ABSTRACT It has been demonstrated in animal experiments that heparin accelerates the coronary collateral development induced by repeated coronary occlusion. We used this effect of heparin for the treatment of patients with stable effort angina. In 10 patients, treadmill exercise was performed according to standard Bruce protocol twice a day for 10 days. A single intravenous dose of heparin (5000 IU) was given 10 to 20 min before each exercise period. Exercise with heparin pretreatment increased the total exercise duration from 6.3 ± 1.9 (SD) to 9.1 ± 2.2 min (p < .001) and the maximal double product (DP) from 18,900 ± 5100 to 25,500 ± 6800 mm Hg·beats/min (p < .001). The DP at the onset of angina was also increased by 35% (p < .01) and the DP at which ST depression (0.1 mV) first appeared was 19% (p < .05) greater after treatment. Repeat coronary cineangiography revealed an increase in the extent of opacification of collaterals to the jeopardized myocardium. In an additional six patients, treadmill exercise was performed with no medication twice a day for 10 days. All of the above-mentioned variables of treadmill capacity remained unchanged, despite 20 exercise periods without heparin pretreatment. Thus, heparin accelerates exercise-induced coronary collateral development by promoting angiogenesis. The development of such a therapeutic modality will open a new field for the treatment of patients with ischemia.


THE PRIMARY GOAL of treatment for effort angina is to alleviate chest pain and to prevent the progression to acute myocardial infarction. As medical therapy, β-blockers, nitrates, and calcium-channel blockers long have been used to decrease myocardial oxygen requirement. However, some patients with intractable angina need more aggressive treatment, such as percutaneous transluminal coronary angioplasty\(^1\) or aortocoronary bypass surgery.\(^2\) Despite the progress in these techniques, a certain number of patients are not candidates for these therapeutic approaches.

An alternative means of blood delivery to the compromised myocardium is the coronary collateral circulation. Indeed, results from some studies\(^3\)–\(^4\) indicate that the collateral channels serve as significant blood-conveying conduits, at least under resting conditions. However, whether the functional capacity of collaterals is augmented enough to represent a sufficient perfusion reserve against strenuous exercise remains unclarified.\(^5\)–\(^7\) Recently, we have documented in an animal experiment that heparin conclusively increases the speed of collateral development induced by repeated 2 min coronary occlusions.\(^8\)

In the present study, we wished to extend these results to man and to examine whether intravenously administered heparin could accelerate exercise-induced development of the collateral circulation in patients with effort angina due to significant coronary artery disease. Augmented collateral functional reserve was assessed daily as the increase in double product at the onset of angina and at 0.1 mV ST depression during treadmill exercise. Selective coronary cineangiography was performed before and after exercise with heparin pretreatment to directly evaluate collateral development.

**Methods**

**Patient selection.** Sixteen patients (14 men and two women), each with obstruction of at least one major coronary artery, were included in the present study. Their profiles at entrance into the study are given in table 1. The patients were randomly subdivided into two groups. Group A consisted of 10 patients who each underwent 20 exercise periods with heparin pretreatment, and group B was composed of six patients who each underwent 20 exercise periods with no medication. None of the patients
TABLE 1
Clinical and coronary angiographic data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>MI</th>
<th>CAG</th>
<th>Pre-</th>
<th>After</th>
<th>CI</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Group A (heparin)</td>
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<tr>
<td>1 M 54</td>
<td>None</td>
<td>100% middle LCx</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 M 62</td>
<td>None</td>
<td>100% proximal RCA</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 M 61</td>
<td>None</td>
<td>100% proximal RCA</td>
<td>75% distal LCx</td>
<td>3</td>
<td>3</td>
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<td></td>
</tr>
<tr>
<td>4 M 63</td>
<td>None</td>
<td>75% distal RCA</td>
<td>100% middle LAD</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5 M 70</td>
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<td>100% middle RCA</td>
<td>90% distal RCA</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>7 M 58</td>
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<td>90% proximal LCx</td>
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<tr>
<td>8 F 38</td>
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<td>100% middle RCA</td>
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<td>9 M 57</td>
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<tr>
<td>10 M 63</td>
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<td>100% proximal RCA</td>
<td>75% proximal LAD</td>
<td>2</td>
<td>3</td>
<td></td>
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<td></td>
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<tr>
<td>Group B (no heparin)</td>
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<tr>
<td>11 M 44</td>
<td>IMI</td>
<td>90% distal RCA</td>
<td>100% proximal LAD</td>
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<tr>
<td>12 M 61</td>
<td>AMI</td>
<td>100% middle LAD</td>
<td>90% middle LAD</td>
<td>3</td>
<td>—</td>
<td></td>
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<tr>
<td>13 M 60</td>
<td>AMI</td>
<td>100% proximal LAD</td>
<td>100% proximal RCA</td>
<td>3</td>
<td>—</td>
<td></td>
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<tr>
<td>14 F 62</td>
<td>None</td>
<td>90% middle RCA</td>
<td>100% proximal LAD</td>
<td>1</td>
<td>—</td>
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</tr>
<tr>
<td>15 M 60</td>
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<td>100% middle LAD</td>
<td>90% middle LAD</td>
<td>1</td>
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<tr>
<td>16 M 67</td>
<td>None</td>
<td>100% middle LAD</td>
<td>75% middle RCA</td>
<td>3</td>
<td>—</td>
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</tbody>
</table>

MI = myocardial infarction; CAG = coronary arteriography; CI = collateral index; LCx = left circumflex coronary artery; RCA = right coronary artery; LAD = left anterior descending coronary artery; AMI = anterior myocardial infarction; PMI = posterior myocardial infarction; IMI = inferior myocardial infarction.

were in cardiac failure or had serious persistent rhythm disturbances. The criteria for exclusion were the inability to exercise and the predisposition to hemorrhage. Antianginal drugs were stopped before the treatment; all 16 patients were receiving propranolol at the time of the study.

Protocol. After giving written consent concerning the details, objectives, and risks of the study, the patients participated in a supervised treadmill exercise program according to standard Bruce protocol. The patients exercised twice daily until the extent of anginal pain was 60% to 80% of maximal pain previously experienced. Exercise was performed twice a day for 10 days with (group A) or without (group B) pretreatment with a single intravenous dose of heparin (5000 IU), which was given 10 to 20 min before exercise. In the patients in group A, additional exercise without the drug was conducted on the following day after the completion of exercise with heparin pretreatment. Blood pressure was measured every minute by sphygmomanometer. The electrocardiogram was closely monitored throughout the exercise and recovery periods. A horizontally or down-sloping ST segment depression of 0.1 mV, lasting for 0.08 sec in three consecutive QRS complexes in a given lead, was considered indicative of ischemia. In all patients, severe anginal pain gradually subsided without the administration of sublingual nitroglycerin.

Radionuclide ventriculography. Before and after exercise with heparin pretreatment, resting first-pass radionuclide ventriculograms were obtained with a large-field-of-view gamma camera with an all-purpose, parallel-hole collimator, supported by a gantry in a tunnel configuration (General Electric Maxi; 400A/T). A 15 mCi dose of 99mTc pertechnetate in a volume of 1 ml was rapidly injected through an external jugular vein and flushed with 15 ml of 5% dextrose while the patient was positioned in the right anterior oblique view. Counts were recorded at a framing interval of 50 msec during the first pass of the isotope. Left ventricular ejection fraction was determined by the difference-in-counts method according to the formula (EDE - ESC/EDc - BA), where EDE = end-diastolic counts; ESC = end-systolic counts; BA = background activity.

Coronary arteriography. Selective coronary arteriography was performed by the Sones or Judkins technique before and after treatment. Before coronary angiography, a 0.3 mg dose of sublingual nitroglycerin was given. 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 opinion of two observers, who were given no information regarding the clinical data, was taken for visual 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 vessels.

Statistical analysis. Statistical comparisons were performed with paired Student’s t test for parametric comparisons and Wilcoxon’s sign-rank test for nonparametric comparisons. Statistical significance was assumed at p < .05. Values are presented as the mean ± SD.

Results

All 16 patients completed the protocol without complications or adverse effects. No hemorrhagic tendency was noted in any of the patients treated with heparin. Weekly urinalysis and stool guaiac tests revealed negative results.

Effects of exercise with or without heparin pretreatment on exercise capacity and ischemic electrocardiographic responses. Figure 1 illustrates the day-to-day changes in the total exercise time and maximal attainable double product in a representative patient (No. 4). The changes in the total exercise duration and maximal double product in both groups before and after treatment are shown in figure 2.

In group A (mean age 58 ± 9 years), exercise with heparin pretreatment increased total exercise duration from 6.3 ± 1.9 to 9.1 ± 2.2 min (p < .001), as well as the maximal double product from 18,900 ± 5100 to 25,500 ± 6800 mm Hg-beats/min (p < .001). Before heparin exercise treatment, the end point of
exercise was angina pectoris in all 10 patients. After treatment, angina pectoris was completely abolished during exercise in two of 10 patients, and exercise was terminated because of dyspnea or leg fatigue in three of 10 patients, while one of three patients had mild anginal pain. Figure 3 shows the relationship of exercise time to double product during exercise before and after exercise with heparin pretreatment in the same patient as in figure 1. In this patient (No. 4), there was no downward shift of the curve of the relationship between the exercise time and double product, indicating that peripheral effects of exercise are minimal. The changes in double product at the onset of angina pectoris before and after treatment are shown in figure 4, left. Exercise with heparin pretreatment increased the double product at the onset of angina pectoris from 16,600 ± 4800 to 22,400 ± 7300 mm Hg-beats/min (p < .01). After treatment, the double product at which ST segment depression (0.1 mV) first appeared also increased from 16,600 ± 4100 to 19,800 ± 6600 mm Hg-beats/min (p < .05; figure 4, right). The maximal ST segment depression was less than 0.1 mV in one of 10 patients. These changes in double product in the presence of comparable myocardial ischemia suggest an increase in blood delivery to the myocardium at risk.

In addition, the relationship between the magnitude of ST segment depression and rate-pressure product during exercise before and after exercise with heparin pretreatment in a representative patient (No. 3) is shown in figure 5. In this patient, there was less ST segment depression at any given rate-pressure product during exercise after treatment than before treatment.

In group B (mean age 59 ± 8 years), the total exercise duration remained unchanged despite 20 exercise periods without heparin (6.0 ± 1.9 vs 6.6 ± 2.1 min) as did the maximal attainable double product (20,300 ± 4700 vs 17,900 ± 3000 mm Hg-beats/min) (figure 2). The rate-pressure product at the onset of angina was comparable before and after exercise without heparin (16,700 ± 3900 vs 14,900 ± 4100 mm Hg-beats/min) (figure 4). The double product at 0.1 mV ST segment depression was also unchanged (17,400 ± 5400 vs 15,700 ± 3800 mm Hg-beats/min) (figure 4). In all of the above comparisons, the changes were nonsignificant.

Effect of exercise with heparin pretreatment on left ventricular function at rest (figure 6). In group A, before and after treatment the mean left ventricular ejection fraction at rest was 70 ± 10% and 75 ± 9%, respectively. Although this change was not statistically significant,
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site of the left circumflex coronary artery, the treatment developed the collateral circulation to the myocardium at risk and the distal epicardial segment of the left circumflex artery became clearly visible (figure 7).

Discussion

In animals, it has been well established that collateral vessels can be developed by strenuous exercise in the presence of decreased coronary flow reserve. However, in patients with significant coronary artery disease, whether exercise alone promotes the collateralization and results in an amelioration of myocardial oxygen balance during exercise has yet to be clarified.

In the present study, 20 vigorous exercise periods on a treadmill without drugs were not effective in promoting the development of collaterals, as evaluated by the double product at the onset of angina. Also, exercise time remained unchanged after 20 successive exercise periods without drugs, suggesting that both the central and peripheral effects of exercise were minimal in our patients. The failure of exercise to promote the collateralization may in part be due to the shorter duration of our study compared with others in which patients took part in a vigorous 6 week or 12 month exercise program. Thus, because the six patients in group B participated in only 20 successive strenuous exercise periods, the effect of exercise on the

FIGURE 2. Changes in exercise time (left) and maximal double product (right) before and after 20 treadmill exercise periods with (closed circle, solid line) and without (open circle, broken line) heparin pretreatment. ***p < .001 compared with values before exercise with heparin pretreatment.

there was a trend toward improved resting left ventricular function with this treatment.

Effect of exercise with heparin pretreatment on coronary collateral circulation. In the 10 patients of group A who underwent further coronary angiography after treatment, the collateral index increased significantly from 2.2 ± 0.9 to 3.0 ± 0 (p < .005; table 1). In patient 1, who had an occlusion of the proximal

FIGURE 3. Relationship between exercise time and double product during the treadmill exercise before (open circle, broken line) and after (closed circle, solid line) exercise with heparin pretreatment. Data from the same patient as in figure 1. Asterisk indicates occurrence of angina.
development of collateral vessels cannot be determined from this study.

The efficacy of heparin in the acceleration of collateral development has been shown in an animal experiment. In previous studies, the alleviation of myocardial ischemia due to collateralization was assessed as an improvement in regional myocardial function in the collateral-dependent zone and a decrease in reactive hyperemia after the release of coronary occlusion. In the present study, the increase in myocardial oxygen delivery, presumably due to the active proliferation of collateral vessels, was recognized as higher double product at the onset of angina and at 0.1 mV ST segment depression. Furthermore, the attenuation of myocardial ischemia at a comparable double product was documented by an upward shift in the relationship between the double product and ST segment depression (figure 5). These findings suggest an increase in myocardial oxygen delivery by a developed collateral circulation or prevention of clot formation on the ulcerated atherosclerotic plaque.

In the present study, the increase in double product at the onset of angina was approximately 31%. This was greater than that in Redwood's study, in which a triple product at the onset of angina showed a 14% increase after training. The increase in double product at which ST depression (0.1 mV) first appeared was 19%, which was smaller than the 22% increase in double product in Ehsani's study. Thus, 10 days of exercise with heparin pretreatment is not more effective than 1 year of intense training with respect to raising rate-pressure product threshold to the level necessary to induce 0.1 mV ST segment depression, although the comparison must be made with great caution because of variations

FIGURE 4. Changes in double product at the onset of angina (left) and double product at 0.1 mV ST segment depression (right) before and after 20 exercise periods with (closed circle, solid line) and without (open circle, broken line) heparin pretreatment. *p < .05; **p < .01 compared with values before exercise with heparin pretreatment.

FIGURE 5. Relationship between double product and extent of ST segment depression in lead V5 from patient 3. Data plotted were obtained during exercise before (open circle, broken line) and after (closed circle, solid line) exercise with heparin pretreatment. Asterisk indicates occurrence of angina.
in populations with regard to the severity of coronary disease and the time after infarction.

The dose of heparin used in this study deserves comment. In the aforementioned animal experiment, we administered approximately 500 IU/kg of heparin once a day. In the present study, the daily dose of heparin was approximately 150 to 200 IU/kg. This dose was determined arbitrarily to prevent hemorrhagic complications due to heparin use. Therefore, future study with the use of a fragment of heparin that possesses the intensifying action of angiogenesis secondary to various stimulating factors but is free from the anticoagulating action appears warranted.

The effects of heparin exercise treatment on the development of functionally significant collaterals were quite variable in individual patients. Two major factors in coronary circulation may be responsible for the disparities in responses to this treatment. First, in patients (Nos. 7, 8, and 9) with previous myocardial infarction, collateral channels may have been developed by the stimulation of infarction. Consequently, the treatment reported here may be less effective in patients with previous infarction. Second, a pressure gradient across the collateral network is a prerequisite for effective collateral circulation. It is likely that the pressure in the distal part of the completely obstructed coronary artery is low enough to establish a pressure gradient between the donor and recipient coronary arteries. On the other hand, if there were a severe (90% or more) narrowing of donating coronary arteries, the pressure gradient across the collateral network would be compromised. Under these conditions, even in the presence of well-developed collaterals, the collateral circulation may not be effective. Indeed, in a patient (No. 7) with severe coronary stenosis of the donating arteries, the salutary effect of collaterals was not as apparent as in patients with nonjeopardized donating arteries.

Beneficial effects of heparin exercise treatment on recruitment of collateral perfusion may have been achieved at the expense of "myocardial stunning" or patchy myocardial necrosis due to repetitive episodes of myocardial ischemia. However, in the present study, left ventricular contractile performance evaluated by radionuclide angiography did not reveal any depression of ventricular function. It is likely that episodes of transient ischemia occurring in our patients were probably not as severe as those that occur with 15 min of total coronary occlusion in the dog. These findings regarding the destiny of myocardium undergoing repetitive ischemic insult are in accordance with those of previous studies, although the comparison is difficult because of the differences in the severity, interval between, and total number of exercise periods.

The angiographic approach to evaluation of collateral development may have inherent limitations because only collateral vessels of over 100 μm in diameter are visualized. Therefore, the most important collateral channels in subendocardial layers may not be opacified even in the presence of fairly well-developed collaterals. Under resting conditions, especially in patients without myocardial infarction, preexistent collateral channels are adequate for myocardial oxygen requirement in the region at risk. Accordingly, the increases in collateral perfusion reserve and resultant angiographic opacification may be appreciated only in the presence of augmented myocardial oxygen demand. In this regard, further studies are required to clarify the actual increase in this collateral reserve and the degree to which myocardial ischemia can be attenuated under the conditions of increased myocardial metabolic activity. Radionuclide ventriculography immediately after exercise and/or postspacing left ventriculography would be useful for this purpose.

A possibility that another effect of heparin may
FIGURE 7. Coronary angiograms from patient 1. Before exercise with heparin pretreatment, the distal site of the obstructed left circumflex coronary artery was opacified incompletely by the collateral circulation from the left anterior descending coronary artery (A). After treatment, the same site of the left circumflex coronary artery was visualized clearly, as shown by the arrow in B.

Improve myocardial performance during exercise must be considered. It is well known that heparin treatment activates lipoprotein lipase in capillaries, which increases triglyceride breakdown and plasma free fatty acid levels, thereby improving ventricular function. However, under conditions such as in the present study, this effect of heparin would be minimal, if present at all. In the 10 patients receiving heparin pretreatment, plasma triglyceride levels remained unchanged before and after treatment (150 ± 84 vs 138 ± 59 mg/dl), as was the case in the six patients not receiving heparin (120 ± 39 vs 116 ± 38 mg/dl).

All patients enrolled in this therapeutic program participated in a 10 day heparin exercise protocol with no complications. These preliminary results lend support for exercise with heparin pretreatment as one of the possible therapeutic modalities for treating patients with stable angina.

We thank Masami Kosugi and Kyoko Tanioka for preparation of the manuscript.

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Erratum
In the "In Appreciation" column that appeared in the December issue of the Journal (Circulation 76: 1437, 1987), the name Stanley A. Rubin was inadvertently omitted. Dr. Rubin did serve as a reviewer during the period from September 1986 through August 1987, and his name should have been included.
Improvement of treadmill capacity and collateral circulation as a result of exercise with heparin pretreatment in patients with effort angina.
M Fujita, S Sasayama, H Asanoi, H Nakajima, O Sakaï and A Ohno

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