Alleviation of Myocardial Ischemia After Kawasaki Disease by Heparin and Exercise Therapy

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Background—Heparin promotes angiogenesis. We evaluated the effects of combined treatment with heparin and exercise on myocardial ischemia in the chronic stage of Kawasaki disease.

Methods and Results—This study was conducted in 7 patients (aged 6 to 19 years) who had a totally occluded coronary artery and stress-induced myocardial ischemia in the collateral-dependent areas. Twice-daily exercise using a bicycle ergometer was performed with increments of 0.5 W/kg every 3 minutes up to maximal exertion for 10 days. Heparin, which immediately increased circulating hepatocyte growth factor, was given intravenously 10 minutes before each exercise period. Newly developed myocardial infarction, ventricular tachyarrhythmia, anginal attack, or hemorrhagic complication was not observed in any patient. Dipyridamole-loading single photon emission computed tomography documented improved myocardial perfusion in the collateral-dependent areas and a significant reduction in total defect scores in all patients after the completion of 20 sessions (P<0.01). In control patients who did not receive the heparin-exercise therapy, however, stress defect scores remained unchanged (n=1) or increased (n=2) during follow-up. Computerized quantitative coronary angiography provided evidence that the heparin-exercise therapy increased the diameter of the occluded artery to which collaterals terminated (P<0.001) but not that of the reference artery with which collaterals were not connected (P=0.96).

Conclusions—The findings suggest that a series of heparin and exercise treatments over 10 days may have a dramatic effect on the alleviation of myocardial ischemia in collateral-dependent regions. This may be a safe, noninvasive revascularization therapy for patients with coronary artery occlusion in the chronic stage of Kawasaki disease. (Circulation. 2001;103:2591-2597.)

Key Words: mucocutaneous lymph node syndrome ■ heparin ■ angiogenesis ■ hepatocyte growth factor

Coronary obstructive lesions of Kawasaki disease (KD) have been treated with a variety of coronary interventions.1-3 Surgical bypass procedures are effective when the stenotic lesions are proximal.1 Recently, percutaneous transluminal coronary rotational ablation has been performed as an alternative strategy for revascularizing stenotic coronary lesions with calcification.3 Despite the progress of these techniques, there are some patients for whom surgical or catheter revascularizing procedures are not feasible because of the extent of the occluded lesions. Alternative therapeutic options to conventional interventions are required for such patients to prevent progressive myocardial ischemia.

A number of in vitro observations suggest that heparin promotes angiogenesis.4,5 In addition, the combination of heparin and exercise improved exercise capacity in adult patients with stable angina,6,7 and the combination of heparin and ischemia enhanced collateral vessel growth in experimental models.8,9 KD patients who develop coronary artery occlusion exclusively usually have collateral arteries for the occluded artery.10,11 In most cases, however, naturally developing collaterals cannot prevent stress-induced myocardial infarction and sudden death,10,12 suggesting insufficient blood flow into collateral-dependent areas of the myocardium. Such patients may be suitable candidates for heparin-induced angiogenic therapy. Improvement of collateral circulation would be expected to reduce the risk of infarction and death.13 The present study was designed to investigate the hypothesis that combined treatment with heparin and exercise may be a feasible therapeutic strategy to encourage the development of collaterals and to alleviate myocardial ischemia in children and adolescents with coronary artery occlusion in the chronic stage of KD.
Methods

Patients
We enrolled patients from December 1996 through December 2000. Patients were selected for heparin-exercise therapy if they had myocardial ischemia caused by coronary artery occlusion after KD, as proven by selective coronary angiography and dipyridamole-loading single photon emission computed tomography (SPECT). The documentation for the patients meeting the criteria to enter the study was (1) moderate to extensive perfusion defects by SPECT analysis, (2) evidence of stress-induced myocardial ischemia in collateral dependent areas, or (3) anatomic limitations to the practicality of surgical or interventional revascularization. Subjects were excluded if they had any of the following: exercise-induced ventricular tachyarrhythmia, congestive heart failure, extensive areas of infarcted myocardium, or a left ventricular ejection fraction <50%. Informed consent was obtained from patients and their parents before the heparin and exercise therapy was started.

Heparin and Exercise Therapy Protocol
The therapy was performed according to the protocol described by Fujita et al, with modifications. We used a bicycle ergometer for exercise. Exercise was performed with an initial work rate of 0.5 W/kg that was increased in increments of 0.5 W/kg every 3 minutes up to maximal exertion under ECG and blood pressure monitoring twice a day for 10 days. Thus, 20 exercise sessions were performed for each patient. Heparin at 100 IU/kg (maximum, 5000 IU) was given intravenously 10 minutes before each exercise session. Exercise was continued for at least 10 minutes as long as the patient did not develop ischemic ST-T changes, ventricular tachyarrhythmia, or hypotension. Serum creatine kinase was measured at the first, 10th, and 20th exercise sessions. All samples were frozen at −80°C until the assay. The levels of hepatocyte growth factor (HGF) were evaluated by an ELISA kit (R&D Systems). All assays were performed in duplicate. The detection limit was 0.04 ng/mL.

Quantitative Coronary Angiography Analysis
Selective coronary angiography was performed 1 to 3 months before the first exercise session and <3 months after the 20th exercise session in 6 patients (patients 1 to 6). We used quantitative coronary angiography15 to evaluate collateral circulation. Quantitative coronary angiography analysis was performed off-line using a computer-assisted, automated edge-detection algorithm (Cardiovascular Measurement Systems, Version 3.04) and a CAP-35E II telecine converter featuring a zoom lens and CCD camera by an operator who was blinded to the sequence of study. The luminal diameter of the occluded artery distal to the occluded segment, which is responsible for ischemic areas, was measured in the diastolic phase. For reference, the luminal diameter of a coronary artery that was neither the artery from which collaterals originate nor the artery to which collaterals terminate was measured in 5 patients (one patient did not have such a coronary artery to be evaluated). The external diameter of the contrast-filled catheter was used as the calibration standard.

Measurement of Hepatocyte Growth Factor
From each patient, EDTA-2Na–treated plasma was collected before heparin infusion, 10 minutes after heparin infusion (just before exercise), and after the end of exercise at the first and 20th exercise sessions. All samples were frozen at −80°C until the assay. The levels of hepatocyte growth factor (HGF) were evaluated by an ELISA kit (R&D Systems). All assays were performed in duplicate. The detection limit was 0.04 ng/mL.

Statistical Analyses
The calculated mean values with SD are shown for all measured study parameters. Comparison of values before and after therapy was performed using a paired, 2-sided Student’s t test. P<0.05 was considered significant.

Results

Clinical Characteristics
The heparin-exercise therapy was conducted in 7 patients. Baseline characteristics and coronary angiographic data are shown in Table 1. Patients ranged in age from 6 to 19 years (mean, 14±4 years) during the study. The interval between initial angiographic documentation of coronary artery occlusion and initiation of the heparin-exercise therapy protocol ranged from 1 month to 8 years (mean, 4 years). In all 7 patients, several collateral arteries into the distal occluded site were developed. Before heparin-exercise therapy, long-term antiplatelet therapy with aspirin or aspirin plus dipyridamole was given to all patients in combination with a Ca²⁺ channel blocker or isosorbide dinitrate. Catheter rotablator intervention was not feasible in any patient because all patients had
segmental total occlusion, which makes the procedure difficult. In addition, surgical intervention was not performed for the following reasons: young age (patient 1), small caliber of distal left anterior descending artery (LAD) for connecting with a graft (patients 1 through 3), and distal occluded lesions (patients 4 through 7).

**Heparin and Exercise Therapy**

All patients underwent 20 cycles of exercise over 10 to 12 days. All patients exercised for at least 10 minutes and up to 15 minutes without any anginal attack. Peak rate-pressure products ranged from 22,176 to 33,099 mm Hg · beat/min (mean, 27,825 mm Hg · beat/min). Ventricular arrhythmia was not observed in any patient during exercise. Serial ECGs and SPECT images showed no evidence of newly developed myocardial infarction in any patient. The therapy did not affect the left ventricular ejection fraction, as determined by angiography (56.6 ± 3.3% versus 56.6 ± 3.3%). Elevated levels of creatine kinase were not detected in any patient.

Bleeding was not observed, except one patient who developed mild epistaxis on one occasion. No prothrombin or activated partial thromboplastin time was abnormal before treatment.

**SPECT Images After Therapy**

The mean interval between the SPECT scans taken before and after treatment was 8 weeks. Baseline stress SPECT showed moderate (patients 1, 4, 6, and 7) to extensive (patients 2, 3, and 5) perfusion defects in the collateral-dependent areas in all patients. These were anteroseptal plus anteroapical or apical wall ischemia (patients 1 to 3) and inferoposterior wall ischemia (patients 4 to 7; Table 2). In addition to collateral-dependent areas, 3 patients had perfu-

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**TABLE 1. Baseline Patient Characteristics and Coronary Angiographic Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age During Study, y</th>
<th>Age at KD Onset, y</th>
<th>Age at Initial Documentation of Coronary Occlusion, y</th>
<th>CABG</th>
<th>Occluded Coronary Artery Segment*</th>
<th>Coronary Segment of Associated Severe Lesions</th>
<th>Collaterals to Occluded Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>No</td>
<td>LAD segment 6</td>
<td>Recanalized RCA segment 1</td>
<td>LAD via RCA, LAD via CX</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>13</td>
<td>1</td>
<td>7</td>
<td>Yes</td>
<td>LAD segment 6; bypass graft to LAD segment 7</td>
<td>Recanalized RCA segment 2</td>
<td>LAD via RCA, LAD via CX</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>13</td>
<td>1</td>
<td>11</td>
<td>No</td>
<td>LAD segment 6</td>
<td>Recanalized RCA segment 4</td>
<td>LAD via RCA, LAD via CX</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>15</td>
<td>6</td>
<td>7</td>
<td>No</td>
<td>RCA segments 1–3</td>
<td>Giant aneurysm of LAD segment 6</td>
<td>4AV via CX, 4PD via CX</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>17</td>
<td>10 mo</td>
<td>16</td>
<td>No</td>
<td>RCA segment 4</td>
<td>Recanalized RCA segments 1–3; giant aneurysm of LAD</td>
<td>4AV via CX, 4PD via proximal RCA</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>19</td>
<td>3 mo</td>
<td>14</td>
<td>No</td>
<td>RCA segments 2–3</td>
<td>Giant aneurysm of LAD</td>
<td>4AV via CX, 4PD via LAD</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>15</td>
<td>1</td>
<td>10</td>
<td>No</td>
<td>RCA segment 2</td>
<td>Small aneurysm of LAD</td>
<td>RCA via LAD</td>
</tr>
</tbody>
</table>

4AV indicates segment 4 atrioventricular branch; CABG, coronary artery bypass graft; CX, circumflex artery; and 4PD, segment 4 posterior descending branch.

*Coronary artery segment is expressed by the segment number of coronary arteries according to an American Heart Association Committee report.21

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**TABLE 2. SPECT Findings and Total Defect Scores in 7 Patients Before and After the Therapy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ischemic Areas</th>
<th>Total Defect Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>1</td>
<td>Anteroseptal wall and anteroapical wall</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Anteroseptal wall, apical wall, and inferoposterior wall</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Anteroseptal wall, apical wall, and inferior wall</td>
<td>23.7</td>
</tr>
<tr>
<td>4</td>
<td>Inferoposterior wall</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>Inferoposterior wall and anteroseptal wall</td>
<td>18.7</td>
</tr>
<tr>
<td>6</td>
<td>Inferoposterior wall</td>
<td>11.7</td>
</tr>
<tr>
<td>7</td>
<td>Inferoposterior wall</td>
<td>9.0</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>14.2±6.5*</td>
<td>8.3±4.8*</td>
</tr>
</tbody>
</table>

SPECT defect scores indicate mean scores between 3 independent observers.

*P=0.01, before vs after treatment.
Sion defects in the right coronary artery (RCA; patients 2 and 3) or LAD (patient 5).

In all 7 patients, the heparin-exercise therapy sessions were associated with improved myocardial perfusion in the collateral-dependent regions (Figures 2 through 4). Stress defect scores decreased from 14.2 ± 6.5 to 8.3 ± 4.8 (P < 0.01; Table 2). In addition, rest defect scores decreased in 4 of 5 patients who had baseline perfusion defects.

Control SPECT Studies Without Therapy
Dipyridamole-loading SPECT was performed at baseline and at follow-up in 3 patients who did not receive the heparin-exercise therapy or any other coronary intervention therapy during an observed period of 8 weeks through 3 years (mean period, 15 months). Their ages ranged from 6 to 15 years (mean, 11 ± 4 years) at the baseline SPECT. Mean interval between initial angiographic documentation of coronary ar-

Figure 2. Coronary angiography and SPECT imaging in a 6-year-old boy (patient 1). A, RCA angiography before therapy. Proximal RCA is recanalized. Diffuse irregularity is seen in mid-RCA. Collaterals from the conus branch of RCA terminate to LAD segment 7. Giant aneurysms over LAD segment 6 to 7 regressed, but the remnant irregular lesion makes segment 7 ungraftable. B, Coronary angiogram of left coronary artery before therapy. LAD segment 6 is completely occluded, diagonal artery is recanalized, and circumflex artery is connected with diagonal branch. C, Dipyridamole stress SPECT imaging before and after treatment. Perfusion defect on anteroseptal and anteroapical walls decreased in size after therapy.

Figure 3. Coronary angiography and SPECT imaging in a 13-year-old boy (patient 2). This patient had 99% stenosis between 2 large and long segmental aneurysms in LAD segment 6 to 7 and then underwent CABG using an arterial graft to the LAD distal to the aneurysms at 4 years of age. However, the graft and LAD were occluded at 7 years of age. A, RCA angiogram before the therapy at 13 years of age. Mid-RCA is recanalized. Collaterals from RCA conus terminate to LAD distal to occluded site. B, RCA angiography after the therapy. New epicardial collateral vessel from distal RCA to LAD branch is present after therapy (arrows). C, Treatment SPECT images before and after treatment at rest and during stress. Myocardial perfusion in the anteroseptal wall improved after therapy.
occlusion and baseline SPECT was 5 years. Two had RCA obstruction, and the remaining had LAD obstruction. Selective coronary angiography documented several collateral arteries into the distal occluded site in all patients. Baseline stress SPECT showed moderate (n=2) or extensive (n=1) perfusion defects in the collateral-dependent areas.

Follow-up SPECT demonstrated that stress-induced myocardial ischemia in the collateral-dependent areas did not improve naturally in any patient. Stress defect scores remained unchanged (n=1) or increased (n=2). Mean stress defect scores changed from 8.1±5.4 to 11.4±2.7 (P=0.18).

**ECG Changes**

Two patients (patients 1 and 2) were judged to be difficult to evaluate by ECG for ischemia because of right bundle branch block. Of the remaining 5 patients, two (patients 3 and 5) had ST-segment depressions on their baseline dipyridamole-loading ECGs or exercise-loading ECGs. Ischemic ST-segment depression disappeared after therapy in 1 of these 2 patients (Figure 4).

**Quantitative Coronary Angiography Analysis**

The mean interval between the baseline and post-treatment selective coronary angiography was 5 months. There was evidence of the development of new epicardial collateral vessels in 2 of 6 patients studied (patients 1 and 2; Figure 3). In all 6 patients studied, heparin-exercise therapy dramatically increased the size of the occluded artery to which collaterals terminated (Table 3). The diameter of the occluded artery increased from 1.21±0.40 mm to 1.35±0.45 mm (P=0.001). In contrast, this form of therapy did not influence the diameter of the reference artery with which collaterals were not connected (1.48±0.30 mm versus 1.49±0.27 mm after therapy; P=0.96; Table 4).

**HGF**

In healthy young adults (n=7), the plasma levels of HGF were 0.31±0.09 ng/mL. In all 7 patients, plasma levels of HGF increased from 0.40±0.20 to 28.4±14.1 ng/mL (P=0.001) 10 minutes after heparin infusion. Elevation of HGF levels persisted during exercise. The effect of heparin...
thought that the Rentrop score was not ideal for evaluating collateral circulation in this study. Indeed, in our study patients, the treatment protocol did not influence Rentrop scores (data not shown). Therefore, we assessed whether the size of the occluded artery to which collaterals terminated was changed by the therapy. Computerized quantitative coronary angiography provided new evidence that the study protocol led to a dramatic increase in the diameter of the occluded artery to which collaterals terminated but did not change the size of the reference artery with which collaterals were not connected. We thought that this effect might be due, at least in part, to increased collateral blood flow into collateral-dependent regions. It has been shown that ischemia can upregulate the local production of angiogenic growth factors. Angiogenesis, capillary sprouting, and increased capillary density in the ischemic areas may play a role in the increase in collateral blood flow, because angiogenesis can significantly reduce the vascular resistance of the entire collateral-dependent region. Although we could not obtain direct angiographic evidence of neovascularization in ischemic areas, there was evidence for improvement in myocardial perfusion after the heparin-exercise protocol using SPECT.

The molecular mechanisms by which heparin acts are unknown. Fujita et al showed that exercise capacity was not improved with either heparin infusion or exercise alone. This implies that the combination of heparin and tissue hypoxia/ischemia is required for improvement in collateral circulation. Recently, heparin was shown to increase circulating HGF levels. In the current study, both the first and last heparin infusion resulted in a dramatic increase in plasma levels of HGF, which supports the previous data. HGF can promote angiogenesis in the rat ischemic heart, and it has been shown to increase the expression of vascular endothelial growth factor in vascular smooth muscle cells in vitro.

**Indications for Patients With KD**

In contrast to conventional coronary interventions, the heparin and exercise treatment protocol can be used noninvasively and repeatedly. It seems remarkably safe, inexpensive, and easy to perform. At present, we think that KD patients with collaterals for the occluded artery are good candidates for this therapy. If the patient does not receive the heparin-exercise therapy, myocardial ischemia in the collateral-dependent regions may progress, as demonstrated by our control SPECT studies. If the patient has myocardial ischemia caused by localized stenosis of the proximal portions of major coronary arteries, surgical or catheter intervention should be considered. In this study, we did not apply the heparin-exercise protocol to patients with extensive myocardial dysfunction. Such patients may have to undergo cardiac transplantation or therapeutic angiogenesis.

**Conclusions**

The present findings demonstrate that heparin-exercise therapy is a feasible therapeutic strategy for children and adolescents with stress-induced myocardial ischemia caused by coronary artery occlusion in the chronic stage of KD. We think that this form of therapy is effective in improving the overall quality-of-life of these patients.
Acknowledgments
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