DETERMINANTS OF BENEFICIAL EFFECT OF HEPARIN EXERCISE TREATMENT ON TREADMILL CAPACITY AND LONG-TERM EFFICACY OF THE THERAPY IN PATIENTS WITH CHRONIC EFFORT ANGINA

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The purpose of the present study was to evaluate the factors which influence the effect of heparin exercise treatment on treadmill capacity, and to examine the long-term efficacy of the treatment in 16 patients with chronic effort angina. Treadmill exercise was performed 20 times for 2 to 3 weeks according to standard Bruce protocol. A single intravenous dose of heparin (5,000 IU) was given 10 min before each exercise period. Exercise with heparin pretreatment increased the total exercise duration from 6.6 ± 1.6 (SD) to 9.4 ± 1.9 min ($p < 0.05$) and the maximal rate-pressure product from $19,200 \pm 4,700$ to $24,700 \pm 5,900$ mmHg·beats/min ($p < 0.05$). The rate-pressure product at the onset of angina was also increased by 32% ($p < 0.05$). The ST segment depression at the same exercise time as in control exercise was ameliorated from 0.16 ± 0.05 to 0.12 ± 0.06 mV ($p < 0.05$). Multivariate analysis of the determinants of the effect of the treatment on treadmill capacity indicated that the treatment is more effective in patients without previous myocardial infarction. All of the above-mentioned variables of treadmill capacity did not change significantly during a follow-up period of 13 ± 7 months (range; 4–24 months). These findings lend further support to heparin exercise treatment as a possible therapeutic approach in patients with chronic stable effort angina, and particularly in those without previous infarction. (*Jpn Circ J* 1993; 57: 769–774)

SEVERAL controlled studies have shown that beta blockers, nitrates, calcium antagonists and combination therapy of these agents are effective in the treatment of stable angina pectoris. Some patients who fail to respond to adequate triple therapy are indicated for either balloon angioplasty or

coronary artery bypass surgery. However, in patients with poor distal runoff and extensive diffuse coronary artery disease, an alternative therapy must be considered.

We and others have recently found in animal experiments that heparin conclusively accelerates the development of collateral circulation^{1,2}. We have also reported that exercise with heparin pretreatment improves treadmill capacity and collateral circulation in patients with chronic effort angina^{3,4}.

Key words:

Angina pectoris
Coronary collateral circulation
Rate-pressure product
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TABLE I BASE-LINE CHARACTERISTICS OF 16 PATIENTS

Characteristic	N=16
Mean age (yr)	57±8
<60	8
60–69	7
70–75	1
Sex (M/F)	13/3
Previous myocardial infarction	7
Anterior-lateral Q-wave	4
Inferior-posterior Q-wave	3
Ischemia-related coronary artery	
Right coronary artery	5
Left anterior descending coronary artery	8
Left circumflex coronary artery	3
Extent of coronary artery disease	
One-vessel disease	5
Two-vessel disease	11
Three-vessel disease	0
Stenoses in donor arteries	
Jeopardized collaterals	6
Nonjeopardized collaterals	10
Base-line collateral index	2.1±0.9
0	1
1	3
2	5
3	7
Medication	
Beta-blockers	12
Nitrates	10
Calcium antagonists	9

Figs are numbers of patients; plus-minus values are means±SD.

In the present study, we wished to determine the factors which influence the efficacy of heparin exercise treatment on treadmill capacity and to evaluate whether the newly developed collateral circulation could serve as effective blood conveying circuits over an extended period of time.

METHODS

Study patients

The study population consisted of 16 consecutive patients (13 men and 3 women) who underwent 20 exercise sessions with heparin pretreatment. The patients exercised twice daily until the extent of anginal pain was 60% to 80% of the maximal pain previously experienced. The patients were followed-up for a mean period of 13±7 months. Overall, the follow-up was complete except for 1 pa-

tient who underwent coronary artery bypass surgery 3 weeks after heparin exercise treatment. Their profiles at entrance into the study are given in Table I.

Exercise test

The patients were exercised to a symptom-limited maximal end point on a graded exercise test using the standard Bruce protocol⁵ before and after heparin exercise treatment, and during the follow-up period. All medications were withdrawn 1 day before the exercise test. Blood pressure was measured every min by sphygmomanometer. The electrocardiogram was monitored throughout the exercise and recovery periods. The presence of at least 1 mm horizontal or downsloping ST segment depression measured at 0.08 S after the J point in a given lead was considered indicative of myocardial ischemia.

Coronary arteriography

Selective coronary arteriography was performed by the Sones or Judkins technique before and after treatment. A 0.3 mg dose of sublingual nitroglycerin was administered before coronary angiography. The three major coronary arteries were visualized in multiple projections with a 6 inch image intensifier and recorded on 35 mm film at 60 frames/sec. A consensus of the opinions of 2 observers, who were given no information regarding the clinical data, was considered an assessment of the extent of both coronary vessel disease and collateralization. The degree of opacification of collaterals and epicardial arteries was classified into four grades (collateral index): 0, none; 1, filling of side branches of the artery to be perfused via collateral vessels without visualization of the epicardial segment; 2, partial filling of the epicardial segment via collateral vessels; and 3, complete filling of the epicardial segment via collateral vessels⁶.

Statistical methods

The analysis of variance for randomized block design was used for parametric comparisons. When analysis of variance showed a statistically significant difference, the Bonferroni multiple comparison method was applied. For nonparametric comparisons, Wilcoxon's signed-rank test was used. Pro-

Fig. 1. Percent changes in total exercise time, maximal double product (DP) and DP at the onset of angina, and changes in ST segment depression at the same exercise time as in control exercise before, immediately after, and long after heparin exercise treatment. Error bars indicate SEM.

portional data were analyzed by the chi square test, with Yates' correction if 1 of the frequencies in the 2 by 2 contingency table was less than 5. The significance of variables in the efficacy of heparin exercise treatment was assessed by a multivariate analysis. Statistical significance was assessed at $p < 0.05$. Values are presented as the mean $\pm$ SD.

RESULTS

Patient Profile

The base-line characteristics of the 16 patients are shown in Table I. Seven patients had prior Q-wave infarctions, while 9 patients did not. The prevalence of totally occluded ischemia-related coronary arteries was similar among the 3 major coronary

TABLE II TREADMILL EXERCISE CAPACITY IN PATIENTS WITH AND WITHOUT PREVIOUS MYOCARDIAL INFARCTION

Previous myocardial infarction	(-) (n=9)	(+) (n=7)	P value
Mean Age (years)	58±8	56±8	n.s.
Male/Female	9/0	4/3	n.s.
Collateral index (Before treatment)	2.1±1.1	2.1±0.9	n.s.
% ↑ in Exercise time	58±25	35±22	p<0.05
% ↓ in ST depression	34±25	18±23	n.s.
% ↑ in Double product at the onset of angina	41±18	20±15	p<0.05
% ↑ in Maximal double product	41±15	15±7	p<0.05

Figs are numbers of patients; plus-minus values are means ± SD.

arteries. Five patients had 1-vessel involvement, and 11 had 2-vessel involvement. In 6 patients, there were significant stenoses in 1 of the donating coronary arteries. The remaining 10 patients had a nonjeopardized collateral circulation. In 12 patients, well-developed collateral vessels were visualized, while 4 patients had poor or no collaterals at base-line coronary angiography. The mean value of the collateral index was 2.1 ± 0.9 (Table I). The use of medication for chronic effort angina at base-line was distributed equally among the 3 anti-anginal agents.

Acute effects of heparin exercise treatment on treadmill capacity and collateral circulation

All 16 patients completed the protocol without complications or adverse effects. No hemorrhagic tendency was noted in any of the patients. Heparin exercise treatment increased total exercise duration from 6.6 ± 1.6 to 9.4 ± 1.9 min ($p < 0.05$), as well as the maximally obtained double product from $19,200 \pm 4,700$ to $24,700 \pm 5,900$ mmHg·beats/min ($p < 0.05$). After treatment, the double product at the onset of angina was also increased from $16,400 \pm 4,200$ to $21,600 \pm 6,600$ mmHg·beats/min ($p < 0.05$). The ST segment depression at the same exercise time as in control exercise was ameliorated from 0.16 ± 0.05 to 0.12 ± 0.06 mV ($p < 0.05$) (Fig. 1). In the 12 patients who underwent repeat coronary angiography after heparin exercise treatment, the collateral index increased from 2.1 ± 0.9 to 3 in all patients ($p < 0.05$).

Determinants of the beneficial effect of heparin exercise treatment on treadmill capacity

We hypothesized that 6 variables (sex, age, previous myocardial infarction, multi-vessel disease, jeopardized collaterals and base-line collateral index) would strongly influence the extent of increases in the double product at the onset of angina as a result of heparin exercise treatment. Among these variables, only previous myocardial infarction was a significant ($p < 0.05$) determinant of the efficacy of the treatment on treadmill capacity. As shown in Table II, in the presence of comparable collateral indexes, parameters indicating treadmill exercise capacity were significantly better in patients without previous myocardial infarction than those with infarction.

Long-term effects of heparin exercise treatment on treadmill capacity

At 13 ± 7 months after the treatment, the total treadmill exercise time was 8.1 ± 1.7 min, which was not significantly different from the value immediately after the treatment. The maximal double product was $23,200 \pm 6,600$ mmHg·beats/min, the double product at the onset of angina was $20,500 \pm 6,000$ mmHg·beats/min, and the ST segment depression at the same exercise time as in control exercise was 0.10 ± 0.07 mV. These values were comparable with those immediately after the treatment (Fig. 1).

DISCUSSION

Our results indicated that heparin exercise treatment is more effective in patients without prior myocardial infarction than in those who have had prior myocardial infarction. Ischemia accompanying coronary occlusion is a potent stimulus of collateral development. The effect of additional stimuli in the form of exercise with heparin pretreatment may have been minimized in these patients. This may, at least in part, explain the relatively poor response to the treatment in patients with previous infarction. The results of our study in patients with previous infarction do not differ substantially from those of an experimental study.⁷ The data in the study support the inability of training programs following acute coronary occlusion to promote collateral development beyond that resulting from the coronary occlusion itself. Our findings showed that the extent of coronary vessel disease does not influence the efficacy of this treatment. It was speculated that the effect of this treatment would be more apparent in patients with 1-vessel disease, because a severe (90% or more) narrowing of donating coronary arteries would compromise the pressure gradient across the collateral network.⁸

Our findings confirm the long-term effectiveness of heparin exercise treatment. The finding that the increased rate-pressure product at the onset of angina remained unchanged over 13 months might indicate that the newly developed collateral vessels do not regress anatomically. These data compare favorably with an experimental report by Khouri et al.⁹ They observed that the augmented collateral circulation serves as a functionally significant blood conveying circuit for 3–90 days. In the present study, however, the total exercise time showed a decreasing trend during the follow-up period. This trend in decreased exercise time was more prominent in patients with a longer follow-up period. The dissipation of the peripheral effects of exercise may, at least in part, explain the decrease in exercise time, because our patients did not participate in the cardiac rehabilitation program after heparin exercise treatment.¹⁰

Our study had several limitations: 1) Although the present study showed that the

coexistence of exercise-induced myocardial ischemia and heparin was important for collateral development, it did not reveal whether exercise alone could trigger the proliferation of collateral vessels;^{11,12} 2) Collateral blood flow was not measured in our study and further investigation is needed to better evaluate the changes in collateral flow reserve during strenuous exercise, because the pressure gradient across the collateral network may be compromised by the increased left ventricular filling pressure during exercise;¹³ and 3) In the present study, all medications were discontinued 24 h before the exercise test. However, long-acting β -blockers, nitrates and calcium antagonists may have had some influence on the exercise test results.

In conclusion, repeated exercise with heparin pretreatment was useful for improving exercise capacity in patients with stable effort angina, and particularly in those without prior myocardial infarction. The beneficial effect of the treatment was maintained over a long follow-up period. The further development of such an angiogenic therapy would attenuate the deleterious sequelae accompanying coronary atherosclerosis.

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