Effect of Regular Exercise on Coronary Endothelial Function in Patients With Recent Myocardial Infarction

Shinobu Hosokawa, MD; Yoshikazu Hiasa, MD;
Takefumi Takahashi, MD; Susumu Itoh, MD*

Exercise training improves the endothelial function of arteries in skeletal muscle, but few studies have examined its clinical effect on human coronary endothelial function. Non-infarct-related coronary arteries in 41 patients with a recent myocardial infarction who underwent successful percutaneous transluminal coronary angioplasty were studied. Patients were divided into 2 groups: regular exercisers (n=24, 17 males, mean age: 58 years), and non-exercisers (n=17, 12 males, mean age: 58 years). Acetylcholine (ACh) was infused into the non-infarct-related coronary artery and its diameter was measured by quantitative angiography at baseline and at 6 months after angioplasty. ACh, given in doses of 1, 3, 10, 30 µg/min, increased the coronary artery diameter in a dose-dependent manner in both groups. The mean percent change in the diameter at the site of stenosis change (%DS) was less in the regular exercisers than in the non-exercisers (11%±12 vs 41%±36, p<0.05). Multivariate analysis showed that regular exercise was the only significant determinant of improvement in endothelial function (p=0.01). These findings suggest that regular exercise improves endothelial function in the coronary arteries following myocardial infarction. (*Circ J* 2003; 67: 221–224)

Key Words: Coronary artery; Endothelial function; Exercise; Myocardial infarction

The vascular endothelium plays an important role in the regulation of arterial tone and local platelet aggregation, in part through the release of endothelium-derived relaxing factor,^{1,2} which is stimulated by a variety of mechanisms, including the rise in shear stress associated with acute and chronic increases in blood flow.³ Emerging evidence suggests that exercise improves endothelial function; in animal studies, treadmill exercise training leads to improvement in endothelium-dependent vasodilation and increases in gene expression for endothelial nitric oxide (NO) synthase,^{4–6} and studies involving patients with heart failure have demonstrated improved radial and brachial artery NO-dependent, flow-mediated dilation after exercise training.^{7,8} Several investigators have reported that exercise training improves endothelial function in skeletal muscle arteries,^{9–11} but few studies have examined its clinical effect on coronary artery endothelial function.^{12,13} The present study investigated whether regular exercise improves endothelial function in human coronary arteries.

Methods

Patients

We enrolled 41 presenting with chest pain and subsequently documented to have suffered their first acute myocardial infarction (AMI: ST segment elevation >1 mm, creatine kinase rise >2-fold from baseline concentration).

All patients had undergone a successful percutaneous coronary intervention for single-vessel disease. Patients with any of the following were excluded: age >80 years, documented history of variant angina, left main coronary stenosis, or left ventricular dysfunction (ejection fraction <0.40). Administration of all vasoactive drugs was suspended 24 h before the study with the consent of the attending physician. All patients gave informed consent for participation in the study.

Exercise Training

An initial exercise test was performed on a treadmill according to the Bruce protocol, and was discontinued if 1 or more of the following criteria were met: (1) 85% of maximum age-predicted heart rate, (2) ischemic ST-segment depression defined as >0.1 mV of horizontal or downsloping ST-segment depression on at least one lead, (3) ventricular arrhythmias, and (4) symptoms such as dyspnea or leg fatigue. The mean peak heart rate reached during initial exercise test was 134.4±3.8 beats/min. All patients were asked to perform daily walking at 70% of the peak heart rate in the initial exercise test once or twice daily for 45 min (in addition to a 5-min warm-up and 10 min for cooling down). According to patient compliance evaluated by monthly interviews, they were divided into 2 groups: the regular exercisers (EX; n=24) who undertook exercise training more than 3 times a week for 6 months, and the non-exercisers (NE; n=17) who did not.

Provocative Protocol

Acetylcholine (ACh) was injected into a non-infarct-related artery in 4 incremental boluses (1, 3, 10 and 30 µg) at 1-min intervals. At the completion of the protocol, a 250 µg bolus of nitroglycerin (NTG) was injected into the non-infarct-related artery. Coronary angiography was performed 60 s after each ACh bolus injection and after the

(Received September 9, 2002; revised manuscript received November 21, 2002; accepted December 12, 2002)

Division of Cardiology, Tokushima Red Cross Hospital, Komatsushima and *Second Department of Medicine, Tokushima University, School of Medicine, Tokushima, Japan

Mailing address: Shinobu Hosokawa, MD, Division of Cardiology Tokushima Red Cross Hospital, Shinbiraki, 28-1 Chuden-chou, Komatsushima-city, Tokushima 773-8502, Japan. E-mail: hoso@tokushima-med.jrc.or.jp

Table 1 Clinical Characteristics

	Regular exercisers (n=24)	Non-exercisers (n=14)	p value
<i>Population characteristics</i>			
Age (years)	58.0±12	57.8±12	NS
Male	17 (71)	12 (71)	NS
Diabetes mellitus	11 (46)	6 (35)	NS
*Smoker	16 (67)	13 (77)	NS
*Hypertension	9 (38)	4 (24)	NS
*Hyperlipidemia	16 (67)	8 (47)	NS
<i>Treatment</i>			
HMG-CoA inhibitor	10 (42)	10 (59)	NS
ACE inhibitors	21 (88)	15 (88)	NS
Calcium-channel blocker	3 (13)	5 (21)	NS
Aspirin	23 (96)	17 (100)	NS

Values in parentheses are %. HMG-CoA; 3-hydroxy-3-methylglutaryl coenzyme A; ACE, angiotensin-converting enzyme. Values are mean±SD, NS, not significant. *On admission or from history.

Table 2 Baseline Laboratory Findings

	Regular exercisers	Non-exercisers	p value
Total cholesterol	201±41	185±45	NS
HDL cholesterol	48±24	33±7	NS
Triglyceride	189±37	229±86	NS
LDL cholesterol	117±40	121±41	NS
FBS	132±49	137±45	NS

All results are mg/dl. HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; FBS, fasting blood sugar. Values are mean±SD.

Table 3 Angiographic Characteristics

	Regular exercisers (n=24)	Non-exercisers (n=17)	p value
<i>Infarct related artery</i>			
LAD, n (%)	11 (46)	10 (59)	NS
RCA, n (%)	10 (42)	6 (35)	NS
LCX, n (%)	3 (12)	1 (6)	NS
<i>Non-infarct related artery</i>			
LCA, n (%)	14 (58)	6 (35)	NS
RCA, n (%)	11 (42)	11 (65)	NS

LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; LCA, left coronary artery.

NTG bolus.

Angiography Analysis

Quantitative Coronary Angiography Analysis All angiogram analyses were performed in a blinded manner, regardless of the sequence of infusions, using the Cardiovascular Measurement System (CMS, MEDIS, The Netherlands). Coronary artery diameter was measured in the optimal view at baseline (approximately 1 month after AMI) and at follow-up coronary angiography (approximately 6 months from AMI). The diameter of the proximal segment was measured on end-diastolic frames, and the percent changes from baseline luminal diameter were calculated after each ACh injection. We assessed the following on each coronary angiogram: basal tone, expressed as the percent constriction at baseline with respect to the maximal dilatation achieved by NTG infusion [$100 \times (\text{basal diameter} - \text{NTG diameter} / \text{NTG diameter})$], and the vasodilator response to ACh. We also assessed the vasoconstrictor response, the percent diameter reduction below baseline in a nonspastic segment [$100 \times (\text{ACh} - \text{baseline} / \text{baseline})$].

Statistical Analysis

All values are expressed as mean±SD. Clinical characteristics were compared by Student's 2-tailed t-test for unpaired data or Fisher's exact test, as appropriate. The incidence of different angiographic findings were compared by Yates-corrected χ^2 test or Fisher's exact test, as appropriate. Absolute coronary luminal diameters were compared with Student's t-test for unpaired data. Quantitative vasomotor responses were compared with Student's t-test for unpaired data. Multiple regression analysis was used to determine the predictors of improvement in luminal diameter change in response to maximal ACh infusion. The variables included exercise, lipid lowering, sex, diabetes mellitus, hyperlipidemia, smoking, 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, calcium-channel blocker. Lipid lowering was defined as a decrease of less than 10% in the total cholesterol; diabetes mellitus was defined as a fasting glucose level >140mg/dl or/and receiving relevant therapy; hyperlipidemia was defined as a serum cholesterol >240mg/dl (6.2 mmol/L) or receiving antihyperlipidemic treatment; smoking was defined as current smoking on admission. A $p < 0.05$ was considered statistically significant.

Fig 1. Bar graph showing the change in the serum concentrations of lipid and fasting blood sugar during the 6 months. Serum total cholesterol concentration and the serum triglyceride concentration were significantly decreased in the regular exercisers. EX, regular exercisers; NE, non-exercisers; TCHO, total cholesterol; HDL, high density lipoprotein; TG, triglyceride; FBS, fasting blood sugar.

Fig 2. Individual changes in the luminal diameter of coronary vessels in response to acetylcholine at a dose of 30 µg/min at the initial study and after 6 months. The mean percent change differed significantly between the groups at 6 months ($p<0.05$ for the comparison with the non-exercise group). Each line represents the change in each subject, and the circles and bars represent the means $\pm$ SD. EX, regular exercisers; NE, non-exercisers; M, month; ACh, acetylcholine.

cant. All patients gave written informed consent before the procedure.

Results

Baseline Characteristics

In the initial study, the data from the EX group were similar to those from the NE (Table 1). Medical treatments in the 2 groups were similar at baseline: angiotensin-converting enzyme inhibitors (88% of EX and NE), calcium-channel blocker (13% and 21%, respectively) and aspirin (96% and 100%, respectively). Treatments did not change during the 6 months of the study. Serum lipid and fasting blood sugar glucose concentrations also were similar (Table 2).

Angiographic Findings

The infarct-related artery was the left anterior descending coronary artery in 11 EX and 10 NE, the right coronary artery in 10 EX and 6 NE, and the circumflex artery in 3 EX and 1 NE (Table 3).

Fig 3. Bar graph showing response to nitroglycerin at the initial study and after 6 months. There was no significant difference in dilation between the 2 groups. EX, regular exercisers; NE, non-exercisers; M, month.

Table 4 Multivariate Analysis of Change in the Diameter of the Stenosis in Response to Maximal Acetylcholine Infusion

	Coefficient	p value
Exercise	9.289	0.01
Lipid lowering	3.732	0.08
Sex (male)	0.613	0.45
Diabetes mellitus	0.507	0.49
Hyperlipidemia	0.710	0.42
Smoking	0.493	0.49
HMG-CoA inhibitor	0.043	0.83
Calcium-channel blocker	3.43	0.09

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Clinical Follow-up

No patient in the EX group had any major complication during follow-up. The body weight of patients in both groups remained unchanged (EX -0.5 kg vs NE $+0.8$ kg, NS). However, the total serum cholesterol concentration and the serum triglyceride concentration were decreased in the regular exercisers (EX -29.0 mg/dl vs NE -6.5 mg/dl, $p<0.05$ and EX -89.3 mg/dl vs NE $+9.2$ mg/dl, $p<0.05$, respectively) (Fig 1).

Response to ACh

In the initial study, patients in both groups had similar responses to ACh (Fig 2). After 6 months, the mean vasoconstrictive response to the highest dose of ACh among the regular exercisers, was attenuated in comparison with the responses in the initial study. Coronary artery constriction was reduced by 37% and the mean % diameter stenosis change was less in the EX than in the NE ($11\% \pm 12$ vs $41\% \pm 36$, $p<0.05$). The vasodilator response of the epicardial arteries in response to infusion of NTG remained essentially unchanged after 6 months of exercise training (Fig 3). Multivariate analysis showed that exercise training was the only significant determinant of improvement in endothelial function ($p=0.01$) (Table 4).

Discussion

We found that 6 months of exercise training improved coronary endothelial function following AMI. Coronary vasoconstriction in response to ACh infusion was decreased by exercise training, indicating that exercise has beneficial effects on the endothelium of epicardial coronary arteries. However, in this study, the degree of restoration of the

endothelial response to ACh did not reach the normal level, suggesting that normalization of endothelial function may require a more extended period of exercise training.

Several mechanisms have been proposed to explain the improvement in coronary vasoconstriction in patients with coronary artery disease who undertake exercise training. These include regression of coronary artery disease, recruitment of coronary collateral vessels, and increased blood flow. Most studies have failed to document a net regression in coronary lesions, even with the combination of lipid-lowering strategies and exercise training.¹⁴ As regards the second mechanism, evidence from studies in animals suggests that endothelium-derived relaxing factor/nitric oxide-dependent dilation is enhanced in the coronary arteries by exercise training. Berdeaux et al reported that the dilatation of epicardial coronary arteries during exercise is eliminated by α -adrenergic receptor blocker, and concluded that α -adrenergic receptors are essential for the dilation of the epicardial coronary artery during exercise.¹⁵ Koller et al reported that the sensitivity of skeletal muscle arterioles to wall shear stress in rats is upregulated after short-term daily exercise, resulting in an augmented dilator response that is due to increased release of both endothelium-derived nitric oxide and prostaglandins.⁶ In addition, some studies of human skeletal muscle in patients with chronic heart failure have found that physical training restores flow-dependent dilation, possibly by enhancing the endothelial release of nitric oxide.^{7–11}

We found that exercise has no effect on NTG-induced, endothelium-independent coronary vasodilation. Haskell et al demonstrated that the epicardial coronary arteries of highly trained, middle-aged endurance runners had a greater capacity for dilatation in response to NTG than did those of healthy, but inactive, men.¹⁶ Hambrecht et al reported that short-term exercise training improves endothelium-dependent vasodilatation in both epicardial coronary vessels and resistance vessels in patients with coronary artery disease.¹² Animals studies have conclusively demonstrated that exercise training increases the total cross-sectional area of the vascular bed¹⁷ and enhances the sensitivity of coronary resistance vessels to adenosine¹⁸ and other vasodilator metabolites.¹⁹ However, none of these proposed mechanisms has been confirmed clinically. Our results suggest that the most potent effect of regular exercise may be on impaired endothelium-dependent coronary constriction. A marked decrease in the serum cholesterol concentration is associated with a correction of endothelial dysfunction, improvement in myocardial perfusion, and a decrease in the incidence of myocardial ischemia. In our study, multivariate analysis showed that regular exercise was the only significant determinant of improved of endothelial function. Our study is the first to show by multivariate analysis that regular exercise is a significant determinant of improved coronary endothelial function.

Study Limitations

However, because the target heart rate of exercise training was determined by different endpoints in the initial exercise test, the prescribed exercise intensity varied among patients. In addition, exercise training was not performed under the supervision of a physician. Therefore, we could not evaluate the actual exercise intensity during exercise training. Furthermore, we did not evaluate the

effects of exercise training by a second exercise test after 6 months of exercise training. Future studies will be needed to decide the optimal exercise protocol for improving the endothelial function of the epicardial coronary arteries.

Conclusion

Regular exercise in patients after AMI improves the endothelial function of the epicardial coronary arteries and may be the mechanism responsible for the perception that regular exercise induces cardiovascular 'well being'.

References

1. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373–376.
2. Egashira K. Clinical importance of endothelial function in arteriosclerosis and ischemic heart disease. *Circ J* 2002; **66**: 529–533.
3. Inoue N, Ramasamy S, Fukai T, Nerem RM, Harrison DG. Shear stress modulates expression of Cu/Zn superoxide dismutase in human aortic endothelial cells. *Circ Res* 1996; **79**: 32–37.
4. Wang J, Wolin MS, Hintze TH. Chronic exercise enhances endothelium-mediated dilation of epicardial coronary artery in conscious dogs. *Circ Res* 1993; **73**: 829–838.
5. Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. *Circ Res* 1994; **74**: 349–353.
6. Koller A, Huang A, Sun D, Kaley G. Exercise training augments flow-dependent dilation in rat skeletal muscle arterioles: Role of endothelial nitric oxide and prostaglandins. *Circ Res* 1995; **76**: 544–550.
7. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. *Circulation* 1996; **93**: 210–214.
8. Katz SD, Yuen J, Bijou R, LeJemtel TH. Training improves endothelium-dependent vasodilation in resistance vessels of patients with heart failure. *J Appl Physiol* 1997; **82**: 1488–1492.
9. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998; **98**: 2709–2715.
10. Hambrecht R, Adams V, Gielen S, Linke A, Mobius-Winkler S, Yu J, et al. Exercise intolerance in patients with chronic heart failure and increased expression of inducible nitric oxide synthase in the skeletal muscle. *J Am Coll Cardiol* 1999; **33**: 174–179.
11. Takahashi N, Ishibashi Y, Shimada T, Sakane T, Ohata S, Sugamori T, et al. Impaired exercise-induced vasodilatation in chronic atrial fibrillation: Role of endothelium-derived nitric oxide. *Circ J* 2002; **66**: 583–588.
12. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000; **342**: 454–460.
13. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. *Circulation* 1999; **99**: 963–972.
14. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation* 1994; **89**: 975–990.
15. Berdeaux A, De la Rochelle C, Richard V, Giudicelli JF. Opposed responses of large and small coronary arteries to propranolol during exercise in the dog. *Am J Physiol* 1991; **261**: 265–270.
16. Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation* 1993; **87**: 1076–1082.
17. White FC, Bloor CM, McKirnan MD, Carroll SM. Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart. *J Appl Physiol* 1998; **85**: 1160–1168.
18. Laughlin MH, McAllister RM. Exercise training-induced coronary vascular adaptation. *J Appl Physiol* 1992; **73**: 2209–2225.
19. Muller JM, Myers PR, Laughlin MH. Vasodilator responses of coronary resistance arteries of exercise-trained pigs. *Circulation* 1994; **89**: 2308–2314.