass surgery during the follow-up period.

2.6. Statistical analysis

Data were reported as mean and standard deviation for continuous variables and as percentages for categorical variables. Late lumen loss at 6 months after stent implantation is usually between 0 and 0.8 mm [19]. In a study, LLL after stent implantation was 0.29 mm smaller in the training group compared to the control group [20]. We chose an estimated difference in mean LLL of 0.29 mm between the two groups. To obtain 80% power for detection of this difference, assuming an SD of 0.4 mm in each group, a sample size of 34 patients was needed.

For the testing of significance, comparisons of continuous variables between groups were analyzed by independent *t*-test. Comparison of categorical variables was generated by the Pearson χ^2 test. Statistical comparisons were performed using SPSS, version 15.0 software (SPSS Inc.). All tests were 2-sided, and the results were considered statistically significant at a $p<0.05$.

3. Results

3.1. Patient population

Among 121 patients, 37 patients (40%) participated in CR with ET during the study period. Of the 84 nonparticipants, 37 patients of similar age to those of the participants were assigned to the control group. The patients in the control group were those who were under standard medical care for AMI, including medication, abstinence from smoking, and diet modification, only without ET during the same period. There was no exercise related adverse event throughout the study period.

Table 1 lists the comparative differences between individuals who participated in ET and those who did not. The mean ages for the ET group and control group were 58.8 ± 10.8 and 60.3 ± 8.7, respectively. Gender, body mass index (BMI), smoking status, history of hypertension or diabetes, and systolic and diastolic pressure were similar between the ET and control groups. Left ventricular ejection pressure and type of MI; ST-segment elevation myocardial infarction (STEMI) vs. non-ST segment elevation myocardial infarction (NSTEMI) were also similar between two groups (Table 1). Adherence to medication, type and dose of lipid lowering agents and smoking status during the study period were not different between two groups (Table 2).

The initial level of WBC count, neutrophil count, and lipid profiles was not significantly different between two groups (Table 3).

3.2. Impacts of exercise training on angiographic outcomes

Comparisons of angiographic parameters between two groups were summarized in Table 4. Target vessels, reference vessel diameter, lesion length, stent length and maximal stent application pressure were similar between two groups. The median number of stents implanted per patients was one and the types of DES were similar between two groups. Preprocedural and postprocedural TIMI flows were also similar between two groups. Post PCI MLD was not different between two groups (2.56 ± 0.31 vs 2.58 ± 0.44 mm, respectively; $p = 0.80$; Table 4).

Follow up angiography at 9 months revealed that late lumen loss per stent was significantly smaller in the ET group than the control group (0.14 ± 0.57 vs 0.54 ± 0.88, respectively; $p = 0.02$; Table 5, Fig. 2). Diameter stenosis at 9 months was significantly larger in the control group (15.1 ± 23.4 vs 29.1 ± 18.7, respectively; $p = 0.01$; Table 5). Binary stenosis occurred more frequently in the control group compared to the ET group (2.7 vs 12.8%, $p = 0.20$, Table 5). However, it was not statistically significant.