Improvement of Peripheral and Cardiopulmonary Performance After a Short-Term Exercise Program with Additive Prostaglandin E_1

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In patients with intermittent claudication, the walking distance can be increased, both by means of several months of intensive training and administration of IV prostaglandin E_1 (PGE_1) for 4 weeks. The aim of this study was, therefore, to investigate whether the combination of intensive training and PGE_1 infusions during pedalergometry can increase peripheral and cardiopulmonary performance after 2 weeks. Ten patients with intermittent claudication received a once-daily intravenous infusion of 60 μg PGE_1 over 2 hours during pedalergometry. In addition, a physical training program was carried out mornings and afternoons, as well as progressive treadmill training. Walking distance (3 km/h, 12%) and cardiopulmonary performance were determined at the beginning and end of the 2-week treatment. Results were compared with those of a historical control group having received a similar training program without PGE_1. The initial walking distance increased from 71 to 166 m (134%). At the same time, peak work load increased by 108%, and the physical work capacity by 100%. Cardiopulmonary function improvement was reflected in all the parameters investigated (peak VO_2; peak VO_2/peak work load ratio; slope of $\Delta VO_2/\Delta t$; RER). Compared with the historical control group, the difference between the two groups with regard to the increase in walking distance was significant in favor of the combined training program with PGE_1.

The combination of short-term intensive training and PGE_1 infusions during pedal ergometry significantly improves both the peripheral as well as the highly restricted functional capacity in patients with intermittent claudication.

Introduction

There is general agreement that the primary treatment of intermittent claudication (peripheral arterial occlusive disease stage II according to Fontaine's classification) should be conservative.[1-5] Numerous clinical studies have shown that in these patients a supervised physical training program improves walking capacity.[2,5-14] Because of differences in the parameters—intensity, frequency, and duration—of such exercise programs, wide variability in the increase in walking distance has been noted. Moreover,

Angiology 52:381–391, 2001

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there is evidence that the compliance of patients participating in these programs is limited,[15] particularly when at least 6 months are needed to achieve an optimal effect. Alternatively 4 weeks of treatment with prostaglandin E_1 (PGE_1) can result in an average improvement of the initial walking distance of about 100% as various studies have demonstrated.[16-22]

Even greater improvements in walking distance—up to 263%—are seen with a combination of 4 weeks of intensive training and IV PGE_1 infusions during pedalergometry.[23] These better-than-average results prompted us to carry out a similar investigation with the aim of establishing whether a relevant improvement in intermittent claudication is possible with a shorter period of treatment. Since it is known that a major training mechanism is the improvement in oxygen supply-demand mismatch, but nothing is known about the effect of PGE_1 treatment on this parameter, our pilot study also examined cardiopulmonary function using spiroergometry. The choice of the relative short treatment period of 2 weeks was prompted both by the length of stay in our hospital, but also by the wish to improve patient motivation and compliance by achieving visible results more rapidly, while at the same time realizing a socioeconomic effect by lowering costs by shortening treatment times.

To compare the results of our pilot study, a previous study[8] with 23 patients receiving a similar training program without PGE_1 served as a historical control group.

Methods

Study Population

Ten inpatients (7 men, 3 women; average age, 57 ±14 years) in our hospital participated in our pilot study. They all met the inclusion criteria: stable intermittent claudication of at least 2 months standing, absolute walking distance on the treadmill (3 km/h, 12%) between 50 and 200 m. Stenoses or occlusions of the upper thigh or lower leg were confirmed by Duplex ultrasonography or angiography. The ankle-brachial index (ABI) of the affected extremity had to be < 0.85 at rest, and the absolute arterial pressure at the ankle after 1 minute of walking on the treadmill (3 km/h, 12%) had to decrease by more than 10%. Patients with diseases (eg, decompensated cardiac insufficiency, severe coronary heart disease, severe ventilation disorders) for whom the treadmill test might involve an addition risk, were excluded from the study. Also excluded were patients with rest pain and necroses, as well as those with other conditions limiting walking distance, and patients with inflammatory vascular disorders. Within the 4 weeks prior to initiation of the pilot study, and also during the treatment period, surgical and interventional measures, additional walking training, and/or other vasoactive medications were not permitted. All the patients gave their written informed consent to participate in the study. The investigation conforms with the principles outlined in the Declaration of Helsinki.

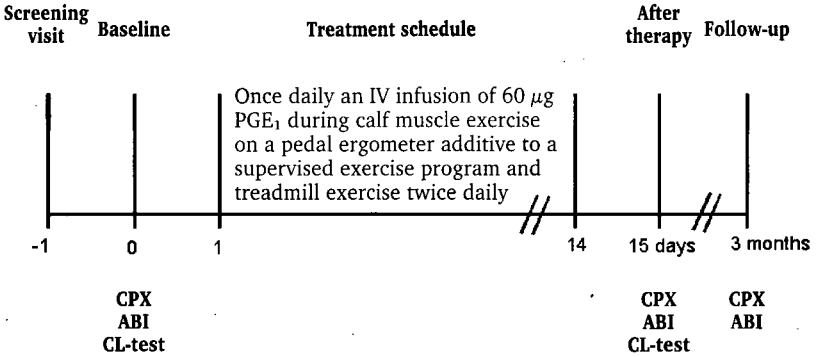

Figure 1. Study design. CPX = cardiopulmonary exercise test; ABI = ankle-brachial systolic blood pressure index; CL-test = constant load test at 3 km/h and 12% grade.

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Table I. SELT-treadmill testing protocol for peripheral arterial occlusive disease.

Stage	Time (sec)	Grade (%)	Speed (km/h)	Work Load (W/kg)	Walking Distance (m)
1	120	3	3.0	0.25	100
2	120	5	3.5	0.50	117
3	120	7	4.0	0.75	133
4	120	8	4.5	1.00	150
5	120	11	5.0	1.50	167
6	120	14	5.0	2.00	167

Testing Protocol

Constant-Load Exercise Test and ABI

At admission, the suitability of the patient for inclusion in the study was tested on the basis of the inclusion and exclusion criteria. For this purpose, initially, a resting ECG and an exercise ECG (75 watts) were obtained. Following a period of familiarization of the patient with the treadmill, the initial (ICD) and absolute (ACD) walking distance at 12% and 3 km/h (constant-load test) were then determined. Preference was given to this treadmill protocol since in a recent study in patients with severe claudication (ACD < 200 m) the constant-load test proved superior to the graded-exercise test with regard to the coefficient of variation.[24] The ankle-brachial index was determined both at rest and after 1 minute of exercise on the treadmill. In the absence of angiographic and/or Duplex ultrasonographic findings, or if such findings were older than 6 months, these examinations were repeated to document the stenoses or occlusions.

Cardiopulmonary Exercise Test (SELT Protocol)

At baseline (see study design, Figure 1), the spiroergometric investigation of the patients suitable for inclusion in the study was carried out under standardized treadmill ergometric loading, and the height and weight of the patients were measured. A maximum incremental exercise test was performed using the SELT protocol[25] (Table I) and the Trackmaster TM-310 treadmill (JAS Fitness System, Pensacola, FL) as a test device. Expired air was sampled continuously using the breath-by-breath technique, and metabolic gas exchange measurements were performed (MedGraphic cardiopulmonary exercise system CPX/D; Medical Graphic Corp, St. Paul, MN). The system was calibrated before each test. The ECG was monitored continuously, and blood pressure measured before and after the exercise test. The patients were instructed to lightly touch the handrail of the treadmill only to maintain balance, and to walk until they could no longer bear the claudication-related pain. For online data processing and reporting, a PC-work station (SCS software packages CPX-D, Predicted Normals, DTD Integration) was used. The following parameters were documented in accordance with the SELT protocol: walking time (sec), work load (W), physical work capacity in % (work load achieved/work load predicted × 100), oxygen uptake (VO_2) in mL/min and VO_2/mL/kg/min, carbon dioxide output (VCO_2) in mL/min, respiratory exchange ratio VCO_2/VO_2 (RER), heart rate (HR) in beats per minute, linear regression

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coefficient "*b*" (ratio of increase in VO_2 to increase in treadmill exercise time), and ratio peak VO_2/peak work load (mL/min/W) as a coefficient of oxygen demand.

To determine capillary blood lactate concentrations, blood samples were taken from the hyperemized ear lobe at rest and 30 sec after the test. Measurements were made using the Accusport portable system.[26] This was followed by a repeated measurement of the systolic arterial pressure at ankle at rest and after exercise, as also, after an adequate period of rest, determination of the initial and absolute walking distance (constant-load test) as described previously.

Treatment Schedule

On the next day, the 2-week period of treatment was begun, during which, every morning, the patient received an intravenous infusion of 60 μg of prostaglandin E_1 (Prostavasin® Schwarz Pharma, Germany) administered over 2 hours during intermittent pedalergometric exercise. Pedalergometry was performed using a pedalergometer manufactured by HWK, Germany (Profitrainer Tübinger Modell), the target frequency being 60–90 cycles/min at a load of 2.5 kg. As soon as claudication pain was experienced, the patient stopped exercising and continued again immediately on disappearance of the pain. Directly after the infusion, the 30-minute standardized physical training program was initiated under supervision. The program comprised loosening up and stretching exercises, walking at varying speeds, tiptoeing, knee bends and balancing exercises. This was followed by training on the treadmill with weekly adaptation of performance to 66% of the absolute walking distance. The training comprised two sessions of exercise separated by a 10-minute pause. The 30-minute exercise program, and the treadmill training were repeated every afternoon. This combined treatment schema involving PGE_1 infusions and training was carried out 5 times a week for 2 weeks. On weekends, the patients received only PGE_1 infusions.

One day after the end of the treatment period, the spiroergometric examination, determination of the ankle-brachial index and the constant-load exercise test were repeated. Thereafter followed a 3-months follow-up period, without test medication and training. At the end of this time, the patient returned to our hospital and again underwent the spiroergometric examination and determination of the ankle-brachial index.

Historical Control

A previous multicenter study[8] with 23 inpatients with intermittent claudication served as a historical control. Inclusion and exclusion criteria, as well as the intensive standardized physical training program, were identical with our study. The only difference was the fact that the 23 patients did not receive additional PGE_1 infusions and that the training program was carried out for 4 weeks. Weekly, the initial and absolute claudication distances were measured. Therefore, a comparison of the data obtained after 2 weeks (as in our study) was possible. We compared the mean change of ICD and ACD between the two groups using the Student's t test for independent samples.

Statistical Analysis

Statistical analyses were performed using the statistical software package SAS® 6.12 under the Microsoft Windows® operating system at the

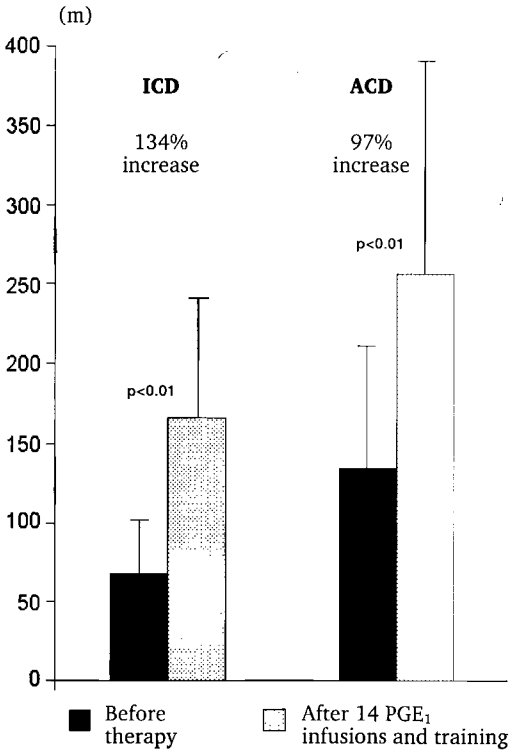

Figure 2. Treadmill exercise test (constant load test at 3 km/h and 12% grade). Initial claudication distance (ICD) and absolute claudication distance (ACD) before and after therapy.

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computer facilities of IFNS GmbH, Germany. In accordance with the study design, mainly descriptive statistical methods were used. Standard descriptive summary statistics were calculated for continuous and categorical variables. In addition, exploratory interferential statistical analyses were carried out: changes from baseline were analyzed with the Wilcoxon signed rank test. Pearson's product-moment correlation coefficient, r, was used to analyze the linear association between two continuous variables.

Results

Constant-Load Exercise Test and ABI

Following the 2 weeks of treatment with a combination of PGE_1 and physical training, the initial walking distance increased significantly by 134% from 71 to 166 meters ($p < 0.01$). The absolute walking distance also showed a significant increase from 132 to 260 meters (97%) (Figure 2). The ankle-brachial index at rest and after exercise remained virtually unchanged, both following treatment and at the end of the follow-up period (Table III).

Comparison of the ICD and ACD with the Historical Control Group

In the previous study receiving an identical training program but without PGE_1[8] which served as a historical control, 21 patients were included into the per-protocol analysis. The ICD increased from 83 to 92 m after 1 week, to 102 m after 2 weeks, to 109 m after 3 weeks, and to 134 m after 4 weeks. The ACD increased from 127 to 145 m after 1 week, to 152 m after 2 weeks, to 167 m after 3 weeks, and to 222 m after 4 weeks.

Regarding a 2-week treatment, the ICD increased only by 23% (from 83 to 102 m) compared with an increase of 134% (from 71 m to 166 m) in our study. The difference between the two groups in mean change of ICD was significant ($p = 0.006$) in favor of the group treated with a combination of training and PGE_1 infusions (see Table II, Figure 3). The difference between the groups with regard to the ACD was significant as well: there was an increase from 132 to 260 m (97%) with training and PGE_1, and from 127 to 152 m (20%) with training only ($p = 0.002$).

Cardiopulmonary Exercise Test

The peak walking time measured during graded exercise using the SELT protocol, showed a significant increase after the 2-week treatment, from 225 to 397 seconds, and reached 421 seconds at the end of the follow-up period (Figure 4). At the same time, peak work load increased significantly by 108%, from 34 W (baseline) to 71 W (after 2 weeks of treatment), and 79 W (follow-up). The improvement in functional capacity was reflected by the significant increase in peak oxygen uptake from 15.7 to 17.3 and 19.1 mL/kg/min, respectively while, at the same time, peak oxygen uptake per work load (peak VO_2/peak work load) decreased significantly by 41% (Figure 5). Overall, there was a significant reduction in the rate of increase in VO_2 during the graded exercise (expressed by the regression coefficient *"b"*

Table II. Difference of ICD and ACD after 2 weeks training with or without PGE_1 compared to baseline.

Parameter	Physical Training With PGE_1, n = 10 (this study)		Physical Training Without PGE_1, n = 21 (historical control, reference 8)		t-test (2-sided)
	Mean	SD	Mean	SD	
ICD (m)	**95**	68	**18**	**29**	$p = 0.006$
ACD (m)	129	79	**25**	**46**	$p = 0.002$

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Table III. Peripheral hemodynamics and treadmill performance at baseline and at 14 days and 3 months after additive intravenous prostaglandin E_1 to supervised exercise training.

	Baseline	14 Days	3 Months
Hemodynamics			
Resting ABI	0.61 ±0.15	0.61 ±0.13	0.67 ±0.09
Postexercise ABI	0.16 ±0.08	0.19 ±0.11	0.20 ±0.10
Cardiopulmonary exercise testing (SELT-protocol)			
Body weight (kg)	72.05 ±9.04	72.40 ±8.50	75.11 ±8.52
Peak walking time (sec)	224.90 ±125.24	396.60 ±122.85**	421.44 ±144.64**
Peak work load (W)	34.10 ±20.20	70.90 ±25.37**	79.33 ±38.43*
PWC (%)	24.40 ±14.89	48.70 ±20.65**	48.11 ±14.79**
Peak VO_2 (mL/kg/min)	15.74 ±4.61	17.26 ±3.82*	19.08 ±4.16*
Peak RER	0.81 ±0.11	0.88 ±0.06*	0.88 ±0.10
Peak VO_2/Peak WL (mL/min/W)	31.64 ±13.05	18.94 ±3.35**	18.37 ±3.43**
Regression coefficient "b"	205.24 ±101.36	93.86 ±23.31**	104.91 ±22.13**
Peak HR (beats/min)	106.30 ±17.66	114.00 ±14.28	115.33 ±23.61
Peak systolic BP (mm Hg)	159.50 ±25.44	155.00 ±30.55	155.00 ±18.71
Peak diastolic BP (mm Hg)	82.50 ±5.40	80.50 ±8.96	80.56 ±10.74
Capillary blood lactate (mmol/L)	2.39 ±0.50	2.69 ±0.66	2.96 ±1.18

Values are mean ± SD. *$p < 0.05$, **$p < 0.01$; ABI: ankle-brachial systolic blood pressure index; PWC (%): physical work capacity (% of predicted); RER: respiratory exchange ratio (ratio of carbon dioxide output to oxygen uptake per unit time); WL: work load; Regression coefficient "b": ratio of increase in VO_2 to increase in treadmill exercise time ($\Delta VO_2/\Delta t$); HR: heart rate; BP: blood pressure.

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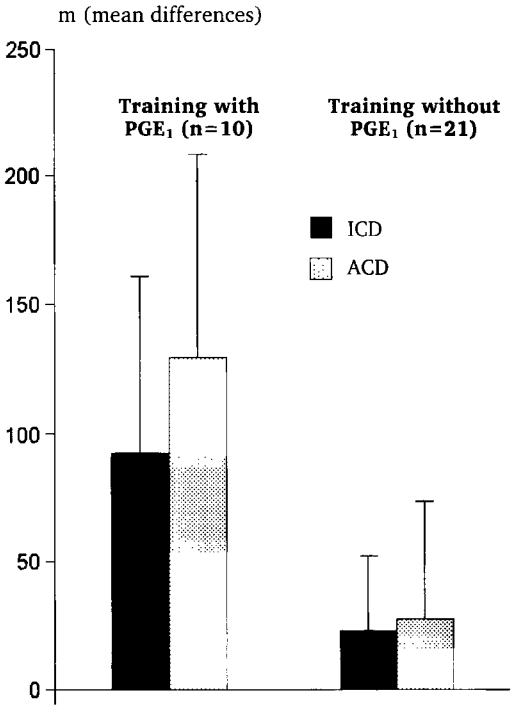

Figure 3. Differences of the initial claudication distance (ICD) and absolute claudication distance (ACD) after 2 weeks training with PGE_1 (this study) or without PGE_1 (historical control[8]) compared to baseline.

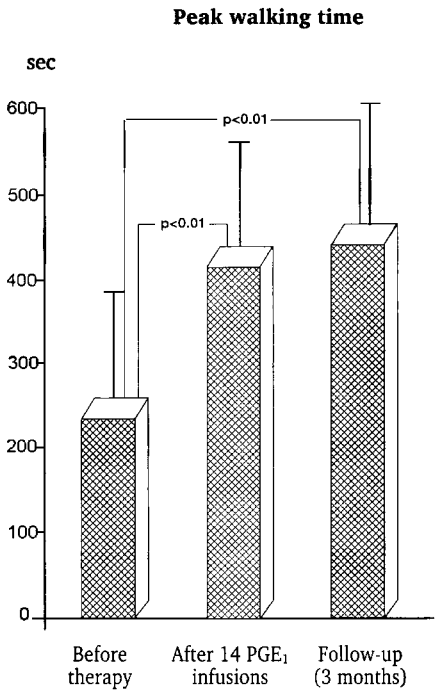

Figure 4. Peak walking time (sec) during cardiopulmonary exercise testing (SELT-protocol, see "Methods" and Table I) before and after therapy and after follow-up.

as ratio of increase in VO_2 to increase in treadmill exercise time)—of 54%. The predicted physical work capacity increased significantly by 100%, from 24 to 49%, and remained unchanged up until the end of follow-up. The peak heart rate and peak blood pressure values, as also capillary blood lactate concentrations showed no significant change. The anaerobic threshold was not reached in any of the cases. All the relevant data are shown in Table III.

Between work load and oxygen uptake, there was a tight correlation with r = 0.94; a good correlation was found between absolute walking distance (graded protocol) and oxygen uptake (r = 0.91). Taking into account the functional classification of Weber,[27] the peak VO_2 clearly reveals that, prior to treatment, most of the patients belonged in functional class C ($VO_{2\ max}$ 10 – 16 mL/kg/min). Following the 2 weeks of treatment and at the end of follow-up, the majority belonged in functional class B ($VO_{2\ max}$ 16 – 20 mL/kg/min) or class A ($VO_{2\ max}$ > 20 mL/kg/min). At baseline, 6 of 10 patients were highly limited in their walking ability; by end of the follow-up period, all the patients showed an improvement in their walking tolerance on the basis of the SELT test criteria (impairment of walking ability in terms of physical work capacity: PWC < 20% = severe claudication; PWC 26%–50% = moderate claudication; PWC 51%–75% = mild claudication/walking through; PWC > 75% = asymptomatic), from Fontaine stage IIb (PWC < 25%) to Fontaine stage IIa (PWC 26%–50%) or better.

During the 2-week examination period, no undesirable effects occurred, neither during PGE_1 treatment nor during training.

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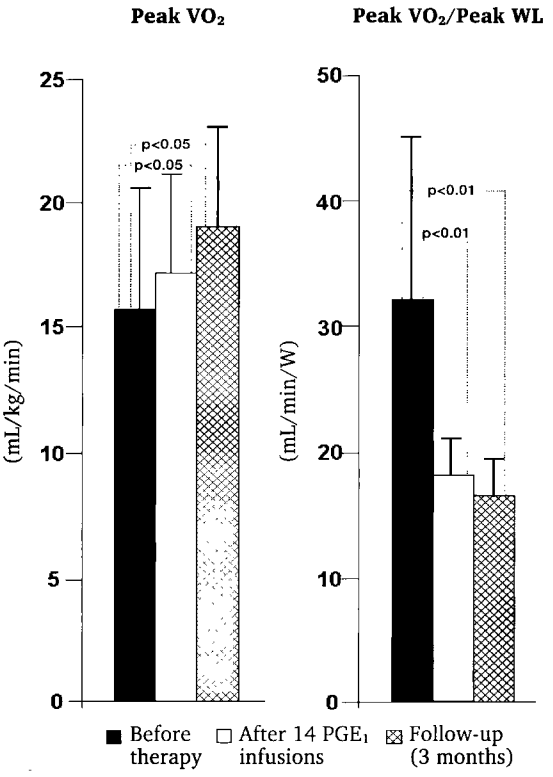

Figure 5. Cardiopulmonary exercise test (SELT-protocol): Improvement of walking efficiency due to a significant increase in peak oxygen uptake (peak VO_2; left figure) and a significant decrease in the ratio of peak oxygen uptake per work load (peak VO_2/peak WL; right figure).

Discussion

Exercise Training

For more than 30 years, exercise training has been recommended to improve walking capacity in patients with intermittent claudication.[12] In the meantime, a considerable number of studies have been carried out, all of which report increases in walking distance, although of varying magnitude. Due to inhomogeneous patient populations, differences in training modalities, differences in the intensity, frequency and duration of such programs, and methodological differences in the determination of walking distances, reported improvements in walking distance have ranged from 44% to 300% (for review, see reference 5). On the basis of a meta-analysis of 21 methodologically widely differing studies on physical training—which, however no longer meet current trial recommendations—Gardner and Poehlmann conclude that an optimal training program needs to be carried out for at least 6 months.[9] It is therefore all the more noteworthy that, in this study, a combination of PGE_1 infusion and physical training achieved—after only 14 days—clinically relevant improvements in walking distance that were comparable with those reported for training programs applied over several months.

Our results are compatible with those reported by Scheffler, who investigated walking distance improvement under supervised intensive physical training with added PGE_1 treatment (IV infusion during pedal ergometry BID) in comparison with physical training alone. An analysis of the results of all the patients (15 per group), showed that, after 4 weeks of treatment in the combined PGE_1/training group, the ICD of 81 m increased by 604%—to 570 m.[23] If patients with an increase in walking distance to more than 1,000 m are excluded, the improvement was still a remarkable 263% after 4 weeks; 90% after 2 weeks. It must, however, be emphasized that Scheffler's study involved an extremely demanding exercise program that was applied twice a day (including weekends) and comprised more than 2 hours of supervised gymnastics and treadmill training as well as 4 hours of pedal ergometry during the infusions.

In contrast, the same 1-hour exercise program employed in our investigation was carried out in the previous multicenter study that served as a historical control.[8] Even the demographic data of the patients were similar to those in our study; thus, a comparison of the results would seem appropriate. The significant difference between the increase in ICD of 134% in the present study and the small increase of 23% in the previous study (without PGE_1) might be explained only by the additive PGE_1 infusion.

Additive PGE_1

Baseline Findings

Due to its vasodilatory, antithrombotic, leukocyte- and endothelium-stabilizing properties, PGE_1 has for years been an integral part of the therapeutic strategy in the treatment of severe peripheral arterial occlusive disease (critical limb ischemia).

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Data from numerous controlled studies are also available for intermittent claudication, showing an increase of 100% in walking distance after, on average, 4 weeks of treatment.[16-22] In most of these studies, a once-daily dose of 60 μg PGE_1 was administered intravenously—a regimen that we also used in our study. On the basis of hemodynamic investigations in patients with intermittent claudication, it is known that intravenously administered PGE_1 at a dose of 60 μg increases limb perfusion by up to 161%. At the same time, the transcutaneous PO_2 and the skin temperature increase significantly.[28] With the exception of the study by Scheffler,[23] PGE_1 was always administered to patients at rest. It therefore appeared expedient to have patients perform muscular exercise during and after PGE_1 infusion while perfusion of the leg was improved. For this purpose, pedal ergometry is eminently suitable, since the patient, comfortably seated, performs muscle exercise for the duration of the 2-hour PGE_1 infusion. It may be assumed that the combination of muscle exercise and simultaneous infusion of PGE_1—a prostanoid that effects not only an increase in blood flow, but also an improvement in the utilization of oxygen and glucose[29]—leads to an enhanced activation of the oxidative capacity of the muscle. Our data obtained during spiroergometry using the SELT test support the hypothesis that the increase in walking distance is related, in part, to a lower metabolic cost of the exercise.[2,30] Thus, all the patients demonstrated not only an increase in walking distance, but also an improvement in cardiopulmonary function, as reflected in all the parameters measured by spiroergometry. There was a high correlation between walking distance and peak oxygen uptake ($r = 0.91$). By the end of the 2-week treatment period, the latter had increased significantly, from 15.7 to 17.3 mL/kg/min. Almost identical data were reported by Hiatt and co-workers after a 12-week training program (15.0 to 16.9 mL/kg/min).[30] While in our study the peak oxygen uptake had increased to 19.1 mL/kg/min by the end of the 3-month treatment-free follow-up, Hiatt and colleagues observed a value of 17.8 mL/kg/min only after 24 weeks of training. Similar figures were also found in a study conducted by Gardner to compare three different exercise protocols, and in an investigation by Regensteiner carried out in patients with intermittent claudication 6 weeks after a bypass operation with regard to peak exercise performance (maximum walking time and peak VO_2).[10,31] Depending on age, lifestyle, and training conditions, similar increases in peak VO_2 can be seen following exercise training of varying duration (between 8 and 26 weeks), even in healthy, elderly persons.[32-38]

In addition, in our study, both the improvement in walking efficiency and oxygen utilization were reflected in a significant change in the profile of VO_2 response to exercise (regression coefficient *"b"*) and a significant decrease in peak oxygen uptake (VO_2) per workload (W). Assuming that the onset of claudication is due to an oxygen demand/delivery mismatch, optimization of the kinetics of oxygen and the lower VO_2 at a given workload may permit longer walking distances before claudication pain stops the activity.

These results are in conformity with earlier findings showing that a substantial part of the training-related improvement in walking tolerance is caused by regional distribution of the available blood flow to the active muscles[39,40] and by increases in local aerobic work capacity that might, in part, be explained by increased oxygen extraction[40,41] and by more effective peripheral oxygen utilization due to metabolic adaptation in leg muscle.[42-44] In addition, an improvement in biomechanical efficiency due to improved coordination of the working muscles, or a decrease of in-between-step intramuscular pressure,[45] which is an important pathophysiological mechanism in intermittent claudication,[10,46,47] has also been demonstrated in our study. Apart from this, and in agreement with other authors,[39,44,46,48] we found no changes in general or arterial hemodynamics capable of explaining the 134% increase in pain-free walking distance.

The use of the SELT protocol developed by us[25] proved advantageous on account not merely of the quantification of the increase in performance, but also of the possibility of eliminating such confounding factors as, for example, changes in body weight, on the determination of walking distance. Since the first load already begins at 0.25 W/kg, the physical work capacity, which correlates positively with oxygen uptake, can be estimated and used as a suitable parameter for assessing the severity of the claudication or the effects of treatment.[49]

Our study has confirmed that patients with intermittent claudication are characterized both a highly restricted functional capacity and a low exercise tolerance. A positive linear correlation has been found between the claudication-limited peak oxygen uptake and impairment of walking performance. A short-term exercise program with additive PGE_1 resulted in an impressively significant improvement in walking performance and

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thereafter in functional exercise capacity. It is probable that the lowering effect on oxygen demand (improved walking efficiency, microcirculatory effects, enhanced oxygen utilization) were first responsible for the 134% increase in ICD and the 97% increase in ACD following treatment. Apparently, following the improvement in the ability to walk seen after 14 days, a further increase in aerobic capacity with a 20% enhancement of peak oxygen uptake occurred after 3 months follow-up. However, none of the patients reached the anaerobic threshold during a task of moderate duration, and the peak work load, peak respiratory exchange ratio (RER) and capillary blood lactate concentrations were lower than in healthy subjects. Neither systolic and diastolic blood pressure nor the heart rate showed any change, so that an unchanged sympathetic nerve activation under peak exercise conditions may be assumed.[46]

Conclusions

It is generally accepted that, in patients with intermittent claudication, the supervised physical training program leads to an improvement in walking capacity. With our treatment regimen comprising intensive supervised training program together with once-daily IV infusions of PGE_1 during pedal ergometry, it has proved possible to increase the pain-free walking distance after only 14 days by an average of 134%, while at the same time improving oxygen uptake and utilization, and thus cardiopulmonary performance. With the aim of checking these positive results, a placebo-controlled trial is currently being undertaken.

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