

The effect of aerobic training on endothelium-dependent vasodilatation in patients with coronary artery disease who were revascularized and young men

Seyed Masoud Seyedian, Farzaneh Ahmadi*, Babak Hamidian, Ebrahim Hajzadeh, Afshin Rezazadeh, Ahmad Reza Asare, Mohammad Hasan Adel, Mohammad Nourizadeh

Department of Cardiology, Medical Jundishapur University of Ahvaz, Atherosclerosis Research Center Jundishapur University of Medical Sciences, Ahvaz, Iran; *Corresponding Author: ahmadithc@yahoo.com

Received 13 April 2013; revised 15 May 2013; accepted 19 June 2013

Copyright © 2013 Seyed Masoud Seyedian *et al.* This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Aim: The aim of this study was to determine the effect of training on endothelium-dependent vasodilatation in patients with coronary artery disease (CAD) after revascularization and healthy young men. **Background:** Impaired endothelial function has been observed in patients with CAD and those with CAD risk factors. Studies have shown that exercise can enhance endothelial function. **Methods:** This experimental cross-sectional study was conducted on patients with CAD (3 months after CABG and PCI) and students of medical school in 2011. Endothelium dependent dilation of the brachial artery was determined by using high-resolution vascular ultrasonography through flow-mediated vasodilatation (FMD) after induction of ischemia, and the data were analyzed using SPSS, dependent *t*-test and ANCOVA. **Findings:** The findings showed that at baseline, FMD was reduced in revascularized patients, when compared with healthy young men, after 8 weeks, and exercise training significantly improved FMD in patients underwent training group [from 4.31 ± 1.45 (SD)% to 6.15 ± 0.773 (SD)% , $p < 0.05$] and substantially increased the same in healthy young men [from $9.18\% \pm 1.45\%$ to $11.72\% \pm 1.72\%$, $p < 0.05$] However, in the control group, the FMD remained unchanged, and even after aerobic training, it did not significantly modify the brachial artery diameter in these groups. **Conclusion:** Our study demonstrates that endothelial dysfunction persisting in CAD patients after revascularization and aerobic training can improve endothelial

function in different vascular beds in CAD patients and healthy young men. This may contribute to the benefit of regular exercise in preventing and restricting cardiovascular disease.

Keywords: Endothelium-Dependent Vasodilatation; Coronary Artery Disease; Aerobic Training; High-Resolution Ultrasound; Flow-Mediated Dilation

1. INTRODUCTION

Currently, most patients with angina pectoris have their symptoms controlled with medication or by revascularization by PTCA or CABG. Consequently, and with rare exceptions [1], much of the evidence that exercise training improves effort tolerance in patients with angina pectoris was obtained before 1990. Exercise training increases the exercise time to the onset of angina or even eliminates angina entirely by at least two mechanisms.

First, exercise training reduces the M.O₂ requirements during submaximal exercise [1-3]. Second, exercise training reduces endothelial dysfunction [4-6]. Normal coronary arteries dilate with exercise, whereas atherosclerotic coronary arteries often demonstrate endothelial dysfunction evidenced by exercise-induced vasoconstriction. Few large trials have examined the effects of exercise-based cardiac rehabilitation in patients following PTCA [6,7].

There are very few data for coronary artery disease and healthy young men. In a previous study, we demonstrated that in healthy middle age men, 8 weeks of circuit training did not affect vascular function [8], whereas, brachial artery flow mediated dilation (FMD) was enhanced

after a 10 weeks programme of daily aerobic and anaerobic exercise training in young military recruits [9], also in CAD patients who had had a recent acute myocardial infarction. Aerobic training significantly improved endothelial function, although this beneficial effect was lost after 1 month of detraining [10]. In addition, regular aerobic physical training enhanced vascular function in patients with chronic heart failure [11]. However, there is very little knowledge about a similar benefit from resistance training on CAD revascularized patients and healthy young men.

Therefore, in this study, we have investigated the effects of an 8-week aerobic training program on systemic artery vascular function in coronary artery disease (CAD) patients who have been treated and don't have apparent ischemia, and compared the results with the same of young men, and have demonstrated which is the most significant improvement in endothelium dependent dilation in all groups.

2. METHODS

2.1. Subjects

The study included 20 men with a history of CAD from heart clinic of medical science hospital and they were divided to 10 cases and 10 control groups. The inclusion criteria were as follows: the patients must be known case of CAD, and underwent regular surgical (coronary artery bypass grafting) or non-surgical revascularization (percutaneous transluminal coronary angioplasty) with normal or near normal left ventricle ejection fraction, more than recent 3 month.

On the other hand, patients who had valvular heart disease, chronic obstructive lung disease, renal and hepatic dysfunction, asthma, creatinine > 2.5 mg/dl and subjects performed more than two sessions of light to moderate exercise per week, were excluded week. Medications did not change across the course of control or exercise training periods. Furthermore, 10 young age healthy male subjects without cardiovascular disease and risks factors were randomly selected among the students of a medical school.

The characteristics of revascularization patients and healthy young subjects enrolled in the study are present-

ed in **Table 1**. The ethics committee approved the protocol and all the subjects gave written informed consent.

2.2. Study Design

All subjects underwent baseline assessment, after which CAD patients and young men were randomly assigned to either remain sedentary or undergo exercise training for 8 weeks according to the following protocol, and after 2 months, the assessment was repeated. Patients and young men were requested to maintain their diet and other life style behavior for the duration of the study, and this was confirmed through interview and questionnaire.

Assessment of vascular function was carried out in a quiet, temperature-controlled laboratory after an 8-h fast, 12-h abstinence from caffeine, and 24-h abstinence from alcohol and exercise. For individual subjects, repeat assessments were performed at the same time of the day, and the time of medication use was not changed. Endothelial function was assessed using a noninvasive technique proposed by Celermajer *et al.* [6]. The subjects were made to rest in supine with nondominant arm extended and immobilized with foam supports at an angle of 80° from the torso, the heart rate was continuously monitored with a three-lead electrocardiograph, and the mean arterial pressure was determined using sphygmomanometer (ALPK2, Japan) on the contralateral arm. A rapid inflation and deflation pneumatic cuff was positioned on the imaged arm immediately proximal to the olecranon process to provide a stimulus to forearm ischemia. Brachial artery diameters were analyzed at the time of the ECG monitoring, *i.e.*, at the beginning of QRS complex (end diastole). The forearm cuff was then inflated to 200 mmHg for 5 min. Images were recorded 30 s before cuff deflation and for 2 min after deflation. Brachial artery reactivity was evaluated by two-dimensional ultrasonography (Siemens 40) with a linear, high-resolution probe (10 MHz). Measurements were performed at baseline (**Figure 1**) and during flow-mediated dilation (FMD) for both patients and young healthy men. Changes in vessel diameter were calculated for each subject as the percentage variation of arterial diameter under different stimuli, when compared with the baseline diameter.

Table 1. Study population.

	G ₁ , Aerobic training (CAD)	G ₂ , Aerobic training (young men)	G ₃ , Control (CAD)
	mean SD (Standard Deviation)		
Age (year)	55 ± 4.33	27.7 ± 4.16	53 ± 6.43
Weight (kg)	82.1 ± 11.98	75 ± 7.84	82.85 ± 14.38
High (m)	1.73 ± 45	1.72 ± 5.51	1.741 ± 6.11

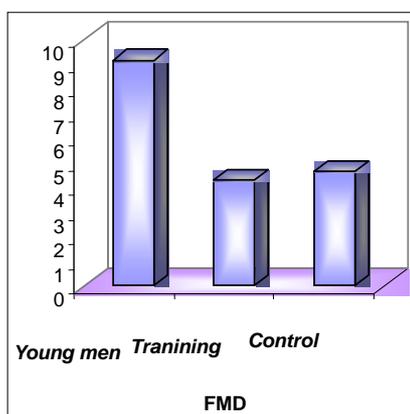


Figure 1. Baseline percentage of FMD in the three groups (pretest).

2.3. Exercise Training Program

After baseline evaluation (**Figure 1**), the patients and young men were randomized to receive aerobic training (Group 1 [G_1], 10 patients) (Group 2 [G_2], 10 young men) or as control not receiving the training (Group 3, [G_3], 10 patients). The subjects in G_1 and G_2 underwent moderate aerobic training thrice a week for 1 week at Tapesh cardiac rehabilitation center. Each session included a 10-min warm up, 30 min of running on a treadmill with telemetry monitoring and intensity set at 60% - 70% of peak exercise heart rate measured in the second ECG stress testing, and a 10-min cool down. G_3 patients avoided regular physical activity. Cardiac rhythm was continuously monitored on a four-channel telemetry system in all trained subjects (patient and young men) and in all sessions throughout the trial. Patients and young men in the aerobic training groups were also encouraged to gradually increase their daily physical level.

2.4. Follow up

All tests were repeated after 2 months and the results were compared with those of the baseline tests. The training program in trained subjects was stopped at this point. The arterial vasoreactivity and treadmill (Bruce protocol) tests were repeated again. Pharmacological therapy remained unchanged throughout the study.

2.5. Statistical Analysis

Statistical analyses were performed with SPSS software (version 17.0 for Windows). The data are presented as mean \pm SD. Baseline values were compared using ANOVA and t -test to determine whether there were significant differences among the three groups, and all the data were analyzed from baseline to post-test using dependent t -test in each group. In addition, Tukey's post-test, was used to study whether the magnitude of brachial

artery reactivity differed among the trained groups and control group (young men and patients) over time (baseline and after 8 weeks). A value of $p < 0.05$ was considered as statistically significant, and the authors had full access to and take responsibility for the integrity of the data. All the authors have and agree to the data presented in the manuscript.

2.6. Results

None of the metabolic parameters considered was significantly different between G_1 and G_3 (patients group), but the young healthy men exhibited significant differences.

2.7. Brachial Arterial Vasoreactivity

At the initial evaluation, the baseline diameter of the brachial artery did not differ significantly among the three groups: 3.81 ± 0.19 SD in G_1 , 3.9 ± 0.41 SD in G_2 , and 4.17 ± 0.76 SD in G_3 . In the CAD patients and young healthy men, the basal brachial artery was not significantly different between untrained and trained groups (**Table 2**). After cuff release, we assessed FMD responses in all the groups, and the results exhibited that the FMD responses were significantly impaired in the CAD patients, when compared with healthy young men: 4.31 ± 1.15 SD for G_1 , 9.18 ± 1.45 SD for G_2 , and 4.64 ± 1.81 SD for G_3 (**Figure 2**). Aerobic training significantly increased the FMD response to forearm ischemia: (6.15 ± 0.77 SD; $p < 0.05$) for G_1 , (11.72 ± 1.72 SD, $p < 0.05$) for G_2 , and did not significantly change in the untrained CAD patients (control group).

3. DISCUSSION

In this study, the effects of moderate aerobic training on endothelial function through the FMD assessment are compared with the patients with artery diseases, who had open-heart surgery, and healthy young men with no exercise activity.

Our research has several findings as following:

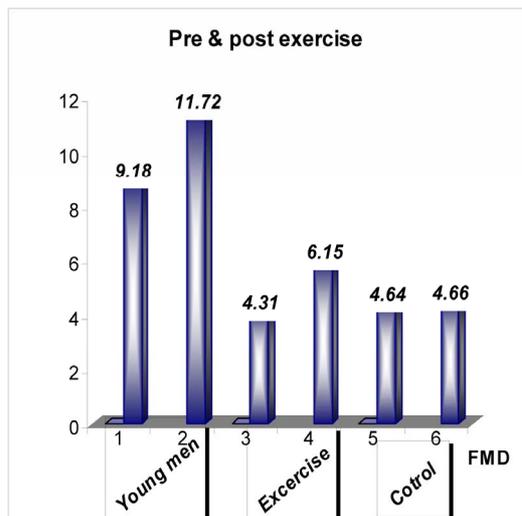
Firstly, in accordance to the previous reports, endothelial function can be reliably assessed by FMD in brachial artery. However, this test was first introduced by German scientist celermajor in which it is illustrated that FMD reduction and brachial artery have a direct relationship with cardiovascular diseases and risk factors or atherosclerosis [12]. In addition, one of the findings in the previous reports has been confirmed that the CAD patients, who had history of myocardial infarction or Coronary artery disease, had significantly lower FMD in comparison to healthy people [13]. In fact, our results are consistent with their findings.

Secondary, regular physical activities have a strong

Table 2. Brachial reactivity results at baseline and follow up.

Items	G ₁		G ₂		G ₃	
	Time 0	Follow up	Time 0	Follow up	Time 0	Follow up
Baseline diameter, mm	3.81 ± 0.196	3.84 ± 0.202	3.9 ± 0.41	3.95 ± 0.33	4.17 ± 0.76	4.18 ± 0.73
FMD%	4.31 ± 1.15	6.15 ± *0.77	9.18 ± 1.45	11.72 ± 1.72*	4.64 ± 1.81	4.66 ± 1.30

G₁: Aerobic training patients (CAD) G₂: Aerobic training young men, G₃: control (CAD); $p < 0.05$ *mean ± SD (Standard Deviation).

**Figure 2.** Indicated FMD% in the three groups.

positive link with vascular function by which flow blood and shears stress would increase the vascular artery. Moreover, it would also improve endothelium function as it can increase the amount of NO in vascular [14].

Previous studies show that eight weeks of resistance training in young men has caused a considerable rise in FMD [15]. De souza did three month endurance exercise on the youth who their Endothelium-dependent vasodilatation function was increased by about 30 percent in the year 2000 [16]. Current research on youths show that 60 to 80 percent increase in maximum heart rate after two month aerobic exercise would lead to 21 percent increase in FMD and finally improve endothelium function which it is in line with Thiken and Suza's studies. Of course the survey on stable coronary patients shows that after eight weeks aerobic and resistance exercises ,a rise and an improvement on FMD and vascular endothelial-dependent vasodilatation function respectively. Furthermore, Hambrekht executed four weeks aerobic exercises on CAD patients [7] and Vona and his colleagues performed different types of exercises such as aerobic and resistance ones on patients who recently had a myocardial infraction [17]. All findings lead to an improvement on the evaluation of coronary endothelial function via FMD assessment which they were in line with subject of current research on interventional treatment like

angiography and open heart surgery. Contrary, but Jodin and his colleagues after three month exercise on CAD patients could not achieve acceptable result and the FMD was not altered [18].

Third, endothelium dysfunction deficiency is one of major dangerous factors in cardiovascular diseases which through brachial artery FMD measurement or high quality sonography as alternative to Non-invasive detection of atherosclerosis patients are used. However, it is considered as easy method to evaluate coronary endothelial function in children and siblings in order to predict and prevent early vascular structural changes [19].

Fourthly, comparison of FMD percentage in both groups, young men and coronary patients, were predictable. However, FMD alterations in CAD patients (control group), three month after drug treatment and diet, remained down and after 8 weeks too lowly. Our results agree with medical therapy (statin) after 10 weeks faield to improve endothelium-dependent function in CAD patients [20] but it is unconvienced with Ling and *et al.*, short term simvastatin therapy increases endothelial function in patients with stable CAD [21]. Furthermore, the exercises considers as method of intervention in cardiac rehabilitation and vascular disease.

Finally, it was described that the major objectives of cardiac rehabilitation centre and sports medicine are as follows:

- decrease the number of deaths and its complications;
- life style improvement;
- prevent their return to health clinics and early prevention and prediction of groups at risk.

4. LIMITATIONS OF STUDY

During the study, there were some restrictions which we attempted to solve them.

The number of people who were interested in research involvement was reduced by prolongation of the project. Additionally, scholar's movement between these two clinics (Cardiac rehabilitation clinic and Sports medicine clinic) caused to increase expenses, project time and lack of coordination. Finally, some of patients were suffered from disability and orthopedic disability which they were removed from the list and replace them with the other candidates.

5. CONCLUSION

The present study demonstrates endothelial dysfunction persisting in CAD patients that were revascularized and aerobic exercise can improve vascular endothelial function in CAD patients and healthy young men.

6. ACKNOWLEDGEMENTS

The research is taken from the thesis of Dr Hamidian and Dr Hajizadeh and the financial and educational supports were received from the heart and vascular center of university of medical sciences of JoundiShapour University and physical education department of Azad University of Shushter Branch.

REFERENCES

- [1] Hambrecht, R., Walther, C., Mobius-Winkler, S., et al. (2004) Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: A randomized trial. *Circulation*, **109**, 1371. <http://dx.doi.org/10.1161/01.CIR.0000121360.31954.1F>
- [2] Leon, A.S., Franklin, B.A., Costa, F., et al. (2005) Cardiac rehabilitation and secondary prevention of coronary heart disease: An American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*, **111**, 369. <http://dx.doi.org/10.1161/01.CIR.0000151788.08740.5C>
- [3] Thompson, P.D. (2005) Exercise prescription and prescription for patients with coronary artery disease. *Circulation*, **112**, 2354. <http://dx.doi.org/10.1161/CIRCULATIONAHA.104.502591>
- [4] Hambrecht, R., Wolf, A., Gielen, S., et al. (2000) Effect of exercise on coronary endothelial function in patients with coronary artery disease. *The New England Journal of Medicine*, **342**, 454. <http://dx.doi.org/10.1056/NEJM200002173420702>
- [5] Moyna, N.M. and Thompson, P.D. (2004) The effect of physical activity on endothelial function in man. *Acta Physiologica Scandinavica*, **180**, 113. <http://dx.doi.org/10.1111/j.0001-6772.2003.01253.x>
- [6] Hambrecht, R., Adams, V., Erbs, S., et al. (2003) Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*, **107**, 3152. <http://dx.doi.org/10.1161/01.CIR.0000074229.93804.5C>
- [7] Taylor, R.S., Brown, A., Ebrahim, S., et al. (2004) Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. *American Journal of Medicine*, **116**, 682. <http://dx.doi.org/10.1016/j.amjmed.2004.01.009>
- [8] Taylor, R. and Green, D. (2001) The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. *Journal of the American College of Cardiology*, **38**, 860-866.
- [9] Clarkson, P., Montgomery, H.E., Mullen, M.J., Donald, A.E., Powe, A.J., Bull, T., Jubb, M., World, M. and Deanfield, J.E. (1999) Exercise training enhances endothelial function in young men. *Journal of the American College of Cardiology*, **33**, 1379-1385.
- [10] Vona, M., Rossi, A., Capodaquio, P., Rizzo, S., Servi, P., De Marchi, M. and Cobelli, F. (2004) Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent myocardial infarction. *American Heart Journal*, **147**, 1039-1046.
- [11] Kobayashi, N., Tsuruya, Y., Iwasawa, T., Ikeda, N., Hashimoto, S., Yasu, T., Ueba, H., Kubo, N., Fujii, M., Kawakami, M. and Saito M. (2003) Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities. *Circ J*, **67**, 505-510.
- [12] Celermajor, D.S., Sorensen, K.E., Gooch, V.M., Spieckhalter, D.I., Miller, O.I., Sulivan, I.D., Liovd, I.K. and Deanfield, I.E. (1992) Non-invasive detection of endothelial dysfunction in children and adult at risk of atherosclerosis. *Lancet*, **340**, 1111-1115.
- [13] Tandon, S., Bhargava, K., Gupta, H., Bansal, M. and Kasliwal, R.R. (2004) Non-invasive assessment of endothelial function by brachial artery flow mediated vasodilatation and its association with coronary artery disease: An Indian perspective. *Journal of the Indian Medical Association*, **102**, 243-246, 251-252.
- [14] Traub, O. and Berk, B.C. (1998) Laminar shear stress: Mechanisms by which endothelial cells transduce an atheroprotective force. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **18**, 677-685.
- [15] Tinken, T.M., Thijesen, D.H., Hopkins, N., Dawson, E.A., Cable, N.T. and Green, D.J. (2010) Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension*, **55**, 312-318.
- [16] De Souza, C.A., Shapiro, L.E., Clevenger, C.M., Sinenno, F.A., Monahan, K.D., Tanaka, H. and Seals, D.R. (2000) Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilatation in healthy men. *Circulation*, **102**, 1351.
- [17] Vona, M., Codeluppi, G.M., Iannino, T., Ferrari, E., Bogousslavsky, J. and Von Segesser, L.K. (2009) Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction. *Circulation*, **119**, 1601-1608.
- [18] Joodin, I., Bussieres, L.M., Tardif, J.C. and Juneau, M. (1999) Effects of a short-term primary prevention program on endothelium-dependent vasodilation in adults at risk for atherosclerosis. *Canadian Journal of Cardiology*, **15**, 83-88.
- [19] Clarkson, P., Celermajor, D.S., Powe, A.J., Donland, A.E., Henry, R.M.A. and Deanfield, J.E. (1997) Endothelium-dependent dilatation is impaired in young healthy subjects with a family history of premature coronary disease. *Circulation*, **96**, 3378-3383.

- [20] Allemn, Y., Vetter, C., Kartal, N., Eyer, S., Stengel, S.M., Sanger, H. and Hess, O.M. (2005) Effect of mild endurance exercise training and pravastatin on peripheral vasodilatation of forearm resistance vessels in patients with coronary artery disease. *European Journal of Preventive Cardiology*, **12**, 318-320.
- [21] Ling, M.C., Ruddy, T.D., de Kemp, R.A., Ukkonen, H., Duchesne, L., Williams, K.A., Mc Pherson, R. and Beanlands, R. (2005) Early effects of statin therapy on endothelial function and microvascular reactivity in patients with coronary artery disease. *American Heart Journal*, **149**, 1137. <http://dx.doi.org/10.1016/j.ahj.2005.02.033>