Heparin and Exercise Treatment in a Patient With Arteriosclerosis Obliterans

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A 65-year-old man was admitted with a diagnosis of arteriosclerosis obliterans. He had a 3-month history of intermittent claudication of the right leg. Physical examination revealed absence of pulsation of the right posterior tibial artery. Contrast angiography of lower extremities showed several severe obstructive lesions below the right popliteal artery. As interventional and surgical approaches were not indicated, the patient was treated with exercise with heparin pretreatment (5,000 IU). As a result, walk distance on a floor was increased from 400 m to 2,000 m, and repeat magnetic resonance angiography revealed increased flow to the right lower extremity. Thus, he was successfully treated with exercise and heparin pretreatment without any side-effects.

(Key Words: Heparin; Exercise; Intermittent claudication; Magnetic resonance angiography)

The primary goal of treatment for intermittent claudication caused by arteriosclerosis obliterans is to improve exercise capacity. As medical therapy, anticoagulants, antiplatelet drugs, and vasodilators have long been used to increase blood supply to the jeopardized region. However, some patients with intractable leg pain need more aggressive treatment, such as percutaneous transluminal angioplasty or bypass surgery. Despite progress in these therapeutic areas, some patients are not suitable for these treatments because of the peripheral properties of their arteriosclerotic lesions. We have previously reported1,2 that exercise with heparin pretreatment successfully increases collateral circulation to the area perfused by the severely stenosed coronary arteries in patients with effort angina. We wished to extend the treatment to a patient with intermittent claudication and to evaluate whether intravenously administered heparin in the presence of exercise-induced ischemia could accelerate collateral development and improve exercise capacity.

Case Report

A 65-year-old man was admitted with a 3-month history of intermittent claudication of the right leg. He had multiple risk factors for arteriosclerosis, such as hypertension, diabetes mellitus, and cigarette smoking. His pulse rate was 84 beats/min, blood pressure 142/58 mmHg, and physical examination was normal except for the absence of pulsation of the right posterior tibial and dorsalis pedis arteries. Laboratory data on admission revealed glucose intolerance with a fasting blood sugar level of 142 mg/dl and hypokalemia of 3.0 mmol/L. Other laboratory data were within normal limits. A 12-lead electrocardiogram revealed left ventricular hypertrophy with strain patterns in leads V5 and V6. Chest and abdominal radiographs showed left first arch protrusion, elongation and dilation of the descending aorta, and calcification along the entire aorta and iliac arteries. Contrast angiography of lower extremities was then performed. There were moderate arteriosclerotic changes but no significant obstructive lesions above the right popliteal artery. There were severely stenosed lesions in the right anterior tibial and

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peroneal arteries (Fig 1). The patient was treated with exercise with heparin pretreatment, because interventional and surgical approaches were not indicated. He participated in a treadmill exercise program using the Balke-Ware protocol to stimulate collateral development from exercise-induced ischemia. He exercised 20 times, twice a day for 2 weeks until the extent of leg pain was intensified to 60–80% of the maximum pain previously experienced. A single intravenous dose of 5,000 IU of heparin was given 10–20 min before each exercise period. Throughout the heparin exercise treatment period, constant oral doses of aspirin, calcium channel antagonist and nitrate were administered. At baseline, average exercise time was 3 min 19 sec (5 metabolic equivalents (METS)), increasing to 8 min 18 sec (8 METS) after heparin exercise treatment. Walk distance on a floor was markedly increased from 400 m at baseline to 2,000 m 1 week after completion of the treatment (Fig 2). Magnetic resonance angiograms revealed visually improved flow of the right anterior tibial artery and new appearance of flow to the calf of the right leg (Fig 3). Before heparin-exercise treatment, the plasma level of basic fibroblast growth factor was below 1.0 pg/ml in both the right femoral vein and the anterior cubital vein. After treatment, the plasma levels of basic fibroblast growth
factor in the right femoral vein and anterior cubital vein were 2.1 and 1.3 pg/ml, respectively. One week after the treatment, the patient was discharged with no side-effects and with a smile.

**Discussion**

In our patient, exercise with heparin pretreatment improved exercise capacity, presumably as a result of increased collateral flow to the jeopardized region. These results compare favorably with those of our previous studies\(^1\) in which collateral development was successfully promoted by repeated exercise stress combined with heparin treatment in patients with effort angina. In a recent elegant study conducted by Yang et al.\(^2\), synergistic action of exercise-induced ischemia and heparin was clearly demonstrated. In the rat without occlusion of femoral arteries, blood flow to the hind limbs was 71 ± 6 (SEM) ml/min x 100 g, whereas it was decreased to 12 ± 2 ml/min x 100 g by acute occlusion of both femoral arteries. Blood flow was increased to 20 ± 4 ml/min x 100 g during the follow-up period of 6 weeks. Moderate and strenuous exercise during the follow-up period further increased blood flow to 24 ± 3 ml/min x 100 g and 34 ± 3 ml/min x 100 g, respectively. In rats with heparin treatment (100 IU/rat), moderate and strenuous exercise increased blood flow to 41 ± 3 ml/min x 100 g and 56 ± 3 ml/min x 100 g. The authors concluded that exercise stimuli induced the production and release of angiogenic factors, and that heparin potentiated the effect of increased angiogenic factors. This experimental framework is very similar to our therapeutic approach to the patient reported here.

The possibility that another effect of heparin may have improved perfusion to the jeopardized region must be considered. It is well known that heparin treatment prevents thrombus formation at the site of severely stenosed arteries, where fibrinolysis predominates, thereby improving local perfusion. Thus, because the ischemia-related peripheral arteries in our patient were not completely occluded, the possibility of hemorrhheologic improvement remains unclarified. Further studies are therefore needed to show that the underlying mechanism of beneficial effects of heparin-exercise treatment is the development of a collateral circulation.

As it has been reported that a regular walking program or other supervised dynamic leg exercise program is associated with an increased pain-free and maximum walking distance in many subjects with intermittent claudication\(^3\) further studies are required to clarify whether the addition of heparin potentiates the collateralization and/or improves hemorrhheologic\(^4\).

To the best of our knowledge this case is the first to apply angiogenic therapy to a patient with arteriosclerosis obliterans. Angiogenic therapy is defined as a treatment whereby collateral circulation to the compromised region is enhanced by acute or chronic administration of some agents. Using rabbits with unilateral hind limb ischemia, Takeshita et al.\(^5\) demonstrated that a single intra-arterial bolus of vascular endothelial growth factor, an angiogenic growth factor, produced a significant increase in collateral vessel.
development and consequent amelioration of the hemodynamic deficit in the ischemic limb. In the near future it will be reported that use of vascular endothelial growth factor and/or its gene may be appropriate for the treatment of selected patients with advanced lower extremity vascular occlusive disease.

References


