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Safety and Effectiveness of Exercise Training in Patients With Silent Myocardial Ischemia

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Abstract

The effectiveness of exercise training in patients with silent myocardial ischemia was examined. Forty patients with coronary heart disease (mean age 55±8 years) were recruited for a 12-week exercise training program. All patients underwent treadmill exercise stress testing, exercise thallium-201 single photon emission computed tomography and left heart catheterization. They were divided into three groups based on the symptoms and the results of exercise thallium scintigraphy, *i.e.*, painful myocardial ischemia (PMI group), silent myocardial ischemia (SMI group), and non-myocardial ischemia (NMI group).

Normalized treadmill time was longer in the SMI group (108±24%) than in the PMI group (86±14%, $p<0.05$). All 40 patients, 14 from the PMI group, 16 from the SMI group and 10 from the NMI group, completed the whole exercise training program. A significant prolongation of treadmill time was attained in all three groups after exercise training [PMI group : from 494±105 to 632±78 sec ($p<0.05$), SMI group : from 609±147 to 746±137 sec ($p<0.05$), NMI group : from 572±112 to 739±13 sec ($p<0.05$)]. The improvement of myocardial ischemia following exercise training was similar in the SMI and PMI groups. No adverse effects were detected throughout the program. The exercise training program adopted in this study proved safe and effective in patients with silent myocardial ischemia.

Key Words
Ischemia (silent myocardial), Myocardial infarction (acute), Exercise, Physical fitness

INTRODUCTION

The prognosis of silent myocardial ischemia resembles that of symptomatic myocardial ischemia in coronary heart disease[1,2]. Outcomes of pharmacological and other therapies for silent ischemia have already been studied[3]. Exercise training in coronary heart disease has been shown to be clinically useful[4,5], but its effect on silent ischemia has yet to be clarified. An improved exercise tolerance has already been observed in patients with silent ischemia[6]. This fact suggests that surplus daily activity in patients with silent ischemia may induce unfavorable outcomes culminating in life threatening events. In addition, it is unclear whether asymptomatic performance of exercise training causes any adverse effects including malignant arrhythmia, severe myocardial ischemia, or heart

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Selected abbreviations and acronyms

HDL-C=high-density lipoprotein cholesterol
NMI=non-myocardial ischemia
PMI=painful myocardial ischemia
SMI=silent myocardial ischemia
SPECT=single photon emission computed tomography

failure during exercise training. Since studies specifying the efficacy and safety of exercise training in patients with silent ischemia are thought to be mandatory, the present study is intended to elucidate the effectiveness of exercise training in patients with silent ischemia.

MATERIALS AND METHODS

Forty patients (55±8 years, 36 men and 4 women) with any coronary heart disease (28 acute myocardial infarctions, 4 old myocardial infarctions and 8 angina pectoris) were recruited for the present study. Informed consent was obtained from all subjects after explaining the purpose of the study and the procedures of the training programs. They were referred to the Life Planning Center for a 12-week exercise training program specifically designed to improve their physical fitness. Patients with acute myocardial infarction entered the program at least 2 months after onset of acute myocardial infarction. All patients were receiving long-acting nitrates, calcium antagonists and antiplatelet medication, but none were receiving β-blockers.

All subjects underwent demographic and physical examinations, routine laboratory and hematology tests, blood chemistry, urinalysis, left heart catheterization with coronary angiography and ventriculography, symptom-limited maximal treadmill stress testing after Bruce's conventional protocol[7], and exercise thallium scintigraphy performed with symptom-limited maximal graded bicycle ergometric testing. In both symptom-limited exercise tests, the reasons for stopping the test were chest pain, leg fatigue, or shortness of breath. The normalized treadmill time was obtained for each individual by age-defined standards. Briefly, age-defined standards of treadmill time were obtained from untrained healthy volunteers, of which details were already described elsewhere[8]. Normalized treadmill time was derived as follows; (obtained treadmill time of patient/treadmill time of age-defined standard)×100. A diseased artery in coronary angiograms was defined as more than 75% stenosis of a coronary artery. Exclusion criteria were physical handicaps precluding regular exercise, left main coronary artery disease, unstable angina, severe decreased left ventricular function (ejection fraction <35%), congestive heart failure, valvular heart disease, as well as other disabling illnesses. In addition, patients who met the following criteria derived from the results of treadmill testing were excluded; duration of exercise less than 6 min, ST depression persisting for more than 1 min after stopping treadmill testing, or maximal heart rate of treadmill testing being less than 90% of age-predicted normal value.

Exercise thallium scintigraphy was conducted using a Hitachi gamma-view R-d. First, 74 MBq of 201-thallium chloride was injected as an i.v. bolus immediately after maximal exercise testing, and a single photon emission computed tomogram (SPECT) was obtained as an initial image. Three hours later, the second SPECT was obtained at rest as a late image after another i.v. bolus injection of 37 MBq of 201-thallium chloride. Thereafter, data were analyzed with the HAAP system (Hitachi) and both images were evaluated visually for myocardial ischemia by two investigators who had no prior knowledge of the patients or their medical background. As previously reported[9], at least three slices of a short-axis tomographic image were selected for comparison of changes in myocardial perfusion. Patients were subdivided into the following three groups based on symptoms defined by ergometer testing and/or treadmill testing and on myocardial perfusion data obtained by stress scintigraphy: the painful myocardial ischemia (PMI) group consisting of 14 patients with stress-induced ischemia and chest pain; the silent myocardial ischemia (SMI) group consisting of 16 pain free patients with stress-induced ischemia; and the non-myocardial ischemia (NMI) group consisting of 10 patients without stress-induced ischemia.

All blood samples were obtained the morning after overnight fasting, and the following parameters were selected for comparison: serum total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides.

The exercise training program used was a combination of supervised and non-supervised training developed at the Life Planning Center, as previously described[10]. To summarize briefly, the exercise in-

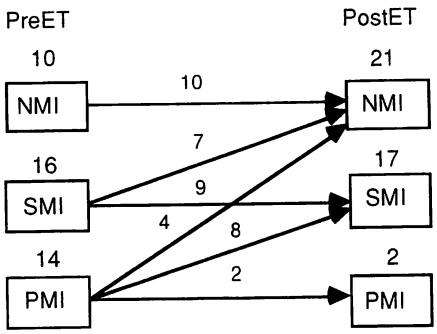

Fig. 1 Changes in myocardial ischemia in response to exercise training

Pre ET=before exercise training; Post ET=after exercise training.

tensity was determined as 70% to 85% of the maximal heart rate attained by symptom-limited maximal treadmill stress testing. The program consisted of a 1-hour training session at the Life Planning Center including circuit training with a rowing machine, treadmill, bicycle ergometer and two-steps once a week, and home sessions of walking and jogging for 20 to 30 min twice a week for 12 weeks at the same intensity level. During supervised sessions, heart rate was monitored by telemetric electrocardiography. During non-supervised sessions, patients checked their heart rate themselves and if the heart rate 10 min after exercise exceeded 100 bpm, they were asked to notify their attending physician for management. Patients who were recruited for the exercise training program received all the above-mentioned clinical evaluations twice, before and after the training program. Left heart catheterization was performed only before the training program.

Data were evaluated using the statistical package soft SPSS and were expressed as mean±standard deviation. Paired variables were analyzed by Student's *t*-test. Comparisons of parametric indices between the three groups were carried out using ANOVA with Bonferroni's correction. The χ^2 test was used to compare the nonparametric indices among groups. A p value less than 0.05 was considered significant.

RESULTS

All patients recruited for the exercise training completed the program without adverse events. All NMI group patients remained non-ischemic and 11 of 30 patients with myocardial ischemia became non-ischemic after the program. Disappearance of

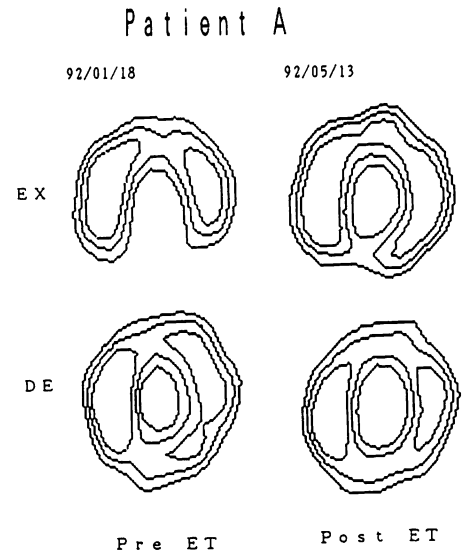

Fig. 2 Short-axis slices of thallium-201 SPECT scans obtained before and after physical training, demonstrating remarkable improvement in an ischemic area seen after the training program

EX=radioactive isotope image just after exercise; DE=radioactive isotope delayed image after exercise. Other abbreviations as in Fig. 1.

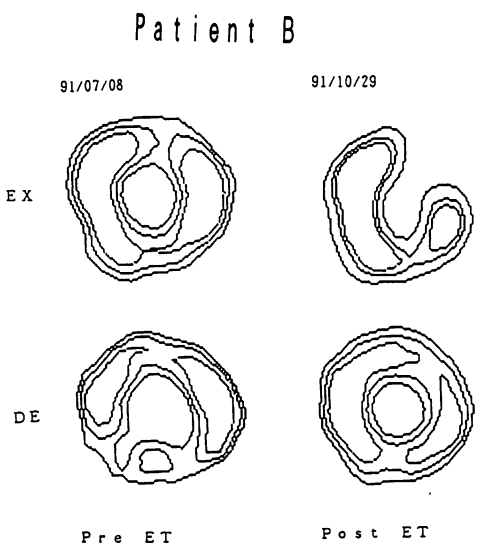

Fig. 3 Short-axis slices of thallium-201 SPECT scans obtained before and after physical training of an asymptomatic patient

Although myocardial ischemia was manifested due to the improvement in physical fitness after physical training, the patient was still asymptomatic.
Abbreviations as in Figs. 1, 2.

myocardial ischemia after the program was observed in 4 of 14 patients in the PMI group and 7 of 16 in the SMI group. Two of the 14 patients in the PMI group remained symptomatically ischemic and 8 remained asymptomatically ischemic. Nine of 16 patients in the SMI group remained asympto-

Table 1 Characteristics and changes in stress testing and biochemical data after exercise training

		NMI ($n=10$)	SMI ($n=16$)	PMI ($n=14$)
Age (yr)		51±8	53±16	55±8
Body mass index		23±4	23±4	24±4
Acute myocardial infarction		7	15	6
Old myocardial infarction		1	1	2
Angina pectoris		2	0	6
Coronary disease				
Single		9	12	6
Double		1	3	6
Triple		0	1	2
Ejection fraction (%)		56±10	52±11	50±10
Body weight (kg)	B	60±23	59±18	63±7
	A	59±22	57±17	63±7
HR_{max} (bpm)	B	157±18	158±14	138±16*
	A	162±15	158±13	145±19*
Ps_{max} (mmHg)	B	159±11	167±25	157±16
	A	161±17	166±22	154±21
PRP (10^2 bpm · mmHg)	B	250±34	268±23	217±35
	A	262±43	263±40	225±44
TMT (sec)	B	572±112	609±147	494±105
	A	739±123†	746±137†	632±78†
TMTn (%)	B	97±22	108±24	86±14*
	A	125±22†	131±20†	110±20†*
PRPerg (10^2 bpm · mmHg)	B	248±40	252±36	221±44
	A	255±38	256±30	219±40
Total cholesterol (mg/d*l*)	B	200±41	193±36	195±45
	A	196±52	200±34	195±38
HDL-C (mg/d*l*)	B	38±9	34±10	36±10
	A	43±9	43±13†	37±10
Atherogenic index	B	5.5±1.6	6.2±2.3	5.4±1.7
	A	4.6±1.4†	5.1±1.6†	5.0±1.4
Triglyceride (mg/d*l*)	B	132±82	158±115	146±110
	A	137±94	160±90	159±115

*=$p<0.05$ SMI and NMI vs PMI, †=$p<0.05$ before vs after exercise training.
HR_{max}=maximal heart rate at treadmill testing; Ps_{max}=maximal blood pressures at treadmill testing; PRP=maximal pressure rate products at treadmill testing; TMT=treadmill time; TMTn=normalized treadmill time; PRPerg=maximal pressure rate products at bicycle ergometer testing; B=before exercise training; A=after exercise training.

matically ischemic and none became symptomatic (**Fig. 1**). **Figs. 2** and **3** demonstrate the effects of exercise training on myocardial ischemia evaluated by radioactive isotope scintigraphy. Patient A in the SMI group demonstrated improvement of myocardial ischemia through exercise training (**Fig. 2**). This exercise training improved bicycle ergometric exercise time (from 920 to 1,050 sec) and elevated pressure rate products at peak exercise (from 222 to 242 10^2 bpm · mmHg). The reason for stopping exercise was leg fatigue both before and after the exercise training. Patient B in the SMI group manifested asymptomatic myocardial ischemia after exercise training due to improvement in physical fitness (**Fig. 3**). This exercise training improved bicycle ergometric exercise time (from 652 to 784 sec) and elevated pressure rate products at peak exercise (from 240 to 243 10^2 bpm · mmHg) : The reason for stopping exercise was shortness of breath both before and after exercise training.

Table 1 illustrates the clinical characteristics and changes in stress testing and biochemical data after exercise training in each group. Normalized treadmill time was longer and maximal heart rate was greater in both the SMI and NMI groups than in the PMI group. All other parameters had no significant

Table 2 Changes in stress testing after exercise training in patients who became non-ischemic

Patients No.	Age (yr)		PRP (10^2 bpm · mmHg)	TMT (sec)	End	PRPerg (10^2 bpm · mmHg)	TIMEerg (sec)	Enderg
1	59	B	187	600	CP	170	734	CP
		A	193	715	SOB	178	801	SOB
2	56	B	172	600	LF	272	682	LF
		A	207	720	LF	270	764	SOB
3	56	B	198	600	LF	222	920	SOB
		A	242	770	SOB	242	1050	SOB
4	61	B	276	625	SOB	284	802	SOB
		A	314	665	SOB	296	840	SOB
5	56	B	315	621	CP	276	724	CP
		A	260	780	SOB	288	802	LF
6	68	B	164	484	CP	176	500	LF
		A	157	600	LF	152	510	SOB
7	42	B	226	844	SOB	315	952	SOB
		A	245	1097	SOB	320	1100	LF
8	45	B	269	543	SOB	192	300	SOB
		A	280	643	SOB	186	332	SOB
9	59	B	287	620	CP	286	740	CP
		A	275	639	SOB	276	792	SOB
10	51	B	225	407	SOB	268	546	LF
		A	244	544	SOB	287	526	LF
11	66	B	291	617	SOB	278	722	SOB
		A	264	735	SOB	269	806	SOB

End=reasons for stopping treadmill testing; TIMEerg=exercise time at bicycle ergometric testing; Enderg=reasons for stopping bicycle ergometric testing; CP=chest pain; SOB=shortness of breath; LF=leg fatigue. Other abbreviations as in Table 1.

differences between the three groups. The exercise training improved treadmill time and normalized treadmill time in all three groups and improved atherosclerotic index in the SMI and NMI groups. The reasons for stopping exercise in treadmill stress testing were as follows: before exercise training; chest pain ($n=12$), leg fatigue ($n=6$), shortness of breath ($n=22$) : after exercise training; chest pain ($n=2$), leg fatigue ($n=8$), shortness of breath ($n=30$). The reasons for stopping exercise in bicycle ergometric testing were as follows : before exercise training; chest pain ($n=11$), leg fatigue ($n=10$), shortness of breath ($n=19$) : after exercise training; chest pain ($n=1$), leg fatigue ($n=10$), shortness of breath ($n=29$).

Table 2 illustrates the changes in stress testing after exercise training in patients who became non-ischemic after the exercise training.

DISCUSSION

The study of de Belder *et al.* found a poor prognosis among patients with silent myocardial ischemia after myocardial infarction[11]. Recently, the outcome of revascularization in patients with silent myocardial ischemia has been reported to be better than that of medical therapy[12]. However, silent myocardial ischemia is a common clinical syndrome, and many patients may not be suitable for interventional therapy. For these patients, exercise training is an additional therapy for improving their pathological situation. However, the validity of exercise training in patients with silent myocardial ischemia has not been carefully studied. The present study confirms an apparent high level of physical fitness in patients with silent myocardial ischemia, so the risk for potential hazards may be equally expected in ordinary daily physical activities such as strenuous exercise. An increased risk of cardiac arrest in patients with ischemic heart disease was reported to be higher during cardiac rehabilitation programs than during routine daily physical activities[13]; therefore, the prognosis of patients with silent myocardial ischemia might be worsened by exercise training programs. Hoberg *et al.* reported that silent myocardial ischemia is the "missing link" between increased risk of cardiac arrest and the

absence of premonitory symptoms during supervised exercise in patients participating in cardiac rehabilitation programs[14]. It is thus essential to appropriately evaluate the pathophysiology of patients before developing any individualized exercise training program to eliminate patients who have severe multivessel disease and/or severely curtailed left ventricular function, the usual contraindication for exercise training. The present study confirmed the effectiveness and the safety of exercise training in patients with silent myocardial ischemia.

The improvement of exercise tolerance in patients with myocardial ischemia after the program may be explained by the following three mechanisms; disappearance of myocardial ischemia, improved aerobic metabolism in peripheral muscles and an increased threshold for pain sensitivity. Recently, thallium-201 SPECT has demonstrated the improvement of myocardial ischemia attained by exercise training[15]. In the present study, the fact that some patients with myocardial ischemia accompanied by pain had disappearance of myocardial ischemia after the program explains some part of the mechanism involved. Another possibility is the peripheral effects of exercise training suggested by the result that treadmill time was prolonged without changes in pressure rate products at peak exercise. The last mechanism may be evidenced by changes in pain threshold induced by exercise training that has previously been reported elsewhere[16,17]. It has been demonstrated that such factors as the extent of myocardial ischemia, hormonal factors, vasoactive substances, and neural influences contribute to pain threshold and also to the mechanisms of silent myocardial ischemia[18]. Although the present study could not pinpoint the precise mechanisms behind the prolongation of exercise tolerance induced by exercise training, it demonstrated that some patients with chest pain only had silent ischemia after the exercise program.

Improvements in cardiac functions, peripheral circulation, and cardiac risk factors such as lipid and glucose metabolism have also been demonstrated with exercise training[4,5,19]. Our data also confirmed favorable effects on lipid metabolism, especially in HDL-C levels that were significantly increased after the training program in the SMI group. Further study is needed to determine the precise mechanisms of these beneficial effects.

The limitations of the present study can be summarized as follows: 1) this retrospective study was not designed to elucidate the safety of exercise training in patients with silent myocardial ischemia as a prospective study, 2) patient populations were relatively small, 3) the diagnostic criteria of silent myocardial ischemia may be tentative, 4) severity of the background coronary disease was mild and moderate, 5) patient selection for the exercise program might have been biased with regard to physical and psychosocial aspects of the subjects, and 6) the observation period for the exercise training was relatively short. Those problems may hinder extrapolation of the results of the present study toward more general concepts. Further randomized and controlled studies on a larger scale and for a longer period are needed.

In conclusion, our results of the exercise training program for patients with silent myocardial ischemia clearly demonstrate beneficial effects with specific reference to physical fitness, myocardial ischemia and lipid metabolism without any adverse effects. Since our study was conducted for only 12 weeks, a larger follow-up study is required to evaluate the long-term effects of exercise training on the prognosis of silent myocardial ischemia.

要　約

無症候性心筋虚血症例における運動療法の安全性と効果の検討

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吉田　秀夫　　道場　信孝　　日野原重明

無症候性心筋虚血症例に対する運動療法の安全性とその効果について検討した．虚血性心疾患患者40例(平均年齢55±8歳)に対し，12週間の運動療法開始前後で運動負荷Tl心筋シンチグラフィー，左心カテーテルおよび症候限界性運動負荷試験を施行した．心筋シンチグラフィーでの心筋虚血の有無および症状の有無より，有症候性心筋虚血群(PMI群)，無症候性心筋虚血群(SMI群)，非虚血群(NMI群)の3群に分類し，各群の指標を対比検討した．

各群は，PMI 群 14 例，SMI 群 16 例，NMI 群 10 例であり，運動療法開始前の補正トレッドミル時間は，SMI 群 (108±24%) で PMI 群 (86±14%) より有意に良好な値を示した ($p<0.05$). いずれの群においても運動療法は安全に施行された．運動療法によりトレッドミル時間は，PMI 群 (494±105→632±78 sec)，SMI 群 (609±147→746±137 sec)，NMI 群 (572±112→739±13 sec) といずれの群でも有意に延長した (おのおの $p<0.05$).

無症候性心筋虚血症例でも運動療法は安全に施行可能であり，有効であることが確認された．

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