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Treadmill Testing for the Evaluation of Intermittent Claudication

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Abstract The usefulness of treadmill testing to evaluate treatment efficacy for intermittent claudication objectively was studied in 20 patients who received an infusion of prostaglandin E_1 incorporated in lipid microspheres (Lipo-PGE_1, 10μg/day) into a forearm vein daily for 7 consecutive days.

The pain-free walking distance, maximum walking distance and ankle pressure index (API) were measured on a treadmill (3.0 km/hour, 5% slope) before and after the Lipo-PGE_1 infusion. The pain-free walking distance increased from 72.5±41.4 m before therapy to 92.0±53.7 m 7 days after Lipo-PGE_1 infusion ($p<0.01$). However, Lipo-PGE_1 did not improve the API nor lengthen the tolerated maximum walking distance.

We concluded that the measurement of the pain-free walking distance on a treadmill is useful in the objective evaluation of intermittent claudication.

Key Words : Intermittent claudication, Lipo-PGE_1, Treadmill, Pain-free walking distance

Introduction

Recently, the incidence of intermittent claudication has increased, however, the incidence of severely ischemic extremities, characterized by foot ulcers and rest pain, has not. The use of new vasoactive substances have yielded encouraging results in patients with intermittent claudication. However, objective evaluation of drug efficacy in claudication is difficult since the pain of claudication intrinsically is a subjective experience. Therefore, in Japan, the efficacy of new vasoactive agents is evaluated only in patients with ischemic ulcers.

This study investigated the usefulness of treadmill testing in the evaluation of drug efficacy in patients with intermittent claudication treated with a single infusion of prostaglandin E_1 incorporated in lipid microspheres (Lipo-PGE_1).

Methods

We studied 20 patients (15 men and 5 women, 39 to 73 years of age) with intermittent claudication secondary to atherosclerosis. Patients with rest pain, paresthesias, and/or skin ulcers were excluded from the study. Arterial occlusive lesions were defined angiographically. Fifteen patients had aortoiliac lesions and 5 had femoropopliteal obstructions. Associated diseases included severe hypertension in 8 patients and diabetes mellitus in 3. Blood pressure in the brachial, posterior tibial, and dorsalis pedis arteries was measured by Doppler flow meter with the patient in the supine position, and the

ankle pressure index (API) was calculated.

The treadmill tests were conducted, and the absolute distance that patients were able to walk on a 5% incline at a metronome-controlled speed of 3.0 km/h was recorded. During the treadmill test, pain-free walking distance, tolerated maximum walking distance, and the API were measured prior to and 7 days after Lipo-PGE_1 infusion. Lipo-PGE_1 was infused daily via a forearm vein at a dose of 10 μg/day in 20 ml of saline daily for 7 consecutive days. Measurements of pain-free walking distance, maximum walking distance, and API were performed 1 hour after Lipo-PGE_1 infusion 7 days after completion of the course of Lipo-PGE_1 therapy. The lengthened ratio of pain-free walking distance (LRPWD) was calculated as follows:

$$LRPWD = (B - A) / A$$

Where A indicates pain-free walking distance prior to Lipo-PGE_1 infusion and B this distance 7 days after infusion.

Student's t-test was used for the statistical analysis.

Significance was defined as $p<0.05$.

Results

A significant positive correlation existed between objective (tolerated maximum walking distance) and subjective (maximum walking distance reported by the patient to the examiner) assessments of the patients ambulatory capacity, although the tolerated maximum walking distance was slightly shorter than proposed maximum walking distance (Fig. 1)($p<0.01$).

The effect of Lipo-PGE_1 on lower extremity blood flow was variable. The pain-free walking distance was significantly longer 7 days after Lipo-PGE_1 infusion than before Lipo-PGE_1 infusion (92.0±53.7 versus 72.5±41.4 m)($p<0.01$), and the tolerated maximum walking distance increased from 209±138.8 to 240±130.4 m, but this difference was not significant (Fig. 2).

Systolic brachial artery pressure at rest was unchanged by Lipo-PGE_1 infusion (136.5±25.2 mmHg prior to infusion and 137.1±19.3 mmHg at 7 days after infusion). The mean API at rest was 0.83±0.25 and 0.55±0.

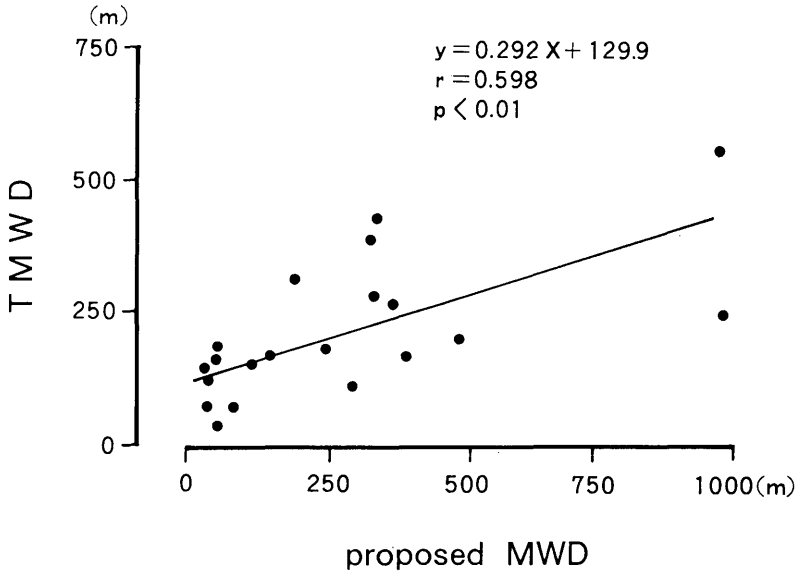

Fig. 1 Correlation between tolerated maximum walking distance and proposed maximum walking distance. Correlation between tolerated maximum walking distace during treadmill testing and the patients' proposed maximum walking distance was statistically significant.
TMWD: Tolerated maximum walking distance
MWD: Maximum walking distane

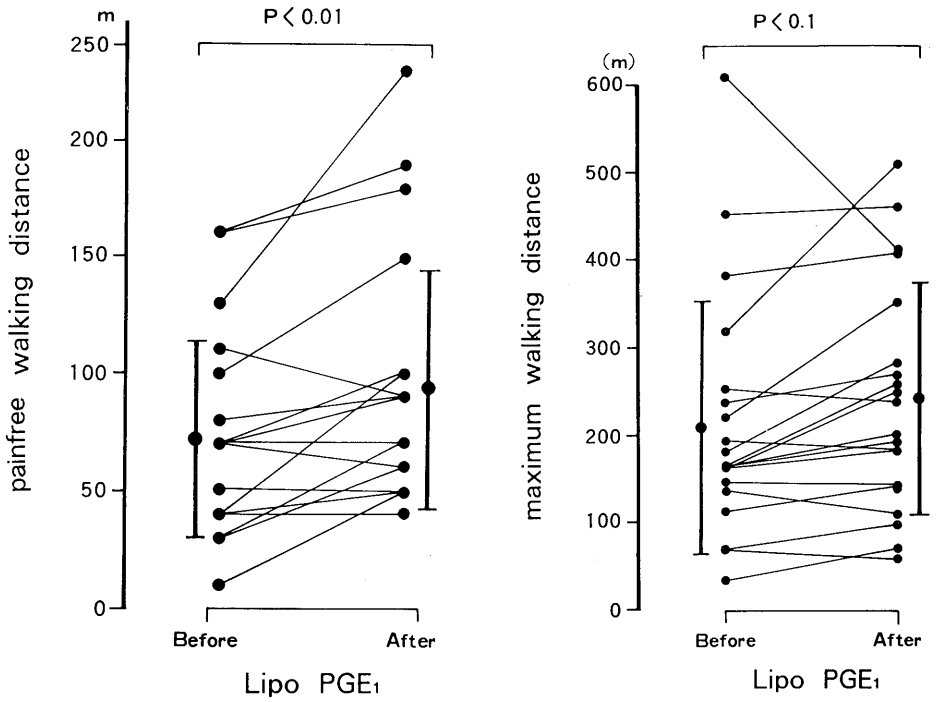

Fig. 2 Left: Pain-free walking distance on the treadmill prior to and after Lipo-PGE_1 infusion. Pain-free walking distance after therapy was significantly greater than that prior to therapy.
Right: Maximum walking distance on the treadmill prior to and after Lipo-PGE_1 infusion. Maximum walking distance prior to and after Lipo-PGE_1 infusion was not significantly different.

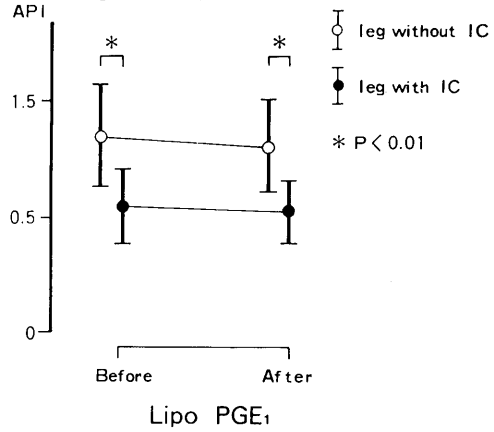

Fig. 3 Ankle pressure index (API) prior to and after Lipo-PGE_1 infusion. Although mean ankle pressure index in the legs without claudication was significantly higher than that in the legs with claudication prior to and after therapy, the difference in ankle pressure index prior to and after therapy in legs with claudication was not significant.
IC: Intermittent claudication.

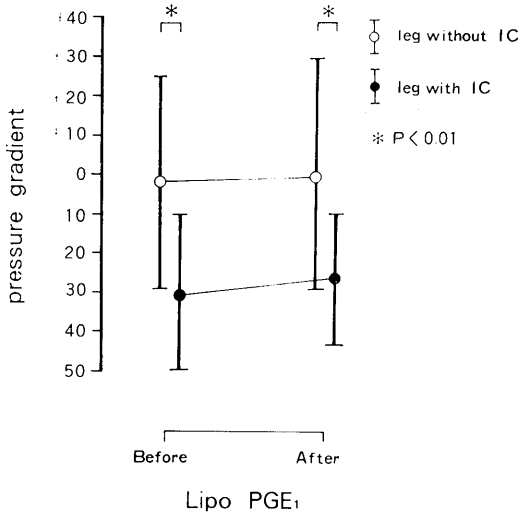

Fig. 4 Pressure gradient prior to and after Lipo-PGE_1 infusion. The difference in pressure gradient prior to and after therapy was small, regardless of claudication status.
IC: Intermittent claudication

15 prior to Lipo-PGE_1 infusion, and was 0.81±0.21 and 0.54±0.13 at 7 days after Lipo-PGE_1 infusion in the leg without and with claudication, respectively. Neither difference was significant (Fig. 3).

The mean difference in pedal pressure (post-minus pretest pressure) was 2.7±27.8 mmHg prior to Lipo-PGE_1 infusion and 0.35±20.3 mmHg at 7 days after infusion in the leg without claudication, and was 30.5±20.3 mmHg versus 26.6±17.0 in the leg with claudication. These changes were small, though the difference in the leg without claudication was lower both before and after Lipo-PGE_1 infusion ($p<0.01$)(Fig. 4).

The pain-free walking distance prior to Lipo-PGE_1 infusion was 78.7±44.4 m in the aortoiliac and 54.0±26.0 m in the femoropopliteal group. This difference was not significant. Nor was there any difference in the lengthened ratio of pain-free walking distance (0.35±0.55 versus 0.92±1.74, respectively).

Discussion

Objective evaluation of treatment efficacy for intermittent claudication is complicated by the fact that pain is intrinsically subjective, and measurements of ambulatory capacity are influenced strongly by factors such as patient cooperation and pain tolerance. To overcome this obstacle, only patients with objective evidence of vascular disease, ischemic foot ulcer, have been used for the evaluation of new pharmacologic agents in Japan. However, the number of patients with ischemic foot ulcer due to peripheral vascular disease has decreased. Therefore, to determine the effectiveness of Lipo-PGE_1 we decided to examine the patients with intermittent claudication.

The efficacy of this drug previously has been evaluated by measuring pain-free and maximum walking distances and duration of treadmill exercise, however, the actual technique for treadmill testing has not been consistent.

Ylitalo et al.[1] have compared iloprost and dextran used in patients with peripheral arterial occlusive disease who undertook treadmill exercise at 3.6 km/h with the grade increased gradually from 0° to 5° during a 10-minute test period. Rudofsky et al.[2] have measured walking distance on the treadmill under standard conditions: a 12.5% incline (= 7°), 3 km/h, and room temperature (21℃). Ballinger and Frei[3] tested patients at 3.2 km/h at a 12.5° grade until claudication forced them to stop. Diehm et al.[4] have investigated walking tolerance on a treadmill at 3.5 km/h at a 10° incline to evaluate the effect of regular physical training. Blume et al.[5] have evaluated the clinical efficacy of intra-arterial PGE_1 in patients with intermittent claudication by treadmill testing at 3 km/h at a 5% incline. In contrast, Roekaerts et al.[6] and Perri et al.[7] have measured absolute walking distance in meters, i.e., the absolute distance that an individual patient was able to walk level at a metronome-controlled speed of 120 steps per minute. As described above, there has not been a definite standard for treadmill testing in the clinical routine. Petersen[8] measured the walking distance with varying the speed and inclination of the treadmill and concluded that an objective measurement of the claudication distance should be carried out during uphill walking with highest walking speed the individual patient can endure. With reference to the result that Petersen reported, we performed treadmill testing with a walking speed of 3 km/h at a 5% incline. It is so difficult to vary the speed of the treadmill for each patients in the clinical routine that we fixed the speed at 3 km/h, it seems to be a little too fast for aged patients.

Prior to and 7 days after Lipo-PGE_1 infusion, pain-free walking distance and maximal walking distance were recorded. Correlation between the tolerated maximum walking distance on the treadmill test and the patients' proposed maximum walking distance was statistically significant. Based upon this, we feel that the treadmill test is a valuable method for evaluation of the efficacy of vasoactive drugs in patients with intermittent claudication.

Although the clinical efficacy of PGE_1 in patients with peripheral arterial occlusion has been confirmed[6], few reports exist concerning the clinical efficacy of Lipo-PGE_1 in patients with intermittent claudication. In

our study, there was a significant improvement in pain-free walking distace with Lipo-PGE_1 treatment, but neither in the tolerated maximum walking distace nor in API. Lipo-PGE_1 are suggested to increase capillary blood flow and oxigen supply probably due to increased deformability of red blood cells and inhibition of platelet aggregation. This seems to be the reason why pain free walking distance was increased by Lipo-PGE_1 infusion but API was not. Reich et al.[9] reported that ability to walk until first experiencing intermittent claudication was more sensitive index than the maximum ability to walk, perhaps beause motivation, tolerance of pain, and reaction to examiner and environmant are not as influential. This agrees well with our results.

Conclusion

Based on our study of 20 patients with intermittent claudication, we conclude the following:

1) There was a good correlation between the tolerated maximum walking distance during treadmill testing and the patients reported maximum walking distance.
2) Measurement of the pain-free walking distance during treadmill testing was useful in the objective evaluation of intermittent claudication.
3) Pain-free walking distance increased when PGE_1 incorporated in lipid microspheres (10 μg per day) was administered intravenously for 7 days.

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