Eur J Vasc Endovasc Surg 30, 164–175 (2005)
doi:10.1016/j.ejvs.2005.03.011, available online at http://www.sciencedirect.com on SCIENCE DIRECT

Improvement of the Walking Ability in Intermittent Claudication due to Superficial Femoral Artery Occlusion with Supervised Exercise and Pneumatic Foot and Calf Compression: A Randomised Controlled Trial

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Objectives. *To compare the effect of unsupervised exercise, supervised exercise and intermittent pneumatic foot and calf compression (IPC) on the claudication distance, lower limb arterial haemodynamics and quality of life of patients with intermittent claudication.*
Methods. *Thirty-four eligible patients with stable intermittent claudication were randomised to IPC (n=13, 3 h/d for 6 months), supervised exercise (n=12, three hourly sessions/week for 6 months) or unsupervised exercise (n=9). In each patient, initial claudication distance (ICD), absolute claudication distance (ACD), resting ankle brachial pressure index (ABPI), and resting hyperaemic calf arterial inflow were measured before, 6 weeks, 6 months and 1 year after randomisation. Quality of life was assessed with the short form (SF)-36, walking impairment (WIQ) and intermittent claudication questionnaires (ICQ).*
Results. *Compared with unsupervised exercise, both IPC and supervised exercise, increased ICD and ACD, up to 2.83 times. IPC increased arterial inflow ($p<0.05$ at 6 weeks) and ABPI. Supervised exercise decreased arterial inflow and increased ABPI ($p<0.05$ at 6 months). Unsupervised exercise had no effect on arterial inflow or ABPI. IPC improved significantly the ICQ score and the speed score of the WIQ, while supervised exercise improved the WIQ claudication severity score. At 1 year clinical effectiveness of supervised exercise and IPC was largely preserved.*
Conclusions. *IPC, by augmenting leg perfusion, achieved improvement in walking distance comparable with supervised exercise. Long-term results in a larger number of patients will provide valuable information on the optimal treatment modality of intermittent claudication.*

Keywords: Intermittent claudication; Supervised exercise; Intermittent pneumatic compression.

Introduction

The annual incidence of intermittent claudication is approximately 20 per 1000 in men and women older than 65 years.[1] In the USA it is estimated that up to 1.3 million elderly persons can be expected to develop disabling claudication symptoms every 2 years during the next 50 years.[2] Therefore, the economic impact of intermittent claudication is substantial.

Treatment options to improve walking distance in patients with intermittent claudication include bypass surgery, percutaneous transluminal angioplasty (PTA), supervised exercise rehabilitation,[2] intermittent pneumatic compression,[3] and pharmacotherapy.[4] These options, however, are not applicable in all claudicants. For example, the majority of patients are not suitable for PTA. In one study approximately 90% of patients who were screened were unsuitable for treatment by PTA because of the pattern of their occlusive disease or because of other diseases.[5] PTA usually is not recommended for superficial femoral artery (SFA) occlusions longer than 10 cm. Exercise rehabilitation, in the form of supervised exercise, is effective for improving claudication symptoms, the distance to maximal claudication pain increased by 122% in a metanalysis;[2] however, the best results were

Presented in part at the XVIII annual meeting of the European Society for Vascular Surgery (ESVS), September 17–19, 2004, Innsbruck, Austria.
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achieved by intense exercise three times a week for up to 6 months. The high costs of this approach prohibit its widespread use. Intermittent foot or foot and calf compression is effective in increasing the claudication distance by two and half times and, therefore, an attractive alternative, suitable for home use.[6,7]

The main aim of our study was to test the hypothesis that intermittent pneumatic compression, used at home, would be at least as effective as supervised leg exercise in improving claudication distance in patients with SFA occlusion and that both treatment modalities were much more effective compared to unsupervised exercise (advice for exercise), which in addition to anti-platelet use and risk factor modification is currently the most popular way to treat this condition in the UK. A secondary aim was to determine the impact of intermittent pneumatic compression, supervised exercise and unsupervised exercise on the quality of life (QoL).

Material and Methods

Patients with stable intermittent claudication for longer than 6 months due to SFA occlusion ≥6 cm in length on ultrasound and/or angiogram were recruited from the vascular outpatient clinics. The San Diego claudication questionnaire was used to assess leg symptoms.[8] Patients were excluded if duration of symptoms was less than 6 months, they had previous angioplasty or arterial surgery to the symptomatic leg, myocardial infarction within the previous 6 months, inability to manage the treadmill examination or training and any psychiatric illness or other reason making follow up difficult, ischaemic rest pain, gangrene or ischaemic ulceration, were not able to attend the supervised exercise programme or had severe peripheral neuropathy (diabetes, etc.), which can probably precipitate soft tissue injury when using the compression device, ankle brachial pressure index at enrolment greater than 0.9 or non compressible calf arteries (diabetes, chronic renal failure, etc.) precluding ABPI measurement, iliac occlusions or stenoses amenable to surgery or angioplasty (based on ultrasound scanning or angiogram), femoral artery occlusion less than 6 cm as shown on duplex, suitable for angioplasty and limited exercise capacity caused by symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease, disease of the spinal column, venous disease, neurological disease, mental illness or arthritis. Treadmill testing was subsequently performed and patients with maximum claudication distance greater than 300 m or less than 50 m, also were excluded. Two screening treadmill tests performed 1 week apart that did not differ by more than 25% in terms of absolute claudication distance was an additional requirement; in such a case, a third treadmill test was performed and if it was different by more than 25% in terms of absolute claudication distance from both screening treadmill tests, the patient was excluded.

Methodology

ABPI measurements

After the patient had rested for 15 min both brachial pressures were measured twice with a standard stethoscope, sphygmomanometer and a wide (12 cm) arm blood pressure cuff and the results averaged. The mean of the measurements of the two arms were taken into account if their difference was less than 10 mmHg, otherwise the maximum pressure was used. Ankle blood pressure was measured bilaterally with a directional continuous-wave Doppler, a narrow (10 cm) ankle pressure cuff and a sphygmomanometer. Posterior tibial and dorsalis pedis pressure measurements were performed three times and the results averaged. The vessel with the highest average pressure was considered the index vessel.

Treadmill testing

This was carried out on a constant load treadmill test (10% gradient, 3.5 km/h), in accordance with the German Society for Angiology (DGA, Deutsche Gesellschaft für Angiologie) guidelines.[9] Since walking distance on the treadmill can vary,[10] the average of two tests was considered. Initial and absolute claudication distance were recorded, which is the distance at which pain first occurs (ICD, bilaterally when both legs were affected) and the maximum distance terminated by pain (ACD), respectively.

Calf arterial inflow

The global resting calf arterial inflow was measured with the venous occlusion air plethysmography technique,[11] in the supine position after 15 min of resting. This was performed by means of an air-plethysmograph (APG-1000; ACI Medical Inc., San Marcos, CA, USA) and a thigh-congesting cuff (17 cm contoured thigh calf) inflated to 60 mmHg for 15-s by a rapid cuff inflator (E10, DE Hockanson Inc., Bellevue, WA, USA) to induce venous occlusion. Five serial measurements were averaged. Arterial inflow following thigh occlusion reactive hyperaemia (abrupt release of a supra-knee thigh occlusion for 5 min at 50 mmHg above the pressure where pedal blood flow ceased, as determined by an audible transcutaneous

Doppler flow probe, to minimise soft tissue compression and subject discomfort) was also measured serially for 4 min.[12] The thigh-congesting cuff was inflated to 60 mmHg for 7.5 s in each 15-s cycle. Three serial measurements were obtained to calculate the mean. Reactive hyperaemic calf arterial inflow was normalized for resting flow (reactive hyperaemic flow ratio), while the hyperaemic index (ratio of the excess area under the hyperaemic curve/peak flow) was also calculated.[13,14]

Quality of life assessment

QoL was assessed with the short form-36 (SF-36) health survey questionnaire, which is a self-administered generic QoL questionnaire developed for the Medical Outcomes Study.[15] Although it has been shown to be sensitive in defining changes following various treatment modalities in patients with claudication, including surgery and PTA,[16] it can miss small but important changes of QOL.[17] For this reason, two disease specific instruments were used, the walking impairment questionnaire (WIQ),[18] and the intermittent claudication questionnaire (ICQ).[19] WIQ is an interviewer administered, disease-specific instrument, while ICQ is a disease-specific QoL questionnaire. The former provides different scores for claudication pain severity for each leg, scores for walking impairment due to other causes (exertional symptoms limiting walking, including chest pain, shortness of breath, joint pain, etc), and three scores for walking distance, speed and stairs climbing.

Randomisation

Patients were randomised to one of the following three groups: unsupervised exercise (control group), supervised exercise or intermittent pneumatic compression. A blind, block 'telephone' randomisation procedure by means of a computer was performed. Patients of the three groups were stratified by age (younger or older than 67 years of age) and absolute claudication distance (less or more than 150 m). Randomisation was performed by the Clinical Trials and Evaluation Unit at the Royal Brompton Hospital in London. All patients gave their written informed consent, the study protocol being approved by the Hospital Ethics Committee.

Treatment

Current smokers were advised to stop smoking, antiplatelet therapy, preferably 75 mg aspirin once daily, was commenced if the patient was not already on it and lipid-lowering agents (statins) were prescribed and titrated to reduce LDL serum levels below 2.5–3 mmol/L, if necessary.

Patients allocated to unsupervised exercise (control group) were advised to exercise daily by walking as much as possible to near maximal pain, for a period of at least 45 min.

Patients allocated to supervised exercise were advised to exercise daily by walking as much as possible to near maximal pain and in addition attend a supervised exercise programme for 6 months.

Patients allocated to intermittent pneumatic compression were advised to exercise daily by walking as much as possible to near maximal pain and in addition have intermittent pneumatic compression of the symptomatic foot and calf for 6 months.

Exercise programme

Patients attended the physiotherapy department for exercise therapy three times per week for the first 6 months. Compliance was assessed with logbooks.

Supervision was provided on an individual or group basis and each session lasted for about 60 min. A session consisted of 5 min warm up activities, 50 min of intermittent exercise and ended with 5 min of cool-down activities. Walking treadmill exercise was started at a low treadmill workload of 2 mph, 0% grade. Patients walked until claudication pain become moderately severe, at which time they step off the treadmill and rest until claudication pain subsides. After the patient had walked 8–10 min at the initial workload, either the grade was increased by 1–2%, or the speed was increased by 0.5 mph as tolerated. Further progressive increases in the speed and grade were performed as tolerated.[20]

Intermittent foot and calf pneumatic compression

Intermittent pneumatic compression of the foot and calf was performed with the patient in a sitting position. The ArtAssist® device (model AA-1000, San Marcos, CA, USA) was used, which has a frequency of three impulses per min, with a delay of 1 s for calf compression and an inflation pressure of 120 mmHg. Patients were advised to use the pneumatic compression daily in a sitting position usually while watching TV at times of their convenience for a total duration of about 3 h. Intermittent pneumatic compression was performed bilaterally in cases of bilateral claudication. Compliance was assessed with the use of built-in time meters.

Follow-up

Patients were re-assessed at 6 weeks and 6 months after randomisation, for the development of adverse events and assessment of claudication using the same methodology as on baseline. Patients who stopped using the IPC device or the exercise programme, continued to be followed-up, unless they withdrew their consent. Finally, patients were re-assessed at 12 months after randomisation to determine the stability of clinical improvement for the 6-month period after the end of 'active' treatment. During the second part of the study, advice on exercise was the same for all patients and similar to that given to the unsupervised exercise group.

Statistical analysis

Power calculations had demonstrated that 15 patients would be needed in each group to demonstrate a 100% increase in claudication distance from 100 to 200 m (comparable to that quoted by Gardner[2] for supervised exercise and Delis for IPC[3]), at significance level of 0.01 ($\alpha=0.01$) and power of 80% ($1-\beta=0.8$). All results are shown as median and interquartile range;

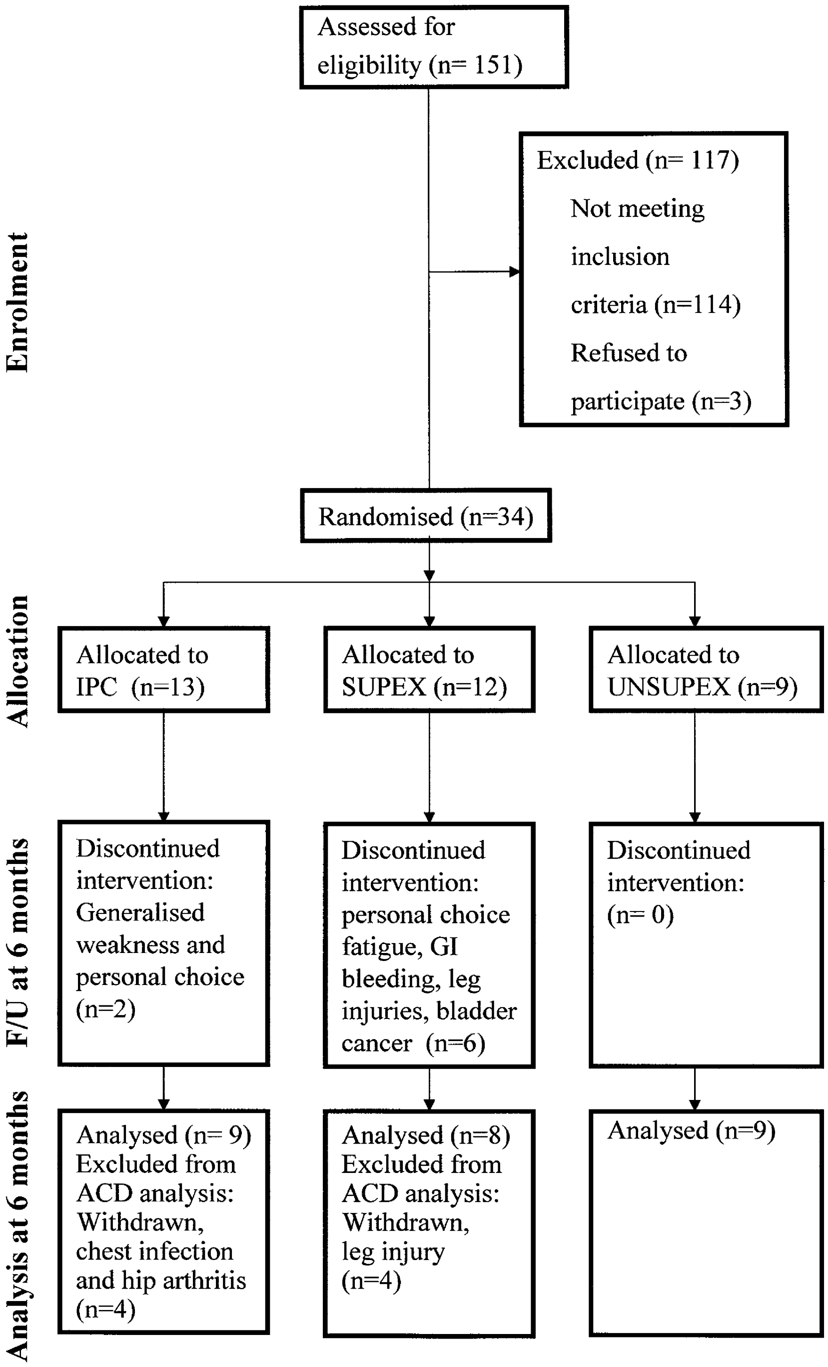


Fig. 1. Flow diagram showing the progress through the phases of the trial, up to the end of active treatment.

because data distribution was skewed, distribution-free tests were used for statistical analysis. Demographic data of the three groups at baseline were compared with the Kruskal–Wallis test (numerical data) or chi-square (categorical data). Analysis was by intention to treat. Inter-groups analysis was assessed with the Mann–Whitney test and intra-group analysis with the Wilcoxon signed-rank test and exact tests were used (2-sided or 1-sided, where appropriate). Categorical data were analysed with chi-square or Fisher's exact test, where appropriate. Multiple intra-group comparisons over time were assessed with the Friedman test. SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA), was the statistical package used for statistical analysis. p values of 0.05 or less were considered statistically significant.

Results

One hundred fifty-one patients were screened and 34 of them (23%) were eligible for randomisation (Fig. 1). Nine patients were randomised to unsupervised exercise, 12 to supervised exercise and 13 to IPC. Patient demographics and risk factors are shown in Table 1. The three groups were matched for risk factors and also for ACD (Table 2). In 19 cases the left leg was the index leg and in 15 cases this was the right one.

Two patients in the IPC group withdrew their consent before their 6 weekly and 6 monthly appointments, respectively, the former patient because of generalised weakness. An additional patient developed hip osteoarthritis and could not be tested on the treadmill at 6 months and 1 year. One more patient who was an inpatient with chest infection could not have his walking distance assessed at 6 months. One patient in the unsupervised exercise developed rest pain due to SFA occlusion of the contra-lateral leg, before his 6-month appointment and subsequently had a femoropopliteal bypass. Only one patient of this group withdrew at 1 year because he moved out of the area. Two patients randomised to supervised exercise withdrew their consent at week 6. Between week 6 and month 6, four additional patients stopped physiotherapy because of fatigue, GI bleeding, minor domestic leg injuries and bladder cancer, respectively. The latter patient, who developed acute leg ischaemia following his cancer operation and subsequently died and the patient with the leg injury did not have their walking distance assessed at 6 months. At 1 year two additional patients allocated to supervised exercise withdrew their consent.

Compared to baseline, IPC and supervised exercise increased ICD and ACD (up to 2.83 times, $p<0.05$, Table 2 and Fig. 2), IPC being more effective. ICD and ACD did not practically change in patients allocated to unsupervised exercise. Patients maintained this improvement at 1 year, although ACD in the IPC was reduced ($p=0.063$ compared to 6 months). Compared with unsupervised exercise (inter-group analysis), both IPC and supervised exercise increased significantly ACD at 6 months ($p<0.05$), which was maintained at 1 year. There was no statistical significant difference in the walking distance (ICD and ACD) achieved by IPC and supervised exercise at 6 weeks, 6 months and 1 year (all p values >0.40).

IPC increased resting arterial inflow by 28% ($p<0.05$ at 6 weeks); this was decreased by supervised exercise, while unsupervised exercise had no effect (Table 2). IPC decreased the reactive hyperaemic flow ratio at 15 and 30 s (at 6 weeks and 6 months, $p<0.05$), as shown in Fig. 3, while exercise had no effect. The hyperaemic index was increased by exercise and decreased by IPC, but the difference was not significant.

Table 1. Patient demographics and risk factors at baseline

Risk factor	Unsupervised exercise ($n=9$)	Supervised exercise ($n=12$)	IPC ($n=13$)	All patients ($n=34$)	p value
Age (years)	66 (10.5)	69 (11.8)	66 (7)	66.5 (8)	0.82
Male gender	8 (89%)	11 (92%)	8 (62%)	27 (79%)	0.13
Coronary heart disease	1 (11%)	2 (17%)	3 (23%)	6 (18%)	0.77
CABG	1 (11%)	0 (0%)	3 (23%)	4 (12%)	0.20
Smoking					
Currently	3 (33%)	2 (17%)	6 (46%)	11 (32%)	0.23
Previously	6 (67%)	8 (67%)	7 (54%)	21 (62%)	0.23
Packs × years	40 (43.7)	41.3 (23)	40 (40)	40 (34.2)	0.91
Hypertension	2 (22%)	4 (33%)	9 (69%)	15 (44%)	0.60
Hypercholesterolaemia	5 (56%)	5 (42%)	5 (54%)	17 (50%)	0.77
Diabetes mellitus	1 (11%)	3 (25%)	3 (13%)	7 (21%)	0.71
Family history of atherosclerosis	3 (33%)	6 (50%)	7 (54%)	16 (47%)	0.62
BMI (Kgr/m^2)	24.7 (10.9)	24.9 (5.3)	24.8 (5.7)	24.7 (5.7)	0.95

Results are shown as number of cases (percentage) or median (IQR). Kruskal–Wallis test or chi-square was used where appropriate.

Table 2. Changes in walking distance, ABPI (including the contralateral leg ABPI-C) and arterial flow in the three study groups

	Group	Baseline	6 weeks	*p*	6 months	*p*	12 months	*p*
ICD (m)	Unsupervised exercise	70 (22.5)	80 (45)	0.57	70 (35)	0.78	80 (55)	0.40
	Supervised exercise	60 (26.25)	80 (35)	0.02	70 (45)	0.02	90 (50)	0.02
	IPC	60 (35)	85 (65)	0.02	90 (77.5)	0.04	101 (95)	0.05
ACD (m)	Unsupervised exercise	135 (87.5)	130 (130)	0.16	140 (60.0)	0.89	135 (57.5)	1.00
	Supervised exercise	145 (108.75)	235 (142.5)	<0.01	220 (282.5)	<0.01	270 (700)	<0.01
	IPC	145 (145)	295 (210)	<0.01	410 (565.0)	<0.01	320 (415)	<0.01
ABPI	Unsupervised exercise	0.60 (0.24)	0.60 (0.20)	0.80	0.63 (0.18)	0.94	0.59 (0.13)	0.57
	Supervised exercise	0.51 (0.14)	0.56 (0.21)	0.47	0.62 (0.15)	<0.01	0.55 (0.13)	0.13
	IPC	0.56 (0.16)	0.60 (0.08)	0.19	0.62 (0.28)	0.32	0.61 (0.16)	0.47
ABPI-C	Unsupervised exercise	0.76 (0.21)	0.73 (0.26)	0.68	0.62 (0.21)	0.40	0.76 (0.36)	0.44
	Supervised exercise	0.80 (0.24)	0.75 (0.35)	0.49	0.75 (0.30)	0.44	0.67 (0.28)	0.08
	IPC	0.88 (0.27)	0.86 (0.27)	0.08	0.87 (0.34)	0.32	0.74 (0.20)	0.06
Resting arterial inflow (ml/sec)	Unsupervised exercise	1.24 (0.81)	1.24 (1.13)	0.89	1.15 (0.56)	0.67	1.35 (0.97)	0.87
	Supervised exercise	1.8 (0.80)	1.32 (1.38)	0.39	1.26 (0.64)	0.32	1.22 (1.12)	0.41
	IPC	0.9 (0.59)	1.15 (1.04)	0.04	1.04 (0.41)	0.18	0.97 (0.67)	0.45
Hyperaemic index	Unsupervised exercise	2.05 (1.40)	1.97 (1.59)	0.68	2.73 (2.09)	0.09	1.26 (2.16)	0.48
	Supervised exercise	2.26 (2.94)	2.37 (2.59)	0.10	2.67 (2.56)	0.29	3.60 (3.74)	0.50
	IPC	3.14 (1.27)	1.93 (3.00)	0.04	2.22 (2.54)	0.12	2.96 (2.11)	0.39

Results are shown as median (IQR). Wilcoxon test was used for intra-group analysis.

Supervised exercise increased ABPI by 0.11 ($p<0.01$) at 6 months, but this decreased after physiotherapy was stopped and was not significant at 1 year. Smaller increase seen in the IPC and unsupervised exercise groups did not reach statistical significance. ABPI of the contralateral leg did not show any consistent changes (Table 2).

Two patients, smokers at the beginning of the study, quit smoking at 6 months, 5 patients reduced the number of cigarettes by 59% on average, while no change was reported by 4 patients. At 1 year two additional patients had quit and another one reduced the number of cigarettes by 33%. Although smoking reduction at 6 months (by at least 40%) was associated with an increase in walking distance (gain 425 m), compared to those who did not reduced by 40% (gain 30 m), the difference was not significant ($p=0.46$). Two patients in the supervised exercise group ($p=0.49$), four patients in the IPC group reduced smoking ($p=0.12$) but none in the unsupervised exercise group. Exclusion of those patients who reduced smoking did not alter significantly ACD, which increased by 4, 52 and 250%, in patients allocated to unsupervised exercise, supervised exercise and IPC, respectively. Patients with less than the median ACD (145 m) increased their ACD from 110 to 120 m, compared to a similar increase (from 210 to 220 m) in the remainder.

Patients younger than the median age (67 years) increased their ACD from 135 to 140 m, compared to a bigger increase (from 160 to 220 m) in the remainder.

Compliance in the IPC group ranged from 7 to 70% (median 35%) of the expected use (548 h). Attendance rates of the supervised exercise classes ranged from 12.8 to 100% (median 60.3%) of the expected attendance (72 days).

General health, as assessed by the SF-36 was not severely affected by this claudication programme (Tables 3 and 4). Score for the general health domain of the SF-36 was significantly improved at 1 year in patients who used IPC. Forty percent of these patients reported that their general health was better compared to 1 year ago versus none of those allocated to unsupervised exercise (4/6 vs 0/6, $p=0.06$). WIQ scores for walking distance, walking speed and stair climbing were reduced in the unsupervised exercise group, remained stable in the supervised exercise group and increased in the IPC group (Fig. 4). Walking speed score in the latter group was increased significantly at 6 months. Supervised exercise improved the claudication (pain) severity score of the WIQ questionnaire (Fig. 5). The most remarkable change seen among the ‘walking impairment due to other causes’ questions of the relevant section of the

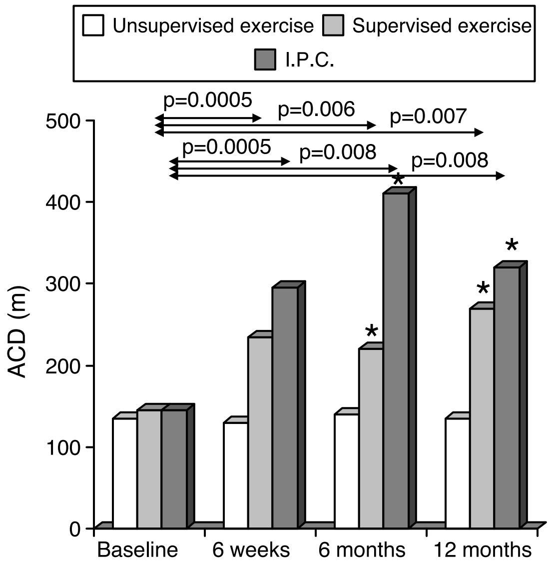


Fig. 2. This figure demonstrates a significant improvement in walking distance, in patients allocated to supervised exercise or intermittent pneumatic leg compression, compared to baseline (at 6 weeks, 6 months and 1 year) and unsupervised exercise (at 6 months and 1 year).

WIC, was in the question exploring joint symptoms ('pain, stiffness or aching in your joints: ankles, knees or hips'), observed in the supervised exercise group at 6 months (50% drop of the medium score, from 100 to 50%). Supervised exercise and IPC reduced (improved) the ICQ score, but this was significant only in the IPC group (Fig. 6).

Discussion

Suction leg devices or devices applying positive pressure in combination with suction have been used for nearly a century to treat patients with Burger's disease or symptomatic peripheral vascular disease.[21–23] These devices produced hyperaemia and increased skin temperature. Subsequent improvement of our knowledge of the physiology of leg compression has resulted in abandonment of the use of leg suction. More recently, our group determined the optimum intermittent pneumatic compression stimulus for lower-limb venous emptying using direct pressure measurements; foot and calf compression at 120–140 mmHg, with a frequency of 3–4 impulses/minute and one-second delay, provides the optimum stimulus.[24] Intermittent pneumatic leg compression using these setting has been subsequently used in claudicants,[7] and in critical limb ischaemia, when surgical reconstruction is not feasible.[25,26]

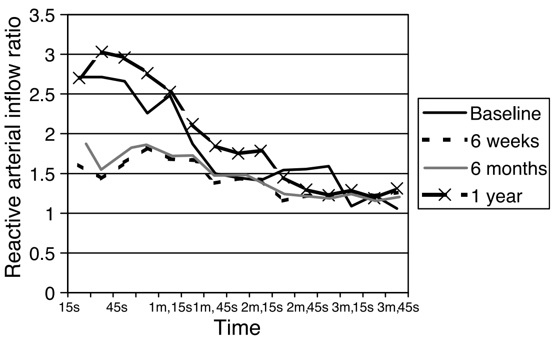


Fig. 3. Reactive hyperaemic flow changes (normalised for resting flow) at 6 weeks and 6 months of IPC. The difference was significant at 15 and 30 s. At 1 year flow returned to baseline.

IPC in this study improved remarkably walking distance, mainly ACD, by 183%. Similar results with the use of foot and calf compression have been previously reported by our group (212% increase),[24] while the use of a foot pump seems to be somewhat inferior (106% improvement).[6] Walking distance improvement with IPC was comparable or even better than supervised exercise; perhaps the relatively high dropout rate in this supervised exercise group explains the inferior results, compared to the mean of 122% reported in a metanalysis.[2] No practical improvement (4% increase in walking distance) was observed in patients allocated to unsupervised exercise, which seems contradictory to previous studies, which reported a small (18%) increase in walking distance;[4] however, ICD was somewhat improved. Most of the patients had already given advice to stop smoking and exercise by their family doctors before entering the study and the fact that they presented with SFA occlusion, with no previous episodes of leg ischaemia (indicating adequate collateral circulation), could explain the stability of their clinical condition.

ABPI increased in both supervised exercise and pneumatic compression. The 11% ABPI increase in the latter group did not achieve statistical significance, probably because the study did not have the appropriate power, however, in a similar but larger study it did reach statistical significance[7] ABPI increase in supervised exercise is not in agreement with previous studies,[27,28] which found no such a finding; perhaps in this selected group of patients with SFA occlusion, exercise results in remodelling of thigh collaterals and therefore ABPI increase. The effect of calf and thigh IPC,[29] on this group of patients can be only speculated. Notably, ABPI of the contralateral leg was rather reduced, indicating a differential effect of exercise in this group. This was remarkably reduced in unsupervised exercise and practically unchanged in supervised exercise.

An increase in resting arterial inflow was observed

Table 3. Physical health domain changes of the SF-36 health questionnaire at 6 weeks, 6 months and 1 year after entry into the study

	Unsupervised exercise	p	Supervised exercise	p	IPC	p
Physical functioning						
Baseline	50 (35–65)		65 (56–70)		70 (50–80)	
6 weeks	50 (43–68)	0.5	55 (50–55)	0.133	68 (48–84)	0.875
6 months	60 (46–69)	0.343	65 (50–73)	0.180	73 (39–85)	0.887
12 months	45 (35–60)	0.531	50 (35–65)	0.063	75 (58–90)	0.242
Role-physical						
Baseline	100 (50–100)		50 (50–94)		100 (50–113)	
6 weeks	100 (75–100)	0.672	50 (50–100)	1.000	50 (50–75)	0.016
6 months	75 (56–94)	1.000	50 (38–50)	0.343	50 (50–81)	0.188
12 months	50 (25–100)	0.250	0 (0–100)	0.250	0 (0–81)	0.004
Bodily pain						
Baseline	60 (32–77)		60 (51–78)		60 (46–75)	
6 weeks	54 (42–92)	0.375	64 (60–84)	0.039	70 (61–80)	0.875
6 months	62 (43–70)	0.813	70 (48–90)	1.000	70 (58–80)	0.297
12 months	51 (31–74)	0.672	62 (41–84)	1.000	72 (61–88)	0.164
General health						
Baseline	35 (28–59)		35 (26–45)		35 (25–48)	
6 weeks	40 (23–55)	0.531	40 (35–55)	0.055	35 (21–39)	0.266
6 months	40 (35–49)	0.625	35 (30–43)	0.797	33 (24–41)	0.203
12 months	40 (35–45)	0.828	50 (42–72)	0.094	61 (45–70)	0.037
Physical composite score						
Baseline	52 (45–62)		49 (41–61)		62 (50–66)	
6 weeks	54 (46–62)	0.383	55 (52–58)	0.331	55 (52–58)	0.458
6 months	53 (50–55)	0.523	52 (35–61)	0.641	56 (51–58)	0.645
12 months	47 (43–57)	0.469	48 (40–54)	0.688	56 (48–64)	0.695

Wilcoxon test was used for intra-group analysis.

in the IPC group, confirming previous findings.[30] In a similar trial, however, resting arterial flow (assessed with ultrasound at the level of the popliteal artery) did not change.[7] These observations after weeks or months of leg compression should be distinguished from findings of acute studies, which measured the clearance time of ^{133}Xe,[31] or arterial flow using duplex ultrasonography;[32,33] these are the result of reactive hyperaemia or a result of decreasing venous pressure and widening the so-called arteriovenous pressure

Table 4. Mental health domain changes of the SF-36 health questionnaire at 6 weeks, 6 months and 1 year after entry into the study

	Unsupervised exercise	p	Supervised exercise	p	IPC	p
Vitality						
Baseline	60 (65–43)		70 (60–70)		65 (50–70)	
6 weeks	60 (50–68)	0.281	65 (50–70)	0.344	55 (48–70)	1.000
6 months	65 (46–70)	0.343	60 (50–75)	0.382	70 (65–71)	0.008
12 months	50 (45–60)	0.500	50 (45–60)	0.078	68 (50–76)	0.313
Social functioning						
Baseline	78 (67–78)		78 (69–89)		78 (67–89)	
6 weeks	78 (44–89)	0.656	78 (67–89)	0.531	78 (58–78)	0.469
6 months	72 (58–78)	0.312	78 (72–83)	0.750	78 (72–89)	1.000
12 months	89 (22–100)	0.938	89 (78–100)	0.343	94 (75–100)	0.068
Role emotional						
Baseline	33 (0–33)		0 (0–25)		33 (0–83)	
6 weeks	33 (17–83)	0.125	33 (0–33)	0.156	33 (0–33)	0.180
6 months	33 (33–33)	0.250	0 (0–33)	0.750	0 (0–8)	0.063
12 months	67 (0–100)	0.125	0 (0–33)	1.000	0 (0–42)	0.156
Mental health						
Baseline	52 (38–66)		44 (32–52)		52 (36–64)	
6 weeks	52 (48–58)	0.914	48 (40–52)	0.602	44 (33–52)	0.078
6 months	44 (37–64)	0.797	56 (40–60)	0.125	42 (31–57)	0.297
12 months	88 (64–100)	0.031	76 (60–80)	0.016	84 (71–89)	0.008
Mental composite score						
Baseline	51 (38–62)		54 (47–62)		57 (47–68)	
6 weeks	58 (49–65)	0.516	57 (46–63)	0.418	58 (43–65)	0.606
6 months	58 (47–66)	0.563	51 (41–63)	0.492	61 (58–68)	0.652
12 months	63 (49–79)	0.078	53 (49–62)	0.813	63 (48–71)	0.084

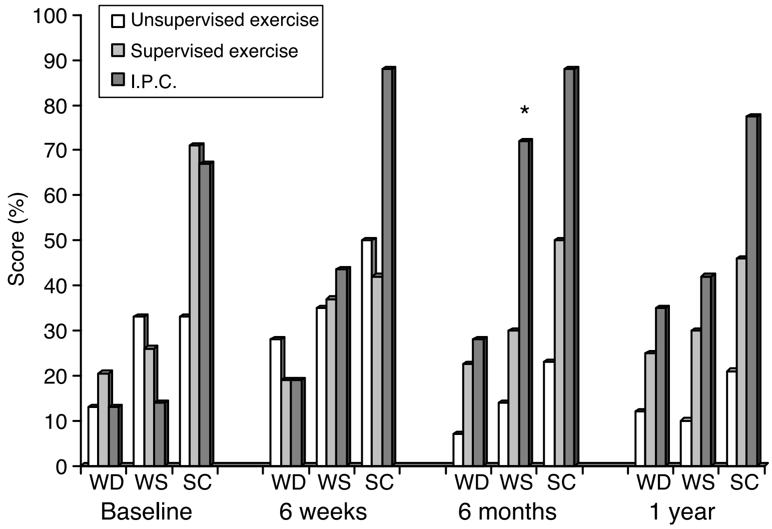


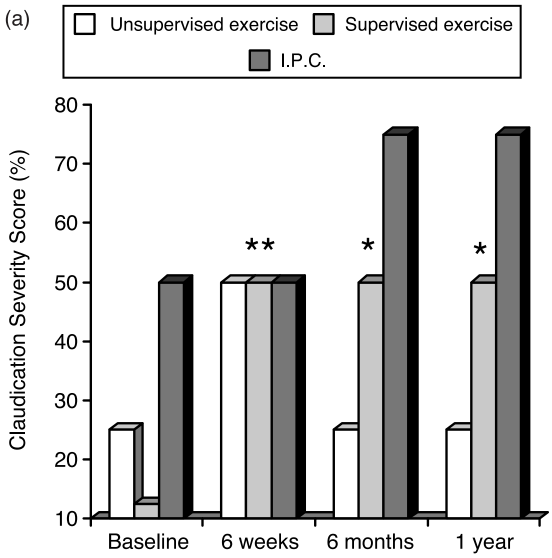
Fig. 4. WIQ scores for walking distance (WD), walking speed (WS) and stair climbing (SC) were reduced in the unsupervised exercise group, remained stable in the supervised exercise group and increased in the IPC group. Higher scores indicate a less severely affected patient. IPC improved walking speed score ($p = 0.007$, exact Friedman test), which was significant at 6 months (asterisk).

gradient. Because flow enhancement is significantly increased in the sitting position by 187%,[31] IPC devices are traditionally used in this position. Interestingly patients allocated to supervised exercise in our study demonstrated a consistent decrease in arterial inflow, which is contradictory to what previously described.[34] Unsupervised exercise was associated with a smaller decrease in resting arterial inflow, confirming previous findings.[35] Distinctive changes in reactive hyperaemic indices were observed; exercise increased the hyperaemic index and IPC decreased it. The latter observation is an indication of improved leg perfusion. Using an isotopic clearance method, normal legs have been reported to have a low post-exercise hyperaemic index,[14] results compatible with the decrease we found in patients who used IPC. Although these results were not significant, the early changes (15 and 30 s) of the reactive hyperaemic curve were significant indeed.

Quality of life improvement is obviously the desired outcome of any treatment. Generic questionnaires have been criticised of missing small but important changes of QOL, therefore, disease specific questionnaires have been introduced. We found that both IPC and supervised exercise, but not unsupervised exercise, improve both the ICQ and WIQ scores. This has enormous implications for future patient management. IPC increased scores for walking distance and speed at 6 months by 115 and 414%, respectively. The corresponding figures reported in one of the cilostazol trials were 61 and 22%, respectively.[4] ICQ score at 6 months in the IPC and supervised exercise groups was reduced by 33 and 17%, respectively. By contrast, the inventors of this score reported a 43% reduction after supervised exercise and a 41% reduction after angioplasty.[19,36] Different patient selection criteria are likely to be responsible for any differences. No consistent changes in the SF-36 domain scores were observed, including physical functioning, previously reported to be improved.[18]

Compliance was relatively poor in both active groups. This is in agreement with previous studies quoting similar use of the IPC device,[25] and supervised exercise dropout rates.[37] This could explain the relatively small improvement at 6 months in the physiotherapy group, taken into account that patient follow-up continued even after they discontinued the study. No patient developed acute ischaemia in the IPC group, which indicates that it is a safe method. Long-term studies to investigate if it alters the natural history of intermittent claudication, as found in patients with leg ulcers, are necessary.[38]

Cost-effectiveness of treatment is obviously a matter of concern. From the outset of the study a conservative estimation of the cost of a 6 month course of supervised exercise per patient at Ealing Hospital was £1000. The rental cost of the IPC for the same period of time was £1263. Additional costs like transportation were not included. The better results at 6 months seen in the IPC group favours this modality with cost per metre of walking distance gained estimated to be about £5 (1263/265) compared to £13 (1000/75) in patients having physiotherapy.



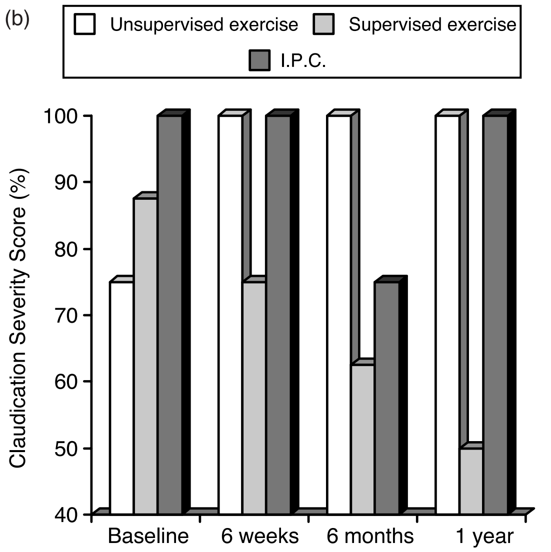


Fig. 5. This figure shows WIQ scores for claudication severity of the index leg (A) and the contralateral leg (B). A 100% score means no claudication pain; a 0% score means patient limited by severe pain. Supervised exercise and intermittent pneumatic leg compression improved the score, although the results were significant only in the supervised exercise group (asterisks). A variable effect was seen in the contralateral leg.

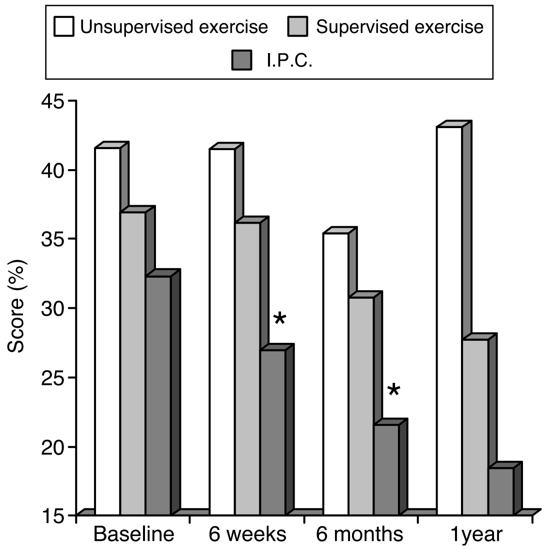


Fig. 6. Changes of the intermittent claudication questionnaire score are shown in this figure. The improvement at the end of active treatment was significant only in the IPC group ($p = 0.037$, Friedman test, asterisks). At 1 year score did not practically change.

Pharmacotherapy (cilostazol) is relatively cheaper, with cost per metre of walking distance gained estimated to be £1.6 (£220/129m) based on the 2004 UK formulary price and the results reported by Beebe,[3] but is less effective than alternative methods. Additionally its effects are not permanent.[39] We believe that our results are applicable to most claudicants. About half of the excluded patients could not manage treadmill testing (mostly shortness of breath) or their walking distance was >300 m. The fact that patients are typically excluded from claudication trials (in an effort to reduce variability and therefore increase the power of these studies) does not imply decreased efficacy of the treatment modalities.[4,6,39]

IPC, by augmenting leg perfusion, achieved improvement in walking distance comparable to that achieved with supervised exercise. No improvement or perfusion changes were seen in patients randomised to unsupervised exercise. Therefore, IPC is an alternative and effective treatment option in the management of patients with intermittent claudication. As a result of its non-invasive nature, further research on IPC will most likely establish this as an attractive alternative in the management of patients with peripheral vascular disease and long-term results in a larger number of patients will provide valuable information on the optimal treatment modality of intermittent claudication. It is anticipated that the long-term need for surgical or percutaneous intervention should be reduced in those patients. We are currently completing the 1-year of follow-up of the patients to see if they maintain their benefit 6 months after the discontinuation of active treatment.

Acknowledgements

We would like to express our sincere appreciation to the following:

- All patients who kindly agreed to take part in the study.
- Hilary Dalton from the Physiotherapy Department of Ealing Hospital for performing supervised exercise.
- ACI Medical (San Marcos, California, USA) for loaning us the ArtAssist® devices.
- Clinical Trials and Evaluation Unit, Royal Brompton Hospital, Sydney Street, London, SW3 6PN (Director Marcus Flather) for computer randomisation.
- Patrick Chong and Alun Davies (Charing Cross Hospital, London) for providing us with the intermittent claudication questionnaire before this became publicly available.

References

1 Kannel WB, McGee DL. Update on some epidemiological features on intermittent claudication: the Framingham study. *J Am Geriatr Soc* 1985;**33**:13–18.

2 Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. *JAMA* 1995;**274**:975–980.

3 Delis K, Nicolaides A, Stansby G, Labropoulos N, Mansfield A, Lumley J. Intermittent pneumatic impulse compression of the foot can improve the condition of patients with stable intermittent claudication. A prospective controlled study. *Br J Surg* 1997;**84**:577–578.

4 Beebe HG, Dawson DL, Cutler BS, Herd JA, Strandness Jr DE, Bortey EB *et al*. A new pharmacological treatment for intermittent claudication: results of a randomised, multicentre trial. *Arch Intern Med* 1999;**159**:2041–2050.

5 Whyman MR, Fowkes FGR, Kerracher EMG, Gillespie IN, Lee AJ, Housley E *et al*. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. *Eur J Vasc Endovasc Surg* 1996;**12**:167–172.

6 Delis KT, Nicolaides AN, Wolfe JHN, Stansby G. Improving walking ability and ankle brachial pressure indices in symptomatic peripheral vascular disease with intermittent pneumatic foot compression: a prospective controlled study with one-year follow-up. *J Vasc Surg* 2000;**31**:650–661.

7 Delis KT, Nicolaides AN, Cheshire NJW, Wolfe JHN. Improvement in walking ability, ankle pressure indices and quality of life in vascular claudication using intermittent pneumatic foot and calf compression: a randomized controlled trial. *Br J Surg* 2001;**88**:605–606.

8 Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med* 1996;**1**:65–71.

9 Heidrich H, Cachovan M, Creutzig A, Rieger H, Trampisch HJ. Guidelines for therapeutic studies in Fontaine's stages II–IV peripheral arterial occlusive disease. *VASA* 1995; **24**:114–119.

10 Harris KA, Meads GE. A single treadmill exercise test does not accurately quantitate claudication. *Can J Surg* 1987;**30**:446–448.

11 Volteas N, Leon M, Labropoulos N, Christopoulos D, Boxer D, Nicolaides A. The effect of iloprost in patients with rest pain. *Eur J Vasc Surg* 1993;**7**:654–658.

12 Clement DL, van Maele GO, de Pue NY. Critical evaluation of venous occlusion plethysmography in the diagnosis of occlusive arterial diseases in the lower limbs. *Int Angiol* 1985; **4**:69–74.

13 Roberts DH, Tsao Y, McLoughlin GA, Breckenridge A. Placebo-controlled comparison of captopril, atenolol, labetalol, and pindolol in hypertension complicated by intermittent claudication. *Lancet* 1987;**ii**(8560):650–653.

14 Angelides NS, Nicolaides AN. Simultaneous isotope clearance from the muscles of the calf and thigh. *Br J Surg* 1980;**67**:220–224.

15 Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–483.

16 Currie IC, Wilson YG, Baird RN, Lamont PM. Treatment of intermittent claudication: the impact on quality of life. *Eur J Vasc Endovasc Surg* 1995;**10**:356–361.

17 Chetter IC, Spark JI, Dolan P, Scott DJ, Kester RC. Quality of life analysis in patients with lower limb ischaemia: suggestions for European standardisation. *Eur J Vasc Endovasc Surg* 1997; **13**:597–604.

18 Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg* 1996;**23**:104–115.

19 Chong PFS, Garratt AM, Golledge J, Greenhalgh RM, Davies AH. The intermittent claudication questionnaire: a patient-assessed condition-specific health outcome measure. *J Vasc Surg* 2002;**36**:764–771.

20 Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;**81**:602–609.

21 Sinkowich SJ, Gottlieb I. Thromboangiitis obliterans—the conservative treatment by Bier's hyperemia suction apparatus. *JAMA* 1917;**68**:961–963.

22 Reid MR, Herrmann LG. Treatment of obliterative vascular diseases by means of an intermittent negative pressure environment. *J Med* 1933;**14**:200–204.

23 Landis EM, Gibbon JH. The effects of alternating suction and pressure on blood flow to the lower extremities. *J Clin Invest* 1933; **12**:925–961.

24 Delis KT, Azizi ZA, Stevens RJG, Wolfe JHN, Nicolaides AN. Optimum intermittent pneumatic compression stimulus for lower-limb venous emptying. *Eur J Vasc Endovasc Surg* 2000; **19**:261–269.

25 van Bemmelen PS, Gitlitz DB, Faruqi RM, Weiss-Olmanni J, Brunetti VA, Giron F *et al*. Limb salvage using high-pressure intermittent compression arterial assist device in cases unsuitable for surgical revascularization. *Arch Surg* 2001;**136**:1280–1285.

26 Louridas G, Saadia R, Speley J, Abdoh A, Weighell W, Arneja AS *et al*. The ArtAssist® device in chronic lower limb ischemia. A pilot study. *Int Angiol* 2002;**21**:28–35.

27 Izquierdo-Porrera AM, Gardner AW, Powell CC, Katzel LI. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *J Vasc Surg* 2000;**31**:670–677.

28 Perkins JMT, Collin J, Creasy TS, Fletcher EWL, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg* 1996;**11**:409–413.

29 Delis KT, Husmann MJW, Cheshire NJ, Nicolaides AN. Effect of intermittent pneumatic compression of the calf and thigh on arterial calf inflow: a study of normal, claudicants, and grafted arteriopaths. *Surgery* 2001;**129**:188–195.

30 Banga JD, Idzerda HHD, Schuurman JD, Eikelboom BC. Intermittent pneumatic compression therapy in patients with leg ischemia. *Int Angiol* 1995;**14**(Suppl 1):202.

31 Gaskell P, Parrott JCW. The effect of a mechanical venous pump on the circulation of the feet in the presence of arterial obstruction. *Surg Gynecol Obstet* 1978;**146**:583–592.

32 Van Bemmelen P, Mattos M, Faught WE. Augmentation of blood flow in limbs with occlusive arterial disease by intermittent calf compression. *J Vasc Surg* 1994;**19**:1052–1058.

33 Eze AR, Comerota AJ, Cisek PL, Holland BS, Kerr RP, Veeramasuneni R *et al*. Intermittent calf and foot compression increases lower extremity blood flow. *Am J Surg* 1996;**172**:130–135.

34 Brendle DC, Joseph LJO, Corretti MC, Gardner AW, Katzel LI. Effects of exercise rehabilitation on endothelial

reactivity in older patients with peripheral arterial disease. *Am J Cardiol* 2001;**87**:324–329.
35 Gardner AW, Montgomery PS, Killewich LA. Natural history of physical function in older men with intermittent claudication. *J Vasc Surg* 2004;**40**:73–78.
36 Cheetham DR, Burgess L, Ellis M, Williams A, Greenhalgh RM, Davies AH. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial. *Eur J Vasc Endovasc Surg* 2004;**27**:17–23.
37 Tan KH, Cotterrell D, Sykes K, Sissons GRJ, de Cossart L, Edwards PR. Exercise training for claudicants: changes in blood flow, cardiorespiratory status, metabolic functions, blood rheology and lipid profile. *Eur J Vasc Endovasc Surg* 2000;**20**:72–78.
38 Vella A, Carlson LA, Blier B, Felty C, Rooke TW, Kuiper JD. Circulator boot therapy alters the natural history of ischemic limb ulceration. *Vasc Med* 2000;**5**:21–25.
39 Dawson DL, DeMaioribus CA, Hagino RT, Light JT, Bradley Jr DV, Britt KE *et al*. The effect of withdrawal of drugs treating intermittent claudication. *Am J Surg* 1999;**178**:141–146.

Accepted 3 March 2005
Available online 10 May 2005