Beneficial effects of exercise beyond the pain threshold in intermittent claudication

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Key words:
Ergometric stress test; Exercise; Peripheral vessels; Quality of life.

Background. **The quality of life and autonomy may be severely hampered in patients with intermittent claudication, but the amputation rate is very low. Supervised exercise training is effective, but still very rarely employed. Many authors think that in these patients exercise over the pain threshold may be dangerous. The aim of this study was to assess whether supervised, 3-month duration, 3 times/week, beyond the pain threshold exercise training is safe and whether it improves both the performance and quality of life in patients with claudication.**

Methods. **Forty-three patients with claudication, confirmed at Doppler study and/or angiography, have been evaluated by means of graded treadmill testing, the ankle-brachial pressure index at rest and after walking and a Walking Impairment Questionnaire before and after 3 months of treadmill training beyond the claudication threshold.**

Results. **Patients showed an 86% increase in time to onset of claudication pain ($p < 0.00001$), a 50% increase in total walking time ($p < 0.000001$) and improved questionnaire scores of pain intensity (+56%, $p < 0.005$), distance covered (+87%, $p < 0.005$), speed (+42%, $p < 0.05$), and stair climbing (+25%, p = NS). The basal and post-exercise ankle-brachial pressure index was not modified by training. Analysis of all subgroups of patients (</> 65years of age, with/without coronary artery disease and diabetes mellitus, pre-training time to onset of claudication pain </> 3 min, with angiographic/Doppler occlusion or stenosis) revealed a statistically significant increase in both time to onset of claudication pain and total walking time.**

Conclusions. **Supervised physical training beyond the claudication threshold significantly improves the walking time and quality of life of patients with claudication.**

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Introduction

Atherosclerosis often manifests as peripheral arterial disease (PAD). One and a half percent of the general population < 50 years, 20% of those > 75 years and 50% of those > 85 years are affected[1-4]. Fortunately symptoms (mainly intermittent claudication) are much less frequent but when they occur, both the quality of life and patient autonomy may be severely hampered[5,6]. Intermittent claudication may be a marker not only of isolated PAD but also of generalized atherosclerosis[7]. In such patients the risk of cardiac and cerebrovascular events is high. Thirty percent of patients with intermittent claudication die within 5 years of the onset of symptoms owing to myocardial infarction or cerebrovascular accidents, a 2- to 4-fold increase in mortality compared with subjects of the same age and sex[6,8]. Surgical revascularization involves a definite risk and its results are not always entirely satisfactory[9]. Percutaneous transluminal angioplasty, though generally effective, particularly in patients with aortoiliac involvement[10,11], and much better tolerated, is beneficial, in most cases, only in the short term[12-15]. Moreover, neither of these therapeutic approaches significantly improves the total cardiovascular mortality. Therefore they are indicated only in patients with ischemic symptoms not ameliorated by conservative treatments[16].

Many studies have shown that in Fontaine stage 2 patients rehabilitative treatment (exercise plus risk factor modification)[7,17,18] improves the results of functional tests and the quality of life and may even lower the total cardiovascular mortality. In particular, treadmill training has been shown to increase both the time to onset of claudication pain (CPT) and the total walking time (TWT)[19-22]. However, hitherto published studies have been performed on small series of patients, often without Doppler or angiographic confirmation of PAD and using different testing and training schedule protocols[23]. In most trials the exercise intensity has been kept well under the claudication threshold for fear of exacerbating ischemia and causing inflammation[2,19,24]. In contrast, a recent randomized study comparing exercise, surgical revas-

cularization and no treatment failed to show any benefit of the first[25].

Moreover, in most trials the constant load approach instead of graded testing has been employed, with loss of reproducibility[26,27]. Besides, patients with coronary artery disease or diabetes mellitus have often been excluded, so that for such subjects the benefits of rehabilitation remain uncertain.

We have attempted to quantify the benefits of a beyond claudication pain threshold physical training in Fontaine stage 2 patients, many with coronary artery disease and diabetes mellitus, by means of graded treadmill testing and a validated quality of life questionnaire.

Methods

Patients. Between May 1998 and March 2002, 43 consecutive patients with Fontaine stage 2 mono or bilateral intermittent claudication lasting at least 6 months, all on antiaggregant treatment, were enrolled in our trial. All patients gave their written informed consent to both testing and training. Doppler testing was performed on each patient and peripheral arterial angiography in 24 (total: 33 limbs). In this subgroup the iliac artery was involved in 3 limbs of 3 patients (stenoses in 2 and total occlusion in 1), the common or superficial femoral in 28 limbs of 19 patients (stenoses in 9 and occlusion in 19) and only the popliteal artery in 2 limbs of 2 patients (occlusion in both). In 17 patients only submitted to Doppler evaluation, the common or superficial femoral artery was involved in 25 limbs (stenoses in 13 and occlusion in 12).

Patients with chronic obstructive pulmonary disease, heart failure, orthopedic ailments or simply incapable of walking at 2 mph (3.2 km/hour) were not included in our trial. Patients with coronary artery disease under full drug treatment were included only after testing their full tolerance to adequate training workloads. One patient with a mechanical aortic prosthesis and bivasal coronary artery disease was excluded because of the onset of heart failure manifesting after 10 sessions. One patient (age 84 years) was not included owing to his inability to accurately describe the onset and severity of claudication in the post-training test. Eleven patients (27%) had diabetes mellitus (3 were on insulin therapy), 24 (59%) systemic hypertension, 31 (76%) high serum cholesterol levels, and 25 (61%) coronary artery disease (previous myocardial infarction in 9, coronary bypass in 7, both previous myocardial infarction and previous coronary bypass in 3, previous percutaneous coronary angioplasty in 2, and angiographic evidence of coronary disease in 4). Four patients had been previously submitted to surgical revascularization of the lower limbs, 7 to percutaneous transluminal angioplasty and 1 to both procedures.

The study design is summarized in figure 1.

Testing. All patients were submitted to pre- and post-training graded treadmill tests (Hiatt protocol: constant speed of 3.2 km/hour and an increasing slope from 0 to 17.5% at 3-min intervals) with continuous ECG monitoring and 12-lead recording at 1-min intervals. For this purpose, a Q5000 computerized system was employed. The blood pressure was recorded using a sphygmomanometer at the beginning and at the end of each stage. The termination criteria were those suggested in the American College of Cardiology/American Heart Association guidelines[28] or the development of a pain score of 7-8 according to the Borg 10-point nonlinear scale. Whenever these criteria were not met the test was arbitrarily stopped after 35 min (7th min of stage 7). In the absence of intermittent claudication in the post-training test, the CPT was assumed to be equal to the TWT. Only patients with a < 25% difference in the TWT and CPT in two consecutive pre-study tests have been enrolled in our trial[29]. Whenever a > 25% difference between the first and the second test was observed a third test was performed and the patient was enrolled only if the difference between the second and the third was < 25%.

Whenever bilateral claudication was present (17 patients), the CPT was analyzed in two different ways: by the patients (taking into account the limb with the earlier onset) and by the single limb (for a total of 58 limbs).

In accordance with Hiatt et al.[26], the pre- and post-training Walking Impairment Questionnaire (WIQ) was delivered to all the patients who were asked to describe

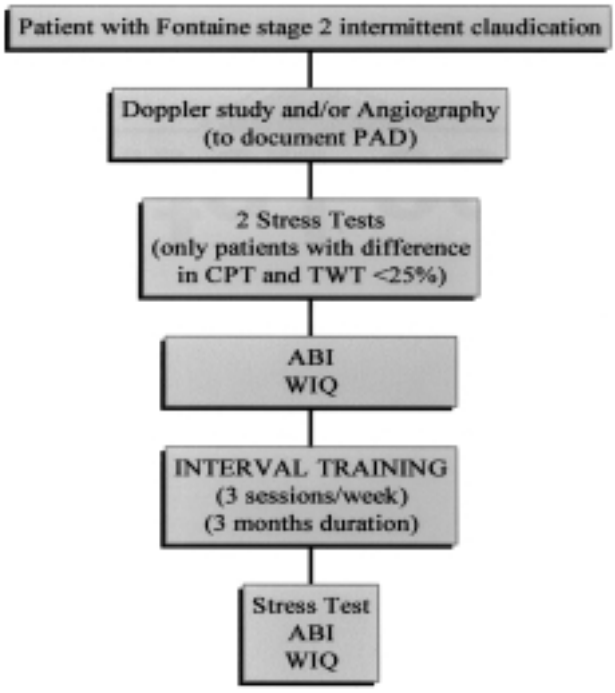

Figure 1. *Study design. ABI = ankle-brachial pressure index; CPT = time to onset of claudication pain; PAD = peripheral arterial disease; TWT = total walking time; WIQ = Walking Impairment Questionnaire.*

their performance on the basis of a scale ranging from 0% (inability to perform because of severe intermittent claudication) to 100% (no impairment at all).

The ankle-brachial pressure index was measured at rest and after 5 min of walking at 3.5 km/hour on a 12% slope and at 3, 6 and 9 min of recovery.

Only patients enrolled after November 30, 1999 were asked to fill in the WIQ and had their ankle-brachial index measured.

Training. During a period of 3 months patients exercised on average 3 times/week with a total of 34 ± 6 sessions per patient. Each session consisted of 4-5 bouts, separated by intervals of at least 5 min and each lasting 8-10 min, of supervised walking on a treadmill under telemetric control. The first bout was generally low intensity, while the following were titrated on the basis of the previous stress test. The speed or treadmill slope (as the patients themselves preferred) was increased at each stage in order to reach the target of Borg 4-6 pain. Heart rate and blood pressure were recorded at baseline, at each bout and at the end of the sessions. Patients with coronary artery disease were never allowed to train at heart rates over the ischemic threshold (defined as the heart rate at which a 1 mm horizontal or downsloping ST-segment depression occurring 80 ms after the J point became recordable).

Subjects were instructed to walk outside the hospital setting for at least 30 min each day.

Endpoints. In accordance with the Transatlantic Conference guidelines[29] we assumed as the primary endpoint an increase in the TWT. The prolongation of CPT and the improvement in quality of life were considered as secondary endpoints. Subgroups have been defined according to age, the presence or absence of coronary artery disease, the presence or absence of diabetes mellitus, a pre-training CPT </> 3 min, and the presence of occlusion or stenosis at angiographic and Doppler examination.

Statistical analysis. The distribution of all variables was tested for normality using the one-sample Kolmogorov-Smirnov test. Paired two-tailed Student's t-tests were used to analyze ergometric parameters. The Wilcoxon signed rank test for paired data has been used to analyze changes in the ergometric parameters with a non-normal distribution, the differences in the Borg scores during stress testing and data regarding the WIQ.

All values have been reported as mean ± SD. A p value of < 0.05 was considered statistically significant. The correlation between patient age with the ΔCPT and the ΔTWT (CPT and TWT post-training change) was analyzed using the Pearson's linear correlation test, after having confirmed that the distribution of such data was normal. Statistical analyses were performed using the SPSS software for Windows, release 11.0.0, 2001 (SPSS Inc., Chicago, IL, USA).

Results

Primary endpoints. In the 41 patients who completed the training the TWT increased by 50% ($p < 0.000001$) (Fig. 2). Moreover, 2 patients did not have intermittent claudication at all at the end of the training period.

Secondary endpoints. The CPT increased by 86% ($p < 0.00001$) and by 100% ($p < 0.000001$) when analyzed by patients and by single limbs respectively (Fig. 2).

The WIQ was delivered to 22 patients at the beginning and at the end of the training period. With the exception of the stair climbing ability, all parameters showed statistically significant improvements (Fig. 3). In this particular subgroup the CPT and TWT respectively increased by 96 and 51%.

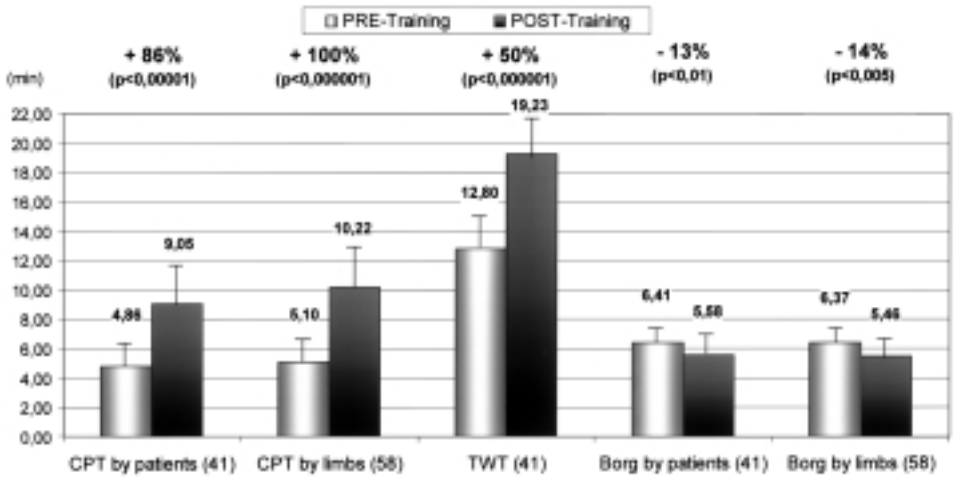

Figure 2. *Pre- and post-training time to onset of claudication pain (CPT), total walking time (TWT) and Borg scores (the number of patients or limbs is indicated between parenthesis).*

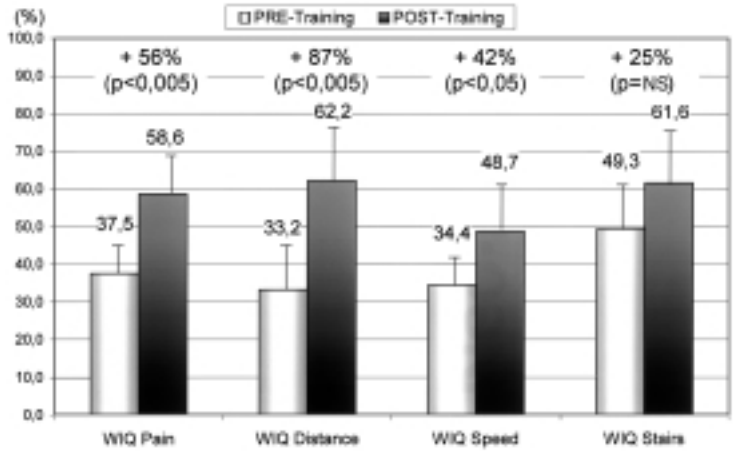

Figure 3. *Pre- and post-training scores on the basis of the Walking Impairment Questionnaire (WIQ).*

Other results and subgroup analysis. The variations in the common ergometric parameters are summarized in table I. Pain intensity at maximal work dropped by 13% ($p < 0.01$) and 14% ($p < 0.005$) if related respectively to patients or single limbs (Fig. 2).

With reference to the primary and secondary endpoints as defined above, we decided to arbitrarily classify patients into three groups: 1) responders (R): patients with a 3-min and at least a 30% increase in the TWT; 2) partial responders (PR): patients with a 3-min and at least a 30% increase only in the CPT; 3) non-responders (NR): patients with less than a 3-min or less than a 30% increase in the TWT or CPT. Sixty eight percent of patients fell in the R category, 15% in the PR, and 17% in the NR category.

The increase in the CPT or TWT was by no means related to age ($r = -0.28$ and $r = -0.002$) and to the number of training sessions ($r = 0.13$ and $r = 0.004$). In patients with angiographic occlusion (22 limbs in 18 patients) a 126% increase in the CPT was recorded while patients with stenosis (11 limbs in 9 patients) showed a 163% increase in this parameter (p = NS occlusion vs stenosis). When patients with occlusion (12 limbs in 7 patients) and stenosis (13 limbs in 7 patients) at Doppler examination were added to patients with angiographic evaluation, no statistically significant differences were found (122 and 168% increase in the CPT respectively).

A statistically significant increase in the CPT and TWT was observed in patients </> 65 years, with or without coronary artery disease or diabetes mellitus and in patients with a pre-training CPT </> 3 min (Fig. 4).

At no time interval (rest, after walking and at 3, 6 and 9 min of recovery) was the ankle-brachial index, measured in 22 patients, modified by training.

Discussion

The aim of treatment of patients with PAD is to improve the ambulatory function and quality of life, stopping or retarding the evolution of disease in critical is-

Table I. Ergometric parameters before and after 3 months of interval training.

	Pre-training	Post-training	Difference (%)	p
Basal				
HR (b/min)	69 ± 17	67 ± 14	-2	NS
BP (mmHg)	143 ± 18	140 ± 20	-2	NS
DP (b/min*mmHg)	99 ± 29	94 ± 25	-5	NS
Stage 2				
HR (b/min)	93 ± 18	83 ± 15	-11	< 0.001
BP (mmHg)	171 ± 24	159 ± 24	-7	< 0.05
DP (b/min*mmHg)	161 ± 47	133 ± 35	-17	< 0.0005
Maximal work				
HR (b/min)	110 ± 20	111 ± 21	1	NS
BP (mmHg)	197 ± 28	207 ± 29	5	NS
DP (b/min*mmHg)	218 ± 61	231 ± 57	6	NS
%CPT	3.2 ± 4.0	8.2 ± 5.6	153	< 0.0001
%TWT	11.8 ± 4.4	16.3 ± 2.6	39	< 0.0001

BP = blood pressure; CPT = time to onset of claudication pain; DP = double product; HR = heart rate; TWT = total walking time.

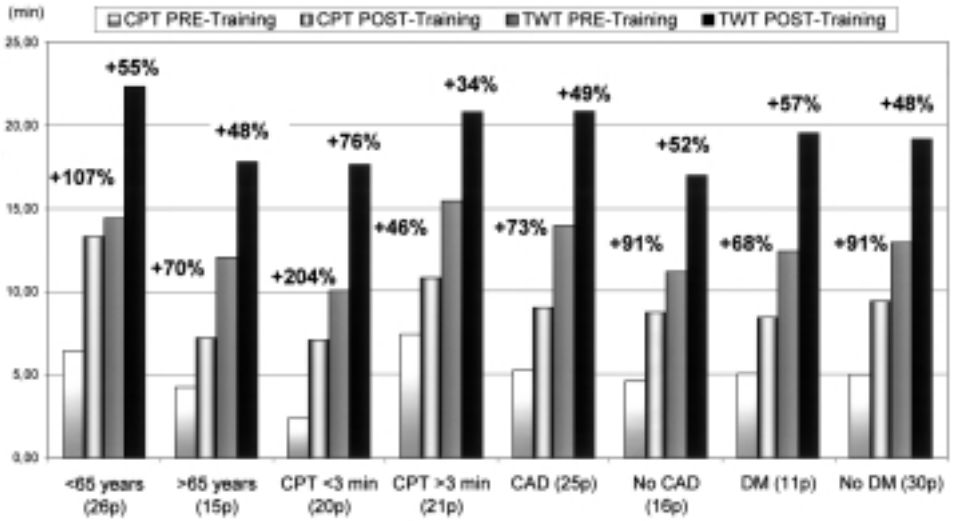

Figure 4. *Pre- and post-training time to onset of claudication pain (CPT) and total walking time (TWT) in the different subgroups of patients (the number of patients is indicated between parenthesis). CAD = coronary artery disease; DM = diabetes mellitus.*

chemia (with the necessity of limb amputation), and also to reduce mortality due to myocardial infarction or cerebrovascular disease. Exercise is considered as the most effective means of increasing walking autonomy in patients with intermittent claudication. Several mechanisms are involved in this process: 1) peripheral blood flow redistribution, 2) inhibition of the progression of atherosclerosis, 3) favorable hematologic alterations, 4) metabolic changes, 5) changes in muscle cell morphology, and 6) an increased pain threshold[30,31]. Nevertheless, this kind of treatment is not yet widespread. This may be due to the low number of patients studied and to the unfavorable attitude of vascular surgeons, radiologists and interventionists who generally defend what they consider a "decisive" form of treatment. Exercise is often prescribed as a last resort measure for patients not amenable to surgery or percutaneous transluminal angioplasty and in such cases only as a plain "walk more" advice in place of strictly supervised exercise (which most trials have already shown to be advantageous)[32-34]. Many authors suspect that exercise beyond the pain threshold might worsen blood flow or that ischemia might induce the inflammation-mediated progression of atherosclerosis[2,35]. In fact, neutrophil activation[36], inflammatory protein release such as thromboxane A_2[37], leukotrienes and endothelial damage markers such as von Willebrand factor[37,38], free radical release[39] and an enhanced glomerular endothelium with ensuing microalbuminuria[40] have all been shown to occur in this context. On the other hand, the reduction of such phenomena as well as the reduction of erythrocyte aggregation have also been proven with continuing exercise.

Gallasch et al.[41] demonstrated, after 2 months of physical training, a decrease in blood viscosity, with a decrease in the erythrocyte-aggregation tendency, and a significant simultaneous improvement in erythrocyte filterability. Tisi et al.[42] observed a fall in renal albumin excretion after exercise in trained subjects. Brendle et al.[43] have shown an improved endothelial function in the arm after 6 months of training at an intensity higher than the claudication threshold. Womack et al.[44] have recently shown that repeated bouts of symptom-limited exercise cause a significant improvement of the fibrinolytic profile by lowering the serum levels of plasminogen activator inhibitor and by increasing tissue plasminogen activator levels up to 1 hour following exercise. Enhanced angiogenesis (as revealed by the mitotic activity of endothelial cells) has also been shown in rats[45].

Clinical evidence too favors beyond the pain threshold exercise training. In their 1993 review, Ernst and Fialka[46] concluded that exercise is effective only if high intensity, supervised and prolonged for at least 2 months. In 1995 Gardner and Poehlman[19] and in 1999 Cachovan[20], in two meta-analyses respectively including 21 trials and 125 publications, demonstrated that exercise was most beneficial when its intensity approximated maximal pain, its duration was at least 30 min and when it was performed at a frequency of at least 3 times/week and for sufficiently prolonged periods.

Another reason why supervised exercise has not become widespread as a form of treatment for PAD is the reigning uncertainty about long-term results. Only a few studies have been published on this subject[33,47,48].

Comparison between our and previous trials. A number of studies on this subject have been published in recent years. In a recent meta-analysis Girolami et al.[21] revised several trials and distinguished them into level 1 (double-blind randomized), level 2 (randomized) and level 3 (non-randomized). These authors found no study of level 1, 6 level 2 studies and 4 level 3 studies. Leng et al.[22] revised 10 studies in which a to-

tal of less than 250 patients had been tested, showing a significant improvement in claudication after 6 months of training with respect to antiaggregant therapy and angioplasty. While, generally speaking, most trials have confirmed the beneficial effects of exercise in PAD, a great variability in outcomes has been observed. Such variability may be due to the differences in patient selection, testing protocols (constant load with different speed and slope vs graded load), duration, frequency and intensity of training[19,20,23]. Most successful ones were usually assessed by means of constant load stress tests, showing improvements up to 150% in the TWT and CPT[20]. Jones et al.[49], in a series of 6 patients evaluated by means of both the constant load and graded stress tests, showed that improvement in the CPT and TWT after training appeared greater with the first test.

Moreover, the literature review of Hiatt et al.[26] has shown a 30-45% variability index in constant load testing vs a 15-25% in graded tests. In 1999 the Transatlantic Conference, though affirming that both constant load and graded exercise testing protocols may be used in evaluating outcomes, gave its preference to graded tests as they allow better differentiation, greater reproducibility in patients able to walk only short distances and also the elimination of the walk-through phenomenon in successive stages[29].

Hiatt et al.[50], using the same protocols we have employed, reported a 165% increase in the CPT and a 123% increase in the TWT, results apparently greater than ours. However, they studied younger patients with the onset of claudication at the first stage of treadmill testing. If, in our series (20 patients), we consider the patients with a CPT ≤ 3 min, a 204% increase vs the 165% increase reported by Hiatt et al. was shown, while the lesser increase in the TWT (76 vs 123%) may be explained by the higher mean age (71 vs 61 years). This is in agreement with the findings of other authors who also noted greater benefits in younger patients[51,52]. The improvements in our series were uniformly distributed in all the subgroups of patients and were independent of the angiographic lesion type (occlusion or stenosis).

The results of ergometric testing are also concordant with the WIQ which shows an improvement in pain, walking distance and speed, while only the increase in stair climbing ability did not reach statistical significance. Recently, Wullink et al.[53] and Gardner et al.[54] could not show any improvement using the same questionnaire (which however did not reach statistical significance) in spite of significant increases in the CPT and TWT as revealed by graded treadmill testing. We therefore think that a questionnaire on the quality of life is always mandatory in this kind of trials.

Study limitations. Our study lacks a control group and consequently randomization. A randomized study would be possible only if one finds enough subjects willing to form part of a control group. Most of our patients wanted "something" to be done. Enrolment of patients with claudication lasting at least 6 months, with PAD confirmed at Doppler or angiography and with an increase in the TWT and CPT < 25% in two basal treadmill graded tests, allowed us to study a homogeneous series of stable subjects. Randomized studies employing a graded treadmill and training schedules similar to ours[50,54] have shown that, within 3-6 months, in the control group the PCT and TWT improvements did not exceed, in the most favorable cases, 20-25% which is much less than in the patients who underwent rehabilitation programs in our study.

Owing to the lack of a direct comparison it is impossible to state whether the same results may be achieved with more prolonged but below threshold pain exercise.

In conclusion, supervised physical training beyond the claudication threshold significantly improves the walking time and quality of life of patients with claudication.

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