Intermittent Claudication—Surgical Reconstruction or Physical Training?

A Prospective Randomized Trial of Treatment Efficiency

FREDRIK LUNDGREN, M.D., PH.D., ANN-GRET DAHLLÖF, M.D., PH.D.,* KENT LUNDHOLM, M.D., PH.D., TORE SCHERSTÉN, M.D., PH.D., and REINHARD VOLKMANN, M.D., PH.D.†

From the Department of Surgery, Rehabilitation Medicine and Clinical Physiology,† Sahlgrenska Sjukhuset, University of Göteborg, Göteborg, Sweden*

This study reports the initial evaluation of treatment efficiency in 75 patients with intermittent claudication who were randomized to three treatment groups: 1) reconstructive surgery, 2) reconstructive surgery with subsequent physical training, and 3) physical training alone. Before treatment, there were no statistically significant differences between the groups in age, sex, smoking habits, symptom duration of claudication, ankle-arm blood pressure quotient (ankle-index), maximal plethysmographic calf blood flow, symptom-free and maximal walking distance, the history of other atherosclerotic manifestations or in the medical treatment. The walking performance was improved in all three groups at follow-up 13 ± 0.5 months after randomization. Surgery was most effective, but the addition of training to surgery improved the symptom-free walking distance even further. In pooled observations of the three groups, age, symptom duration, and a history of myocardial ischemic disease correlated negatively with walking performance after treatment. In the operated group, the duration of claudication and a history of myocardial ischemic disease correlated negatively with the walking performance. This was not the case when patients were censored if limited by other symptoms than intermittent claudication after treatment. In the trained group, the duration of claudication correlated negatively to symptom-free and maximal walking distance. Ankle-index and maximal plethysmographic calf blood flow after treatment and the change of these variables with treatment correlated positively with both symptom-free and maximal walking distance when results were pooled for all patients. Although this mainly was a consequence of the improved blood flow after surgery, the change of maximal plethysmographic calf blood flow also correlated with symptom-free but not with maximal walking distance in the trained group. The results demonstrate that, compared with physical training alone, operation alone or in combination with subsequent training are superior treatment modalities in patients with intermittent claudication.

SEVERAL RETROSPECTIVE STUDIES, both from the era when arterial reconstruction was not generally available[1-4] and more recently,[5-7] have estimated that the risk for limb loss in patients treated conservatively for intermittent claudication is not more than 2–8% during a follow-up period of 2–8 years. The chance of spontaneous improvement of symptoms was also fairly good. In addition to the relative benign natural course of intermittent claudication with respect to limb loss, the risk of perioperative complications from associated cardiovascular disease in these patients,[8] as well as the risk to life in the long run,[9] has been pointed out. Therefore, a conservative approach in the treatment of patients with claudication as only symptom have been emphasized. Studies from the late 1960s have further suggested that, in patients with claudication, exercise can increase the distance that the patient is able to walk,[10,11] and a wealth of literature has evolved dealing with the possible mechanisms behind the effect of training in such patients.[12-21] Irrespective of which mechanisms are responsible for the improved walking performance after conservative treatment including physical training, the need for operation can be eliminated in a large number of patients.[22] Thus, arguments for conservative treatment of intermittent claudication are based on the relatively benign natural course, the general and local risks associated with reconstructive surgery,[23] and the positive effects of physical training. However, the efficiency of conservative treatment in arterial insufficiency with respect to symptom-relief compared with that of reconstructive arterial surgery has not been evaluated in a controlled way.

Therefore, the purpose of this study was to evaluate the relative merits of two treatment modalities in three combinations: reconstructive arterial surgery, supervised physical training, and the combination of both in the treatment of patients with intermittent claudication.

Reprint requests and correspondence: Fredrik Lundgren, M.D., Ph.D., Surgical Clinic, Vrinnevei, Sjukhuset 560182, Norrköping, Sweden.

Submitted for publication: August 9, 1988.

Patients and Methods

Seventy-five patients with intermittent claudication were randomly allocated to two types of standard treatment—arterial surgical reconstruction and supervised physical training—in three combinations: 1) reconstruction without physical training (Op), 2) reconstruction combined with physical training (Op + Train), and 3) physical training without reconstructive surgery (Train).

The patients were re-examined after at least 6 months of treatment. The duration of the arterial insufficiency was more than 6 months in all patients. All patients were handicapped in their professional or social life by claudication when they entered the study. Patients with a maximal walking performance of more than 600 m and those with rest pain, ischemic ulcers, or a blood pressure of the first toe below 30 mmHg were not admitted into the study. Also, patients younger than 40 years of age and those older than 80 years of age were not accepted.

Experimental Protocol

The patients were recruited from our out-patient clinic. A vascular surgeon decided whether the patients were suitable for the study by means of a preliminary evaluation based on the disease history and the results of the bedside investigation, including ankle-arm blood pressure quotient (ankle-index).[24] The patients were then referred to the vascular laboratory for a complete investigation with tests of walking performance on a treadmill (speed of 4 km/hour and slope of 0°). Their walking ability was presented as symptom-free (SFWD) and maximal walking distance (MWD). The patients' ability to exercise on a bicycle ergometer including ECG was registered.[25] Maximal blood flow of the calf after ischemic exercise measured with strain gauge plethysmography (PMBF)[26] and blood pressure of the first toe (BPFT)[27] were registred. If the results from the vascular laboratory confirmed the diagnosis of moderate to severe intermittent claudication (typical pain, consistent pattern of PMBF and ankle-index in response to the treadmill test, MWD $\leq$ 600 m and BPFT $\geq$ 30 mmHg) the vascular surgeon entered the patient in the study after having obtained informed consent. The patients were randomized to one of the three treatment groups with help of an algorithm described by Pocock and Simon,[28] accounting for the distribution of sex, age, and diabetes. The patients randomized to the surgery group underwent operation, the purpose of which was to eliminate hemodynamically important arterial obstructions above the knee level. Thrombendarterectomy, synthetic Y-graft, or bypass with saphenous vein or expanded polytetrafluoroethylene graft was used. The training program was comprised of three sessions per week of dynamic leg exercise beyond the appearance of leg pain due to arterial insufficiency. The training sessions, supervised by a physiotherapist, lasted for 30 minutes, and the patients were also encouraged to perform the exercises during their leisure-time. The patient group randomized to receive combined treatment started their training 6 weeks after the last operation. The minimum training period was 6 months. Re-examination was done 6–12 months after the start of treatment and included patient history, clinical investigation, measurement of ankle-index, and a second visit to the vascular laboratory for measurement of the maximal plethysmographic calf blood flow, BPFT, SFWD, and MWD.

Statistics

Data are presented as mean ± SEM. Comparison between two independent samples was made using Mann-Whitney's U test; comparison of more than two independent samples was made using Kruskall-Wallis' nonparametric analysis of variance (ANOVA); and comparison between two dependent samples was made using Wilcoxon's matched pairs signed-ranks test.[29] Differences between categoric data in the treatment groups were tested with Fisher's distribution-free permutation test.[30] Several surgically treated patients were limited by symptoms other than intermittent claudication after treatment. Therefore, life table technique was used to estimate the effect of different treatments on walking performance. The influence of different covariates on the walking performance was tested using the logrank technique.[31,32] When testing for statistical significance, $p \leq 0.05$ was chosen. Not statistically significant is abbreviated NS.

Ethics

Informed consent was obtained from all subjects. The study was approved by the Committee for Ethics in Medical Investigations, University of Göteborg.

Results

Clinical Characteristics

The mean age of the patients was 64 ± 0.9 years, and the mean duration of the intermittent claudication was 25 ± 3.3 months. Twenty-one per cent of the patients were women and 93% were smokers. Several patients had a history of other diseases associated with atherosclerosis and intermittent claudication, such as diabetes (8%), angina pectoris (25%), myocardial infarction (19%), hypertension (31%), cardiac insufficiency (7%), and transient ischemic attacks (3%), but they were not limited in their performance by factors other than intermittent claudication. The medical treatment of the patients were digitalis (11%), β-blockers (32%), Ca-blockers (5%) and diuretics (21%). Except for having atherosclerotic diseases, they were in good general health, without any signs of renal

TABLE 1. *Clinical Data for Patients with Intermittent Claudication in the Randomized Treatment Groups Before Treatment (mean ± SEM)**

	Treatment Groups			
Data	Op	Op + Train	Train	Significance
Number	25	25	25	
Age (years)	64 ± 2	63 ± 2	64 ± 1	NS
Duration (months)	28 ± 6	21 ± 5	26 ± 6	NS
Ankle-index	0.55 ± .03	0.59 ± .02	0.59 ± .03	NS
BPFT (mmHg)	58 ± 4	58 ± 5	55 ± 3	NS
PMBF (ml/100 ml/min)	14.8 ± 1.5	15.2 ± 1.6	16.7 ± 1.7	NS
SFWD (m)	85 ± 6	70 ± 7	67 ± 7	NS
MWD (m)	209 ± 20	180 ± 20	183 ± 22	NS

* Statistically differences between the groups where tested with Kruskall-Wallis' nonparametric ANOVA.

PMBF = Maximal blood flow after ischemic exercise evaluated with strain-gauge venous occlusion plethysmography.

or hepatic insufficiency. The mean hemoglobin concentration was 148 ± 1.3 g/L, the platelet particle concentration was 266 × 10^9 cells/l, and the serum creatinine concentration was 88 ± 2.4 μmol/l. The SFWD and MWD were 74 ± 3.8 m and 191 ± 11.9 m, respectively. Ankle-index, BPFT, and maximal plethysmographic calf blood flow of the most symptomatic leg were 0.58 ± 0.02 mmHg, 57±2 mmHg, and 15.6 ± 0.9 ml/100 ml/min, respectively. Forty-seven per cent of the patients had the atherosclerotic lesion of the most symptomatic leg below the inguinal ligament, 41% had the atherosclerotic lesion above the ligament, and 12% had combined lesions.

There were no statistical differences among the three randomized treatment groups regarding the distributions of age, duration of the disease, ankle-index, BPFT, maximal plethysmographic calf blood flow, SFWD, and MWD (Table 1). In addition, there were no statistically significant differences among the groups in the distribution of the location of the atherosclerotic lesions, nor in the concentrations of hemoglobin, platelets, creatinine, triglycerides, and cholesterol; there were also no statistically significant differences in the distribution of diabetes, angina pectoris, myocardial infarction, hypertension, cardiac insufficiency, and transient ischemic attacks in the history of the patients, nor in the medical treatment with digitalis, β-blockers, Ca-blockers, and diuretics.

Treatment Compliance and Follow-up

The mean time from randomization to follow-up were 12.6 ± 0.9, 15.2 ± 0.8, and 11.2 ± 0.6 months ($p \leq 0.01$) in the operated (Op), the combined (Op + Train) and the training group (Train), respectively (Table 2). In the group with combined treatment, the longer observation time after randomization was due to the more complicated treatment protocol of this group. Thus, these patients had to wait until they had undergone one or more operations before they could start their training program. Two pa-

TABLE 2. *Subjects Lacking Compliance in the Three Treatment Groups and the Availability of Complete Results at Follow-up*

Group	Patient No.	Compliance Complications	Complete Follow-up
Op	8	Emergency operation for aortic dissection—died of myocardial infarction after 1 week	No
	20	Improved after randomization—no surgery	No
	33	Died 6 months after surgery before follow-up in cerebral apoplexy	No
	62	Unsuitable for surgery except at lower leg level—shifted to training group	No—unable to participate in treadmill testing
Op + Train	3	Refused training after surgery	Yes
	7	Refused training after surgery	Yes
	15	Never treated due to unhealed venous ulcer	No
	24	Improved after randomization—no surgery	No
	48	Unable to train due to cardiac failure	Yes
	55	Died 4 months after surgery in cardiosclerosis	No
Training	6	Developed multiple sclerosis and was never treated for intermitent claudication	No—unable to participate in treadmill testing
	29	Refused training after operation for severe ischemia	Yes
	39	Trained after operation for severe ischemia	Yes
	49	Never treated: claudication was rejected by angiography	No
	51	Developed cardiac failure and was unable to train	No—unable to participate in treadmill testing

The subjects are identified with their randomization numbers.

tients never underwent operations, and complete data at the follow-up were not available for four patients of Op group. Five patients of the Op + Train group were not treated according to the protocol, and complete follow-up data were not available for three of these patients. Four patients of the Train group never started their treatment according to the protocol, and follow-up data for these patients are incomplete.

Operations

Fifty-eight operations were performed in 48 patients (the two patients in the group treated with physical training who underwent operation for limb-threatening ischemia and the patient who underwent emergency operation for aortic dissection are included). Twenty-six of these operations were performed on the aorta and iliac arteries, and 32 were performed on the femoro-popliteal level. Of the 48 patients who underwent operations, 26 underwent reconstructive surgery on the aortoiliac level, 25 on the femoro-popliteal level, three on both levels, and 23 bilaterally.

Complications

Within the first month of surgery, we had to evacuate wound hematomas in three patients, perform thrombectomy in three patients perform re-reconstructive surgery in three patients (Table 2). In two patients, myocardial infarction developed. The emergency case of aortic dissection already had an infarction when the operation was performed. One patient received a pulmonary emboli within 1 month after surgery. Except for the patient who underwent operation for an aortic dissection and died, all of these patients experienced full recovery despite their complications. Later, two of the patients who had undergone operations had reoperations, and two patients died before follow-up. In two of the patients who were randomized to the training group, limb-threatening ischemia developed, and these patients underwent operation. In another two patients, severe cardiac insufficiency developed, and therefore these patients were unable to receive training. However, there were no observed complications caused directly by the physical training.

Hemodynamic Effects

All three groups improved their maximal plethysmographic calf blood flow significantly with treatment (Fig. 1). The improvements were 7.6 ± 1.5, 9.9 ± 2.4, and 3.0 ± 1.2 ml/100 ml/minute for the Op, Op + Train, and Train groups, respectively. The improvement in the trained group was statistically significant even when grouping was based on actual treatment. Two of these patients underwent operation when they limb-threatening ischemia developed after randomization. When the patients were tested, the overall difference for the improvement between groups was also statistically significant ($p \leq 0.02$); however, the difference between the Op group and the Op + Train group was insignificant. The overall difference of the change in ankle-index and BPFT between the groups were also statistically significant ($p \leq 0.0001$). In the Train group, these last two variables did not change with treatment.

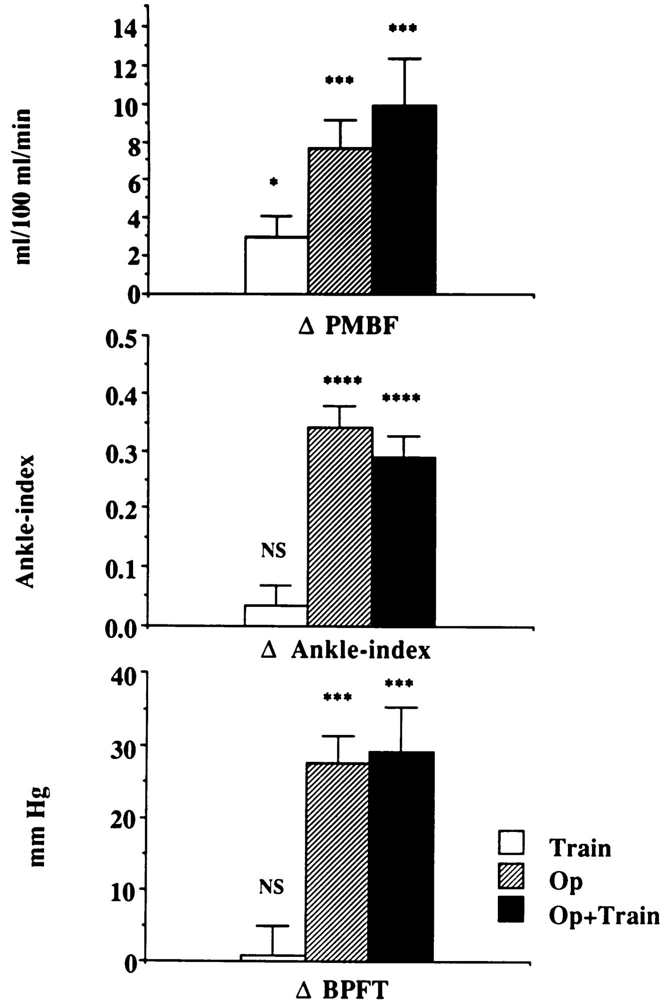

FIG. 1. The change in hemodynamic variables with treatment in the different groups. Grouping is based on randomization (*i.e.*, treatment of intention). Δ Ankle-index = change in ankle-arm blood pressure quotient, Δ BPFT = change in blood pressure of the first toe and Δ Plet = change in maximal calf blood flow measured with strain gauge plethysmography. Data refer to the most symptomatic leg.

*$p \leq 0.05$, ***$p \leq 0.001$, and ****$p \leq 0.0001$, with Wilcoxon's matched pairs signed-ranks test.

Walking Performance

Walking performance was improved in all three groups (Figs. 2–5). In the Op, Op + Train, and Train groups, the changes in SFWD were 320 ± 78, 489 ± 81, and 120

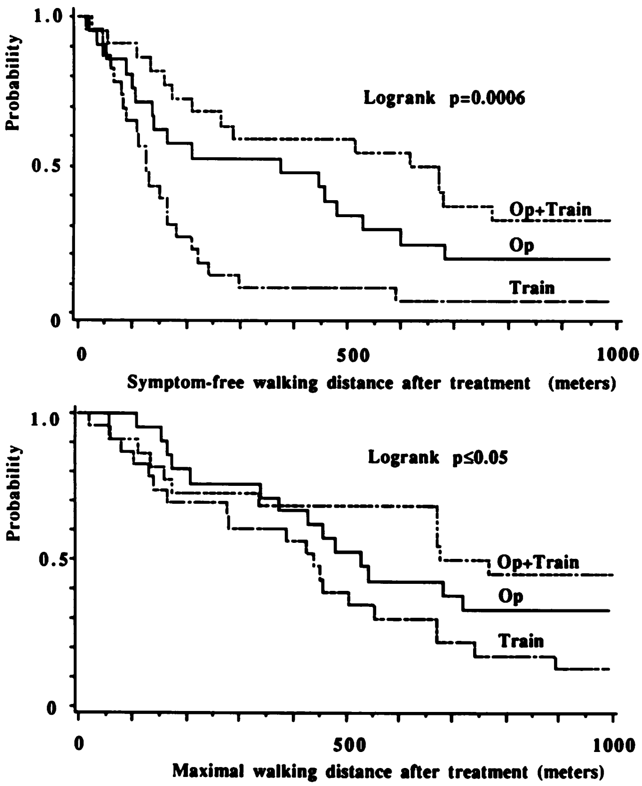

FIG. 2. Life table representation of the symptom-free and maximal walking performance after different treatments. Grouping is based on randomization (*i.e.*, treatment of intention). All causes of limited walking performance were included. Logrank test was used for the comparison.

± 47 m, respectively, and the changes in MWD were 361 ± 73, 474 ± 81, and 276 ± 66 m, respectively. The impression that the MWD/SFWD in the trained group is higher than in the other two groups is explained by the fact that the treadmill test was interrupted after 1000 m.

Several of the surgically treated patients were limited by symptoms other than intermittent claudication at the follow-up, and the life table technique was therefore used in the analysis. Walking performance was analyzed separately based on treatment of intention (randomized group) and actual treatment (actual group) and with and without right censoring of patients limited by other symptoms than intermittent claudication or walking more than 1000 m after treatment. When grouping of the patients was based on treatment of intention and no censoring was used, SFWD was ≥ 600 m in 30% of the patients of the Op group, in 55% of those of the Op + Train group, and in 5% of those of the Train group; MWD was ≥ 600 m in 45% of the patients of the Op group, in 70% of those of the Op + Train group, and in 30% of those of the Train group (Fig. 2). When grouping of the patients was based on treatment of intention and right censoring was used, SFWD was ≥ 600 m in 55% of the patients of the Op group, in 90% of those of the Op + Train group, and in 5% of those of the Train group; MWD was ≥ 600 m in 75% of the patients of the Op group, in 95% of the Op + Train group, and in 35% those in the Train group (Fig. 3). When grouping of the patients was based on actual treatment and no censoring was used, SFWD was ≥ 600 m in 30% of the patients of the Op group, in 60% of those of the Op + Train group, and in 0% of those of the Train group; MWD was ≥ 600 m in 50% of the patients of the Op group, in 70% of those of the Op + Train group, and in 25% of those of the Train group (Fig. 4). When grouping of the patients was based on actual treatment and right censoring was used, SFWD was ≥ 600 m in 55% of the patients of the Op group, in 95% of those of the Op + Train group, and in 0% of those of the Train group; MWD was ≥ 600 m in 80% of the patients of the Op group, in 95% of those of the Op + Train group, and in 25% of those of the Train group (Fig. 5). For compliance data see Table 2.

Covariates to Walking Performance After Treatment (Actual Treatment)

Overall analysis. Age of the patient, duration of the disease, and a history of myocardial ischemic disease cor-

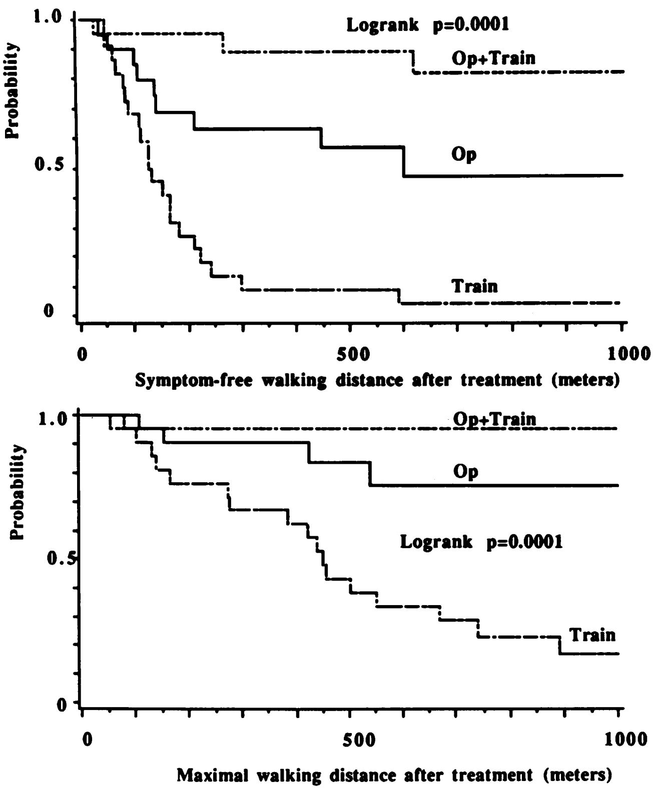

FIG. 3. Life table representation of the symptom-free and maximal walking performance after different treatments. Grouping is based on randomization, (*i.e.*, treatment of intention). Subjects limited by other symptoms than intermittent claudication and those who walked further than 1000 m were right censored. Logrank test was used for the comparison.

related negatively to both SFWD and MWD after treatment (Table 3). Age had no significant influence on the walking performance when patients limited by symptoms other than claudication or those with a walking capacity of more than 1000 m on the treadmill were censored. Diabetes, sex, and the location of the atherosclerotic lesions had no significant influence on the walking performance. Ankle-index after treatment,Δ ankle-index, and Δ PMBF were positively correlated to SFWD, and ankle-index after treatment was positively correlated to the minimal walking distance. When censoring was used, however, ankle-index and maximal plethysmographic calf blood flow after treatment and Δ ankle-index and Δ PMBF were all positively correlated to walking performance (p = 0.01–0.0001).

Analysis within the treatment groups (Table 4–6). In the Op group, duration of the disease and a history of myocardial ischemic disease were negatively correlated to walking performance (p = 0.03–0.0001). When censoring was used, however, these variables had no significant influence on walking performance. In the Op + Train group, ankle-index after treatment was positively correlated to MWD when censoring was used, but no other factor was associated with walking performance in this group. In the Train group, the duration of the disease was negatively correlated to walking performance irrespective of censoring, and Δ PMBF was positively correlated to the SFWD.

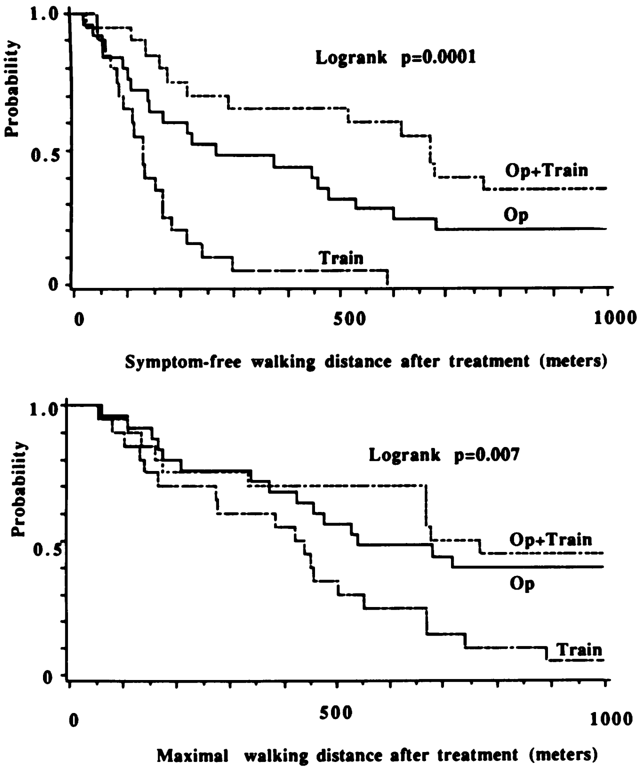

FIG.4. Life table representation of the symptom-free and maximal walking performance after different treatments. Grouping is based on actual treatment. All causes of limited walking performance were included. Logrank test was used for the comparison.

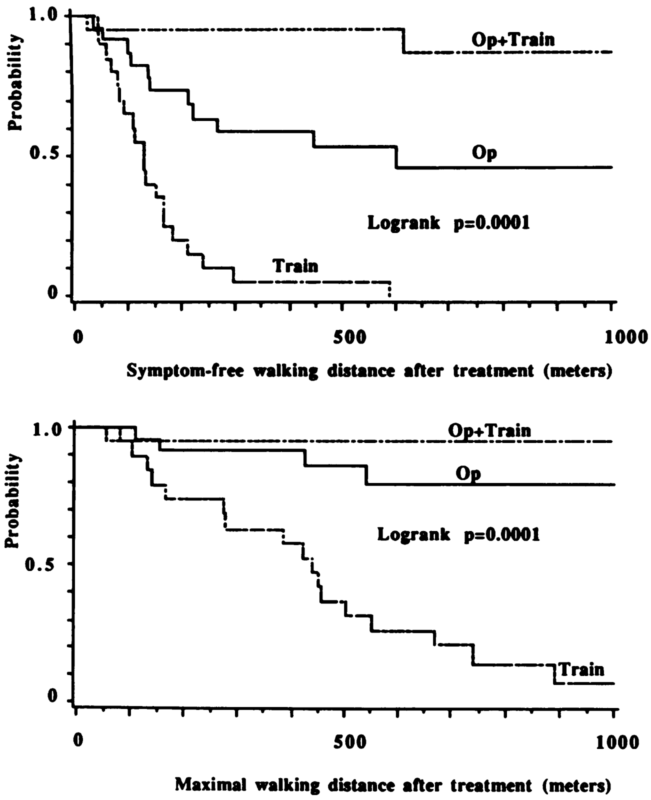

FIG. 5. Life table representation of the symptom-free and maximal walking performance after different treatments. Grouping is based on actual treatment. Patients limited by symptoms other than intermittent claudication and those who walked further than 1000 m were right censored. Logrank test was used for the comparison.

A separate analysis showed that the initial walking performance had no influence on the walking performance after treatment—neither in the overall analysis nor in the different treatment groups.

Discussion

This controlled study has evaluated the effectiveness of three different treatment modalities on the walking performance of patients with well-established intermittent claudication after 6–12 months of treatment. Reconstructive surgery, physical training, and the combination of both increase both the SFWD and the MWD. Surgical treatment of intermittent claudication provided the best relief of symptoms but was also associated with more complications. The addition of physical training to surgery increased the SFWD even further, but none of the measured hemodynamic variables could explain this improvement. Several of the surgically treated patients were limited after treatment by symptoms (mainly of cardiopulmonary origin) other than intermittent claudication and could therefore not fully benefit from the improved

TABLE 3. *The Correlation of SFWD and MWD with Age, Duration of Intermittent Claudication, History of Myocardial Ischemic Disease (MID), Diabetes, Sex, Level of the Artherosclerotic Lesion, Ankle-Index (Ankle-Arm Blood Pressure Quotient), Maximal Plethysmographic Calf Blood Flow After Ischemic Exercise (PMBF) After Treatment, ΔAnkle-Index, and ΔPMBF*

	SFWD				MWD			
	No censoring		Censoring		No Censoring		Censoring	
Variable	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†
Age	0.02	–	NS		0.01	–	NS	
Duration	0.02	–	0.05	–	0.002	–	0.01	–
MID	0.02	–	0.05	–	0.008	–	0.02	–
Diabetes	NS		NS		NS		NS	
Sex	NS		NS		NS		NS	
Lesion level	NS		NS		NS		NS	
Ankle-index	0.05	+	0.0001	+	0.05	+	0.0001	+
PMBF	NS		0.01	+	NS		0.001	+
ΔAnkle-index	0.05	+	0.0001	+	NS		0.0001	+
ΔPMBF	NS		0.003	+	NS		0.01	+

* Logrank test.
† Direction of the association.
Calculations were performed on all treated patients with complete follow-up after treatment. Censoring was done if the patient was limited by symptoms other than intermittent claudication or walked more than 1000 m on the treadmill.

limb blood flow. The treatment results are influenced by old age, the duration of the disease, and a history of myocardial ischemic disease, but are not substantially influenced by diabetes, the location of the atherosclerotic lesion, and sex.

The subjects in this study represent a group of patients with well-established moderate-to-severe intermittent claudication who were referred to our surgical unit for evaluation. They are probably representative of patients actively seeking advice for intermittent claudication; however,they may also represent a selected group of patients with more severe symptoms than patients have overall. Great care was taken to obtain comparable treatment groups. In addition to the equality between the groups with regard to sex, age, and diabetes, which was a result of the balanced randomization, there were no statistically significant differences in the duration of the disease, ankle brachial blood pressure quotient, maximal plethysmographic calf blood flow, and walking performance among the groups before treatment. The distribution of associated atherosclerotic diseases and the medical treatment of the patients were also without statistically significant differences.

Although there were no statistically significant differences in the treatment compliance among the groups, it appears as though surgery was the treatment that was the most easy to fulfill, followed by physical training, which demanded continuous encouragement of the patients in

TABLE 4. *The Correlation of SFWD and MWD with Age, Duration of Intermittent Claudication, History of Myocardial Ischemic Disease (MID), Diabetes, Sex, Level of the Artherosclerotic Lesion, Ankle-Index (Ankle-Arm Blood Pressure Quotient), Maximal Plethysmographic Calf Blood Flow After Ischemic Exercise (PMBF) After Treatment, ΔAnkle-Index, and ΔPMBF*

	SFWD				MWD			
	No censoring		Censoring		No Censoring		Censoring	
Variable	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†
Age	NS		NS		NS		NS	
Duration	0.03	–	NS		0.02	–	NS	
MID	0.02	–	NS		0.0001	–	NS	
Diabetes	NS		0.01	–	NS		NS	
Sex	NS		NS		NS		0.02	+(males)
Lesion level	NS		NS		NS		NS	
Ankle-index	NS		0.05	+	NS		NS	
PMBF	NS		NS		NS		NS	
ΔAnkle-index	NS		NS		0.02	+	NS	
ΔPMBF	NS		0.0001	+	NS		0.04	+

* Probability for random association with the logrank test.
† Direction of the association.
Calculations were performed on patients actually in the Op group with complete follow-up after treatment. Censoring was done if the patient was limited by symptoms other than intermittent claudication or walked more than 1000 m on the treadmill.

TABLE 5. *The Correlation of SFWD and MWD with Age, Duration of Intermittent Claudication, History of Myocardial Ischemic Disease (MID), Diabetes, Sex, Level of the Artherosclerotic Lesion, Ankle-Index (Ankle-Arm Blood Pressure Quotient), Maximal Plethysmographic Calf Blood Flow After Ischemic Exercise (PMBF) After Treatment, ΔAnkle-Index and ΔPMBF*

	SFWD				MWD			
	No Censoring		Censoring		No Censoring		Censoring	
Variable	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†
Age	NS		NS		NS		NS	
Duration	NS		NS		NS		NS	
MID	NS		NS		NS		NS	
Diabetes	NS		NS		NS		NS	
Sex	NS		NS		NS		NS	
Lesion level	NS		NS		NS		NS	
Ankle-index	NS		NS		NS		0.03	+
PMBF	NS		NS		NS		NS	
ΔAnkle-index	NS		NS		NS		NS	
ΔPMBF	NS		NS		NS		NS	

* Probability for random association with the logrank test.
† Direction of the association.
Calculations were performed on patients actually treated with reconstructive surgery and training with complete follow-up after treatment. Censoring was done if the patient was limited by symptoms other than intermittent claudication or walked more than 1000 m on the treadmill.

order to motivate them. Some patients found the treatment with physical training to be time-consuming, and younger patients found it difficult to combine with an active professional life. The more complicated combined treatment was sometimes difficult to carry out, especially in those patients who had achieved excellent results after surgery. Even if operative surgery was readily applied, it was also the type of treatment associated with most complications, including death in one patient (although this patient underwent operation for aortic dissection as an emergency), whereas no complications were directly attributable to the training treatment.

As a consequence of the removal of the arterial obstructions, in the two groups of patients who underwent operation, the ankle-index increased towards normal at the end of the study. The improved ankle-index was reflected by a 70–80% increased maximal plethysmographic calf blood flow and a 50% increased BPFT. However, in the group subjected to training only, there were no significant changes in the ankle-index or the BPFT, but there was a moderate (30%) and significant improvement of the maximal calf blood flow. Walking performance was significantly improved by all three therapies, as measured by both SFWD and MWD. Several of the patients who had undergone operations walked completely unlimited by claudication, but were nevertheless registered with a MWD of 1000 m. This fact explains the smaller differences among the groups in the maximal walking performance compared with the symptom-free performance.

From the comparison of Figures 2 and 3, it is evident

TABLE 6. *The Correlation of SFWD and MWD with Age, Duration of Intermittent Claudication, History of Myocardial Ischemic Disease (MID), Diabetes, Sex, Level of the Artherosclerotic Lesion, Ankle-Index (Ankle-Arm Blood Pressure Quotient), Maximal Plethysmographic Calf Blood Flow After Ischemic Exercise (PMBF) After Treatment, ΔAnkle-Index and ΔPMBF*

	SFWD				MWD			
	No Censoring		Censoring		No Censoring		Censoring	
Variable	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†	p-value*	Sign†
Age	NS		NS		NS		NS	
Duration	0.02	–	0.02	–	0.03	–	0.01	–
MID	NS		NS		NS		NS	
Diabetes	NS		NS		NS		NS	
Sex	NS		NS		NS		NS	
Lesion level	NS		NS		NS		NS	
Ankle-index	NS		NS		NS		0.03	+
PMBF	NS		NS		NS		NS	
ΔAnkle-index	NS		NS		NS		NS	
ΔPMBF	0.02	+	0.02	+	NS		NS	

* Probability for random association with the logrank test.
† Direction of the association.
Calculation were performed on patients actually in the Train group with complete follow-up after treatment. Censoring was done if the patient was limited by symptoms other than intermittent claudication or walked more than 1000 m on the treadmill.

that, at the follow-up, several patients in the groups treated with surgery were limited by symptoms other than intermittent claudication. Despite the fact that most of these patients had an almost normal ankle-index after treatment, they were unable to fully benefit from the improved calf blood flow and were instead limited in their walking performance by cardiac and pulmonary factors of importance for their general physical fitness. This finding was not a consequence of differences in treatment compliance, as is evident from the comparison of Figures 4 and 5, illustrating walking performance after actual treatment, which reveals the same pattern. This observation underlines the importance of a careful selection of patients for surgery to avoid unnecessary risks to life and limb in those who can not fully benefit from surgery.[33] Although cardiopulmonary factors seem most important in this respect, making a prediction for any given individual is difficult, and further studies are needed to develop exact criteria for the selection procedure of such patients. However, the efficiency of reconstructive surgery in the treatment of intermittent claudication in patients unlimited by other factors is evident (Figs. 3 and 5). When patients limited by other symptoms than intermittent claudication were censored, the probability of an unlimited maximal walking performance was 75–95% in the Op group, compared with only 10–20% in the Train group. The probability of an unlimited symptom-free walking performance in patients treated with surgery alone was 50%, as compared to 85% in those who had supplemental training. The influence of the surgical treatment on the walking performance is illustrated by the overall analysis of covariates associated with SFWD and MWD (Table 3). Especially when patients limited by symptoms other than intermittent claudication are censored, ankle-index and maximal plethysmographic calf blood flow after treatment, as well as the change with treatment of these variables, had a highly statistically significant influence on the treatment results.

Even if the substantially improved blood flow and ankle-index in the Op group explain the good results achieved by these patients, it is not evident why the addition of physical training to surgery or physical training alone improve the walking performance. In a subgroup of the patients in the present study, we analyzed glycolytic and mitochondrial enzyme activities in the calf muscle tissue before and after treatment.[34] Increased activities of cytochrome-c-oxidase, citrate synthetase and 3-OH-acyl-CoA-dehydrogenase were found. This metabolic adaptation was positively correlated with the maximal walking performance. In the Op group, the metabolic adaptation was reversed, and in the Train group, the activity of cytochrome-c-oxidase was further augmented, whereas the initially high activity of cytochrome-c-oxidase was maintained in the group with combined treatment. The increased activity of cytochrome-c-oxidase in the Train group was positively correlated with the improvement in symptom-free walking performance. Thus, improved local muscle metabolism with an increased oxidative capacity may explain why physical training improves the walking performance. In physically trained patients, the improved calf blood flow also seems to have some importance, but it is not clear if this is mainly a consequence of an increased collateralization[12] or whether it is due to a redistribution of the available blood flow to the ischemic muscles.[14]

In the present study, we found age, sex, a history of myocardial ischemic disease, diabetes, and the level of the arteriosclerotic lesion to have no influence on the success of physical training. This is in line with the findings of Ekroth et al.,[22] who found no differences in walking performance after training between patients with and without diabetes, nor between those with lesions above and those with lesions below the inguinal ligament. However, Jonason et al.[35] found significantly inferior results after patients with coronary insufficiency underwent training, and in a study where patients with coronary heart disease were excluded, they found that ankle-index was positively correlated to SFWD as well as to MWD after treatment, whereas the symptom duration was negatively correlated with SFWD.[36] They concluded that the possibility of predicting the success of training in individual patients was limited.

The durability of the present results are important. Uncertain long-term patency is also one reason for controversy regarding the advisability of femoro-popliteal surgery in patients with intermittent claudication,[37] whereas the indications for aortic and iliac surgery appear to be more established. However, although several studies of the 5-year patency after aorto-iliac as well as femoro-popliteal surgery in patients with intermittent claudication have reported encouraging results,[37-39] it is not known whether this also is associated with good functional results in the long-run. After conservative treatment with physical training, the risk of limb loss seems small, even in the long-run;[22,40] nevertheless, the durability of the training results with respect to symptom relief is not very well-known.

In conclusion, the results of this controlled study demonstrates that, compared with physical training alone, arterial reconstruction alone or in combination with subsequent training gives superior SFWD and MWD in patients with intermittent claudication. These results refer to a mean follow-up of 13 months after randomization in all treated groups. The improvement in the Op group was probably due to the significantly higher calf blood flow and ankle blood pressure after operation.

References

1. Juergens JL, Barker NW, Hines EA. Arteriosclerosis obliterans: review of 520 cases with special reference to pathogenic and prognostic factors. Circulation 1960; 21:188–195.
2. Singer A, Rob C. The fate of the claudicator. Br Med J 1960; 2:633–636.
3. Bloor K. Natural history of arteriosclerosis of the lower extremities. Ann R Coll Surg Engl 1961; 28:36–52.
4. Taylor GW, Calo AR. Atherosclerosis of arteries of lower limbs. Br Med J 1962; 29:507–510.
5. Imparato AM, Kim GE, Davidson T, Crowley JG. Intermittent claudication: its natural course. Surgery 1975; 78:795–799.
6. Wilson SE, Schwartz I, Williams RA, et al. Occlusion of the superficial femoral artery: what happens without operation. Am J Surg 1980; 140:112–118.
7. Cronenwett JL, Warner KG, Zelenock GB, et al. Intermittent claudication. Current results of nonoperative management. Arch Surg 1984; 119:430–436.
8. Peabody CN, Kannel WB, McNamara. Intermittent claudication: surgical significance. Arch Surg 1974; 109:693–697.
9. Sladen JG, Gilmour JL. Fate of claudicants after femoropopliteal vein bypass: prospective, long-term follow-up of 100 patients. Can J Surg 1985; 28:401–404.
10. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. Lancet 1966; 2:1093–1096.
11. Skinner JS, Strandness DE. Exercise and intermittent claudication II. Effect of physical training. Circulation 1967; 36:23–29.
12. Broomé A, Cederlund J, Eklöf B. Spontaneous recovery in intermittent claudication. Scand J Clin Invest 1967; 99 (suppl):157–159.
13. Alpert JS, Larsen OA, Lassen NA. Exercise and intermittent claudication: blood flow in the calf muscle during walking studied by Xenon-133 clearance method. Circulation 1969; 24:353–359.
14. Zetterquist S. The effect of active training on the nutritive blood flow in exercising ischemic legs. Scand J Clin Lab Invest 1970; 25:101–111.
15. Holm J, Björntorp P, Scherstén T. Metabolic activity in human skeletal muscle. Effect of peripheral arterial insufficiency. Eur J Clin Invest 1972; 2:321–325.
16. Bylund A-C, Hammarsten J, Holm J, Scherstén T. Enzyme activities in skeletal muscle from patients with peripheral arterial insufficiency. Eur J Clin Invest 1976; 6:425–429.
17. Sörlie D, Myhre K. Effects of physical training in intermittent claudication. Scand J Clin Invest 1978; 38:217–222.
18. Hammarsten J, Bylund-Fellenius A-C, Holm J, et al. Capillary supply and muscle fiber types in patients with intermittent claudication: relationships between morphology and metabolism. Eur J Clin Invest 1980; 10:301–305.
19. Henriksson J, Nygaard E, Andersson J, Eklöf B. Enzyme activities, fibre types and capillarization in calf muscles of patients with intermittent claudication. Scand J Clin Lab Invest 1980; 40:361–369.
20. Clyne CAC, Mears H, Weller RO, O'Donell TF. Calf muscle adaptation to peripheral vascular disease. Cardiovasc Res 1985; 19:507–512.
21. Elander A, Sjöström M, Lundgren F, et al. Biochemical and morphometric properties of mitochondrial populations in human muscle fibres. Clin Sci 1985; 69:153–164.
22. Ekroth R, Dahllöf A-G, Gundevall B, et al. Physical training of patients with intermittent claudication: indications, methods and results. Surgery 1978; 84:640–643.
23. Jamieson CW, Clyne CAC. The fate of the ischemic limb. *In* PN Yu, JF Goodwin, eds. Progress in Cardiology. No 7. Philadelphia: Lea and Febiger, 1978; 219–228.
24. Sumner DS, Strandness DE. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. Surgery 1969; 65:763–771.
25. Nordenfelt J, Adolfsson L, Nilsson JE, Olsson S. Reference values for exercise tests with continuous increase in load. Clin Physiol 1985; 5:161–172.
26. Sivertsson R, Hansson L. Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. Cli Sci Mol Med 1976; 51:77–79.
27. Gundersen J. Diagnosis of arterial insufficiency with measurement of blood pressure in fingers and toes. Angiology 1971; 22:191–196.
28. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31:368–375.
29. Siegel S. Nonparametric Statistics for the Behavioral Sciences. New York: MacGraw-Hill, Inc., 1956.
30. Bradley JV. Distribution-free statistical tests. Englewood Cliffs, New Jersey: Prentice Hall, 1968.
31. SAS User's Guide: Statistics, Version 5 ed. Cary, North Carolina: SAS Institute Inc., 1985.
32. Cox DR, Oakes D. Analysis of Survival Data. London: Chapman and Hall, 1984.
33. Jamieson C. Surgical treatment of vascular disease. London: William Heinemann Medical Books Limited, 1982.
34. Lundgren, Dahllöf, Scherstén, Bylund-Fellenius. Muscle enzyme adaptation in patients with peripheral arterial insufficiency: spontaneous adaptation, effect of different treatments and consequences on walking performance. Clinical Science 1989; (accepted for publication).
35. Jonason T, Jonzon B, Ringqvist I, Öman-Rydberg A. Effect of physical training on different categories of patients with intermittent claudication. Acta Med Scand 1979; 206:253–258.
36. Jonason T, Ringqvist I. Prediction of the effect of training on walking tolerance in patients with intermittent claudication. Scand J Rehab Med 1987; 19:47–50.
37. Sonnenfeld T. Reconstructive vascular surgery for intermittent claudication. Acta Med Scand 1982; 212:145–149.
38. Watt JK, Gillespie G, Pollock JG, Reid W. Arterial surgery in intermittent claudication. Br Med J 1974; 1:23–26.
39. Cutler BS, Thompson JE, Kleinsasser LJ, Hempel GK. Autologous saphenous vein femoropopliteal bypass: analysis of 298 cases. Surgery 1976; 79:325–331.
40. Jonason T, Ringqvist I. Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication. Acta Med Scand 1985; 218:27–33.