Effect of Intermittent Pneumatic Compression of Foot and Calf on Walking Distance, Hemodynamics, and Quality of Life in Patients With Arterial Claudication

A Prospective Randomized Controlled Study With 1-Year Follow-up

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Summary Background Data: Perioperative mortality, graft failure, and angioplasty limitations militate against active intervention for claudication. With the exception of exercise programs, conservative treatments yield modest results. Intermittent pneumatic compression [IPC] of the foot used daily for 3 months enhances the walking ability and pressure indices of claudicants. Although IPC applied to the foot and calf together [IPC$_{foot+calf}$] is hemodynamically superior to IPC of the foot, its clinical effects in claudicants remain undetermined.

Objective: This prospective randomized controlled study evaluates the effects of IPC$_{foot+calf}$ on the walking ability, peripheral hemodynamics, and quality of life [QOL] in patients with arterial claudication.

Methods: Forty-one stable claudicants, meeting stringent inclusion and exclusion criteria, were randomized to receive either IPC$_{foot+calf}$ and aspirin$_{[75\ mg]}$ (Group 1; $n = 20$), or aspirin$_{[75\ mg]}$ alone (Group 2; $n = 21$), with stratification for diabetes and smoking. Groups matched for age, sex, initial [ICD] and absolute [ACD] claudication distances, pressure indices [ABI], popliteal artery flow, and QOL with the short-form 36 Health Survey Questionnaire (SF-36). IPC$_{foot+calf}$ (120 mm Hg, inflation 4 seconds × 3 impulses per minute, calf inflate delay 1 second) was used for 5 months, ≥2.5 hours daily. Both groups were advised to exercise unsupervised. Evaluation of patients, after randomization, included the ICD and ACD, ABI, popliteal artery flow with duplex and QOL* at baseline*, $1_{/12}$, $2_{/12}$, $3_{/12}$, $4_{/12}$, $5_{/12}$* and $17_{/12}$. Logbooks allowed compliance control. Wilcoxon and Mann-Whitney corrected$_{[Bonferroni]}$ tests were used.

Results: At $5_{/12}$ median ICD, ACD, resting and postexercise ABI had increased by 197%, 212%, 17%, and 64%, respectively, in Group 1 ($P < 0.001$), but had changed little ($P > 0.1$) in Group 2;

Group 1 had better ICD, ACD, and resting and postexercise ABI ($P < 0.01$) than Group 2. Inter- and intragroup popliteal flow differences at $5_{/12}$ were small ($P > 0.1$). QOL had improved significantly in Group 1 but not in Group 2; QOL in the former was better (P < 0.01) than in Group 2. QOL in Group 1 was better ($P < 0.01$) than in Group 2 at $5_{/12}$. IPC was complication free. IPC compliance (≥2.5 hours/d) was >82% at 1 month and >85% at 3 and 5 months. ABI and walking benefits in Group 1 were maintained a year after cessation of IPC treatment.

Conclusions: IPC$_{foot+calf}$ emerged as an effective, high-compliance, complication-free method for improving the walking ability and pressure indices in stable claudication, with a durable outcome. These changes were associated with a significant improvement in all aspects of QOL evaluated with the SF-36. Despite some limited benefit noted in some individuals, unsupervised exercise had a nonsignificant impact overall.

(*Ann Surg* 2005;241: 431–441)

Although the concept of alternating external limb compression for ameliorating rest pain in patients with critical limb ischemia was introduced in the mid-1930s,[1] for almost 4 decades clinical interest in the method remained dormant. In the late 1970s, the delivery of pneumatic compression to the foot and ankle was reported to enhance perfusion in the skin and muscle of the leg, reflected by a ^{133}Xe clearance enhancement by a mean of 80%.[2] Five years ago, intermittent pneumatic compression (IPC) of the foot was found to significantly improve the walking ability of patients with stable intermittent arterial claudication and to increase their pressure indices,[3] effects that were maintained 12 months after cessation of IPC treatment. High-level pneumatic compression (120 mm Hg) of the foot empties the plantar venous plexus and reduces the venous leg pressure, increasing the arteriovenous pressure gradient.[2,4–6] A significant enhancement of the arterial calf inflow ensues[4,5,7] with IPC foot impulse delivery. It has been suggested that the state of enhanced leg inflow accrued during the application of IPC may promote

arterial collateralization,[3] attenuating the increased fixed component of peripheral resistance due to atherosclerotic occlusion of the main axial arterial lumens.[8]

The immediate hemodynamic impact of IPC on the arterial circulation of the lower limb has been examined using different pneumatic modes,[7,9,10] of which IPC applied simultaneously to the foot and calf ($IPC_{foot+calf}$) is as efficacious as any mode investigated thus far. By emptying the calf veins in addition to those of the foot,[11] $IPC_{foot+calf}$ acutely enhances the calf inflow more than 3 times as much as IPC of the foot, in limbs with superficial femoral artery occlusion and claudication.[7]

As the role of IPC in peripheral arterial disease (PAD) gains momentum,[12] this prospective randomized controlled study examines the early and longer-term effects of $IPC_{foot+calf}$ application on the (a) initial (ICD) and absolute (ACD) walking distances, (b) resting (r-ABI) and postexercise (p-eABI) ankle brachial indices, (c) arterial calf inflow (Q), and (d) the quality of life (QOL) in patients with intermittent claudication.

METHODS

Study Design

Patients meeting the study criteria, depicted in Table 1, were randomly allotted to either receive $IPC_{foot+calf}$ and salicylic acid (75 mg/d) (Group 1), or salicylic acid (75 mg/d) alone (Group 2). All patients were advised to exercise to the best of their ability, and were further encouraged on every scheduled study meeting. However, in the absence of comprehensive hospital facilities, arrangements were not made for a supervised physical training program. Based on power calculations[14] derived from the data of a pilot study,[3] 35 to 40 patients in total would be required to achieve a statistically significant difference ($P < 0.05$) in the main investigation parameters (walking distance and ankle-brachial indices) between the 2 groups.

Randomization

Randomization was conducted using 4 groups of sealed envelopes prepared by an independent public health statistician. The method enabled stratification of randomized subjects for diabetes mellitus and smoking, as well as correction of the patients distribution between the 2 groups in every 5 new entries.

Patients

After approval of the study protocol by the Local Ethics Committee, 85 patients were investigated in total but only 41 were randomized. Forty-four were excluded from the study because of cardiorespiratory limitations (55%, $24_{/44}$); orthopedic complaints (arthritis, sciatica, spinal injury) (18%,

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TABLE 1. Patient Selection Criteria

Inclusion criteria
1. Superficial femoral artery occlusion
2. Aortoiliac vessels free of stenoses (>50%), as confirmed by recent (<30 days) angiography or duplex
3. A patent popliteal artery with minimal atherosclerotic lesions
4. Stable (>12 mos) intermittent claudication with absolute claudication distance >35 m, but no better than 350 m, determined by treadmill (3.8 km/h, 10%) exercise challenge
5. Only unilateral intermittent claudication at baseline.

Exclusion criteria
1. Chronic pulmonary disease (obstructive or restrictive)
2. Symptomatic coronary artery disease
3. Congestive heart failure
4. Shortness of breath prior to or with the onset of claudication
5. Symptomatic chronic venous disease (clinical classes $2–6_{[CEAP]}$)[13]
6. Hip, knee, ankle, or foot joint pathology interfering with walking
7. Sciatica, cerebral, spinal or intervertebral disc lesions with lower limb motor sensory defects
8. Leg edema, infection, ulceration, trauma
9. Recent (<12 mos) abdominal, cardiothoracic or orthopaedic (lower limb) surgery
10. Poorly controlled hypertension
11. Concurrent vasoactive medication
12. Long history (>5 yrs) of diabetes mellitus
13. Aneurysmal disease
14. Morbid obesity
15. Vasospastic syndromes
16. Inconsistent (>25%) claudication distance (treadmill 3.8 km/h, 10%) on 3 assessments (first versus second or third) within 15 days

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$8_{/44}$); or because their walking ability was either very poor (9%, $4_{/44}$) inconsistent (more than 25% variation on 3 consecutive assessments within 15 days) (7%, $3_{/44}$); or exceeded the claudication requirements of the study (11%, $5_{/44}$) (Table 1). Twenty patients were allotted in Group 1, and 21 patients in Group 2. Demographics of the patients are depicted in Table 2. The median duration of claudication was 1.9 years in Group 1 and 2.1 years in Group 2 ($P > 0.1$). The severity of claudication, in terms of walking distance and recovery time, was clinically unchanged for at least 1 year prior to the patients' inclusion into the study.

Examination and Scanning Protocol

Patients were examined on 8 consecutive occasions: a preliminary, a baseline, and one at the end of the first, second, third, fourth, fifth, and seventeenth months (Table 3). If the claudication distances (ICD and ACD) at the preliminary and baseline investigations, conducted within 10 days under optimal conditions, did not differ by more than 25%, the subject, provided that he or she was a suitable candidate for the trial otherwise, would follow the randomization process. A third opportunity was offered to those failing the baseline claudication consistency criteria (Table 1). At 5 months, Group 1 patients were asked to return the $IPC_{foot+calf}$ pumps and they followed the same protocol as for Group 2 (salicylic acid 75 mg/d and unsupervised exercise) until 12 months post-treatment. Both study group patients were reexamined at that time (17 months after the start of the trial) to evaluate the longer-term effects of their treatment (Table 3).

Each study session entailed determination of the following: (a) r-ABI, (b) p-eABI obtained after a 1-minute treadmill test (4.0 km/h, 10%), (c) ICD and ACD evaluated by treadmill exercise challenge (3.8 km/hour, 10%), and (d) resting popliteal artery volume flow on recumbency determined with duplex sonography. Investigation commenced with measurement of popliteal artery volume flow. Before their examination, patients were rested for a period of 20 minutes in the horizontal position. Popliteal artery volume flow estimation was performed with a Hewlett Packard Sonos 2500 fitted with a 7.5/5.5 MHz linear-array probe. Flow was calculated by multiplying the time-averaged velocity over a minimum of 5 cardiac cycles by the cross-sectional area of the popliteal artery. At least 5 flow estimations were obtained on each session per patient per afflicted limb, and these were averaged. The technique and its reproducibility have been reported.[5] Patients were examined in the recovery position, with the investigated leg uppermost and towards the examiner.

After the r-ABI had been obtained, the patients underwent a 1-minute treadmill test, for determination of the p-eABI. A second treadmill test allowed estimation of the ICD and ACD. At least 30 minutes intervened between the 2 treadmill tests. The site of optimal Doppler signal in the foot, along the course of posterior tibial or dorsalis pedis arteries, was marked at rest to enable accurate assessment of postexercise ABIs. Recovering postexercise ankle pressures were obtained with the aid of a pair of identical mercury sphygmomanometers and a programmed stopwatch. Pressure was obtained in the horizontal position, using continuous-wave Doppler equipment (Dyna D 800, AHS, France). The ABIs were measured by dividing the higher ankle pressure (obtained from the dorsalis pedis or posterior tibial arteries) with the higher of the 2 brachial artery pressures. An overview of the working study protocol is depicted in Table 3. Investigations were conducted in temperature-controlled conditions

TABLE 2. Demographics, Walking Ability, Baseline Hemodynamics, and Risk Factors of Study Groups 1 ($IPC_{foot+calf}$ + Aspirin) and 2 (Aspirin)

	Group 1	Group 2	Significance
			Group 1 vs Group 2
Treatment	$IPC_{foot+calf}$ + aspirin	Aspirin	
Number of patients	20	21	—
Male/female	15/5	15/6	ns*
Age (range)	66 (59–82) yrs	67.4 (57–80) yrs	ns†
ICD (iqr)	77.5 (47.5–112.5) m	95 (70–135) m	ns†
ACD (iqr)	137.5 (100–235) m	175 (125–231) m	ns†
Resting ABI (iqr)	0.59 (0.54–0.67)	0.594 (0.526–0.684)	ns†
Postexercise ABI (iqr)	0.217 (0.17–0.27)	0.26 (0.2–0.31)	ns†
Popliteal artery flow (iqr)	77 (68.5–138) mL/min	68 (52–120) mL/min	ns†
Smoking (n)	3/20	3/21	ns*
Diabetes (n)	3/20	4/21	ns*

*Chi-square ($P > 0.05$).
†Mann–Whitney ($P > 0.05$).
ICD, initial claudication distance; ACD, absolute claudication distance; iqr, interquartile range.

TABLE 3. Design and Working Protocol of Study Investigations

| Preliminary Phase | Randomized Group Allocation | Active Treatment Period (months) | | | | | | Follow-up |
		Baseline	1	2	3	4	5	17
Inclusion/exclusion criteria	**Group 1**	Flow	Flow	Flow	Flow	Flow	Flow	Flow
	$IPC_{foot+calf}$ + aspirin	ABIs	ABIs	ABIs	ABIs	ABIs	ABIs	ABIs
Clinical examination	(75 mg)	ICD	ICD	ICD	ICD	ICD	ICD	ICD
		ACD	ACD	ACD	ACD	ACD	ACD	ACD
Duplex or angiography	**Group 2**	Flow	Flow	Flow	Flow	Flow	Flow	Flow
		ABIs	ABIs	ABIs	ABIs	ABIs	ABIs	ABIs
	Aspirin (75 mg)	ICD	ICD	ICD	ICD	ICD	ICD	ICD
Treadmill		ACD	ACD	ACD	ACD	ACD	ACD	ACD

$IPC_{foot+calf}$, intermittent pneumatic compression of the foot and calf; Flow, popliteal artery volume flow; ABI, ankle brachial indices; ICD, initial claudication distance; ACD, absolute claudication distance.

($22 \pm 1°C$), with the examiners blinded on the type of treatment and prior performance of patients. Patients attended morning appointments.

Quality of Life Assessment

Quality of life was evaluated using the Short Form 36-Item Health Survey Questionnaire (SF-36).[15,16] Because a large proportion of the questionnaire addresses issues pertaining to physical function, the SF-36 is accepted as an entirely appropriate health assessment instrument in patients with claudication.[17,18] All patients included in the study were requested to fill in a copy of this questionnaire on day zero and another one at the end of the fifth month. Grading of the answers was performed according to the manual of SF-36.[15]

Intermittent pneumatic compression of the foot and calf ($IPC_{foot+calf}$) was delivered using the ArtAssist® AA-1000 unit (ACI Medical Inc., San Marcos, CA), a mechanical pneumatic pump consisting of a pneumatic impulse generator and 2 plastic inflatable pads specially designed to fit the foot and calf. Two large-bore elastic tubings connect the unit with each pad separately. The pump throughout the study was set to operate at a maximum inflation pressure of 120 mm Hg, minimum deflation pressure of 0 mm Hg, inflation time of 4 seconds, and deflation time of 16 seconds. The onset of foot impulses preceded that of the calf by 1 second. Selection of the settings was based on studies conducted previously in normal subjects and claudicants,[5–7,11] allowing optimal leg inflow enhancement with the lowest possible applied compression. A timer built into the impulse unit, and inaccessible to patients, provided an estimate of the patients' compliance, evaluated at 1, 3, and 5 months. A minimum of 2.5 hours of $IPC_{foot+calf}$ application per day was requested, yet Group 1 patients were advised to exceed 3 hours of treatment a day. A 24-hour help line was offered for pertinent emergencies or medical advice.

Statistical analysis of the data was performed using nonparametric tests with 95% confidence intervals (95% CI) of the estimated median difference or point estimate. When comparisons were made within the same study group, the Wilcoxon signed-rank test for paired data was applied. Comparisons between the 2 groups were conducted with the Mann-Whitney ranking test for unpaired data. Whenever the same test was applied more than once within the same data setting, Bonferroni correction was applied.[14] Use of the Bonferroni correction is marked with an asterisk (*) and the P value is quoted in its corrected value. Differences in proportions were evaluated using the χ^2 test. A two-tailed P value of less than 0.05 was considered significant. Data are presented as median and interquartile (iq) range.

RESULTS

Initial Claudication Distance

The ICD in Group 1 increased from 77.5 (iq range 47.5–112.5) m at baseline to 225 (iq range 140–395) m after 3 months of $IPC_{footcalf}$ therapy ($P < 0.005$*; 95% CI: 108, 245 m), and was 230 (iq range 148–400) m on completion of 5 months of treatment (increase of 197%) ($P < 0.005$*; 95% CI: 115, 330 m). The increments of ICD gained over consecutive investigation sessions were all statistically significant ($P < 0.006$*) until the end of the third month (Fig. 1). The rate of improvement in the ICD over the last 2 months of active treatment (4th and 5th months), however, was less [(95% CI: 5, 98 m for month 4) and (95% CI: −35, 30 m for month 5)]. There were no significant changes in the ICD in Group 2 ($P > 0.05$). When the 2 groups were compared, Group 1 was found to perform better as early as the third month ($P = 0.005$; 95% CI: 28, 150 m). At the end of the fifth month, the 95% CI of the difference was 60, 240 m in favor of Group 1 ($P = 0.0002$). Twelve months posttreatment, the
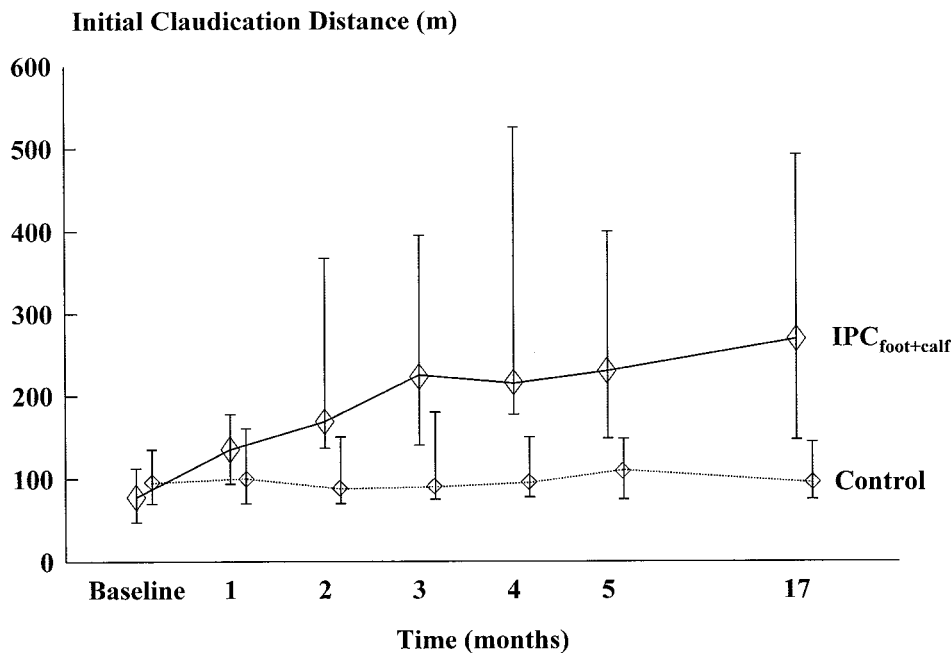
FIGURE 1. Initial claudication distance (ICD) (median and interquartile range) in Groups 1 (IPC$_{foot+calf}$) and 2 (control). The increments of ICD gained by those on IPC$_{foot+calf}$ in the consecutive study sessions were all statistically significant ($P <$ 0.006*) until the third month. Changes in the control patients were not significant. Those on IPC$_{foot+calf}$ performed better than the controls as early as the third month ($P =$ 0.005); ICD in Group 1 was also better ($P =$ 0.0002) on the fifth month. At 12 months' follow-up, the ICD in Group 1 did not differ ($P =$ 0.57*) from that at the fifth month (*Bonferroni correction).

ICD in Group 1, at 269 (iq range 147–493) m, was not different from that at the end of active (5/12) treatment period ($P =$ 0.57*, 95% CI: −10, 31 m).

Absolute Claudication Distance

The ACD in Group 1 increased from 137.5 (iq range 100–235) m on day 0 to 380.5 (iq range 247–656) m by the end of the third month ($P <$ 0.005*; 95% CI: 144, 496 m), and was even higher at the end of treatment (5 months) [median 429 (iq range 275–672) m] representing a median overall improvement of 212% ($P <$ 0.005*; 95% CI: 200, 624 m) (Fig. 2). All the ACD improvements in Group 1 over the consecutive study sessions from the first to the fourth month were significant ($P <$ 0.01*). The rate of improvement was insignificant in the last month of the treatment ($P =$ 0.9*; 95% CI: −20, 42 m). The ACD in Group 2 did not change in
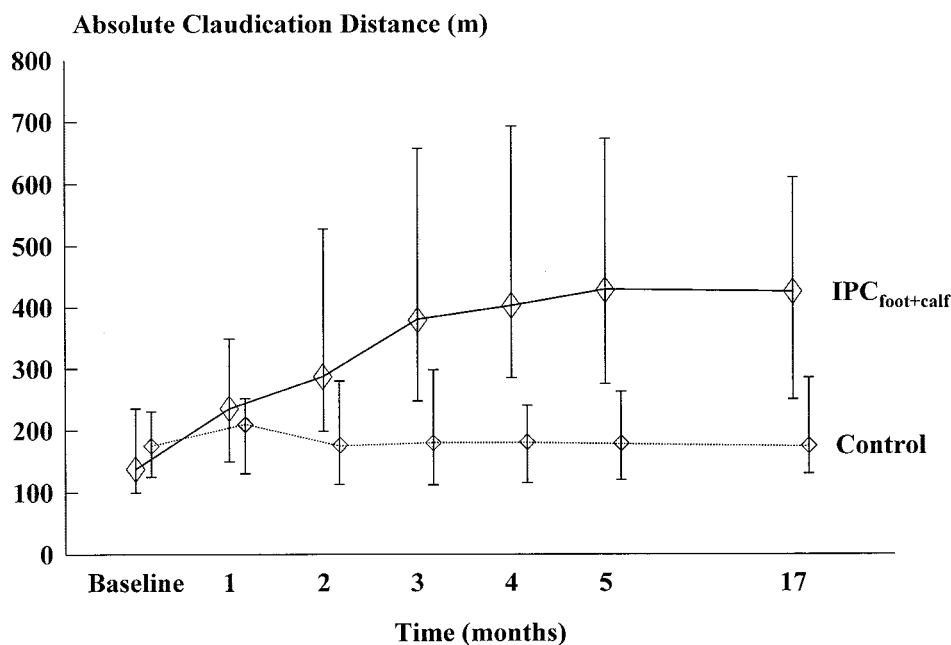

FIGURE 2. Absolute claudication distance (ACD) (median and interquartile range) in Groups 1 (IPC$_{foot+calf}$) and 2 (control). The ICD improvements of those on IPC$_{foot+calf}$ in the consecutive study sessions were significant ($P <$ 0.01*) until the fourth month. Changes in the control patients were not significant. Group 1 had a better ACD than the controls as early as the second month ($P =$ 0.01); the difference was also significant ($P =$ 0.0002) at 5 months. At 12 months' follow-up, the ACD in Group 1 did not differ from that at 5 months ($P =$ 0.75*) (*Bonferroni correction).

the study period ($P > 0.05$*). When the 2 groups were compared, Group 1 performed better as early as the second month ($P = 0.01$; 95% CI: 23, 239). At the end of the fifth month, the 95% CI of the difference was 97, 413 m in favor of Group 1 ($P = 0.0002$). Twelve months posttreatment, the ACD in Group 1 [median 425 (iq range 250–610) m] was not different from that at 5 months ($P = 0.75$*, 95% CI: −34, 32 m).

Resting-ABI

The r-ABI in Group 1 improved from a median 0.59 (iq range 0.546–0.669) at baseline to 0.69 (0.639–0.754) by the end of the third month ($P < 0.005$*; 95% CI: 0.08, 0.16), and was 0.69 (0.625–0.754) at 5 months ($P < 0.005$*; 95% CI: 0.08, 0.15). The r-ABI increments gained by those on $IPC_{foot+calf}$ over the first and second months were both significant ($P < 0.005$*) (Fig. 3). R-ABI changes in Group 2 were not significant ($P > 0.05$*). Group 1 had a better r-ABI as early as the end of the third month ($P = 0.0127$; 95% CI: 0.0188, 0.191). At the end of the fifth month, the 95% CI of the difference was 0.006, 0.2 in favor of Group 1 ($P = 0.03$). Twelve months after the end of treatment, the r-ABI in Group 1 [median 0.658 (iq 0.608–0.735)] was not significantly different from that at 5 months ($P = 0.2$*; 95% CI: −0.03, 0.005).

Postexercise ABI

The p-eABI in Group 1 increased from a median 0.217 (iq range 0.172–0.270) to 0.327 (0.264–0.392) at the end of the second month ($P < 0.005$*; 95% CI: 0.08, 0.2), and was 0.355 (0.284–0.436) at 5 months ($P < 0.005$*; 95% CI: 0.12, 0.2). Increases in the p-eABI among those on $IPC_{foot+calf}$ during the first and second months were both significant ($P < 0.01$*); improvement was attenuated over the last 3 months (months 3, 4, and 5)(Fig. 4). Changes in the p-eABI among the controls were not significant ($P > 0.05$*). Group 1 had a significantly higher p-eABI than Group 2 as early as the end of the second month ($P = 0.04$; 95% CI: 0, 0.12). At the end of the fifth month, the 95% CI of the difference was 0.043, 0.2 in favor of Group 1 ($P = 0.0026$). Twelve months after the end of treatment, the p-eABI [median 0.369 (iq 0.265–0.418)] was not significantly different from that at 5 months ($P = 0.45$*; 95% CI: −0.02, 0.01).

Popliteal Artery Volume Flow

Popliteal artery volume flow in the horizontal position was a median 77 (iq range 68.5–138) ml/min in Group 1 at baseline and was 79 (62–147) mL/min at 5 months ($P = 0.65$*). All flow changes in Group 1 over the period of $IPC_{foot+calf}$ treatment, and a year posttreatment, were nonsignificant ($P > 0.2$*). Baseline volume flow in Group 2 [median 68 (iq range 52–120) ml/min] was not different from that of Group 1 at the same time-point ($P = 0.27$). Popliteal artery volume flow in Group 2 after 5 and 17 months was not significantly different compared with that at baseline (in both $P > 0.1$) (Fig. 5).

Quality of Life

Physical functioning, bodily pain, vitality, social functioning, the perception of general and mental health, and physical and emotional role all improved significantly ($P < 0.001$) within 5 months of treatment with $IPC_{foot+calf}$ (Fig. 6
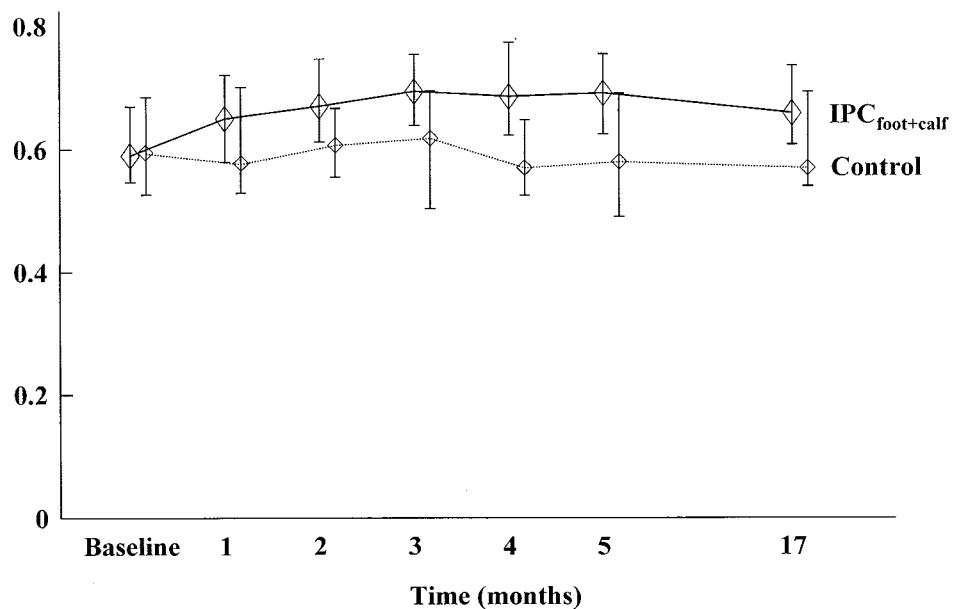

FIGURE 3. Resting ankle brachial index (r-ABI) (median and interquartile range) in Groups 1 ($IPC_{foot+calf}$) and 2 (control). The r-ABI improvements of those on $IPC_{foot+calf}$ in the first and second month were both significant ($P < 0.005$*). Changes in the control patients were not significant. Group 1 had a better r-ABI than the controls in the third month ($P = 0.0127$); this also applied in the fifth month ($P = 0.03$). At 12 months' follow-up, the r-ABI in Group 1 was not different ($P = 0.2$*) from that at 5 months (*Bonferroni correction).
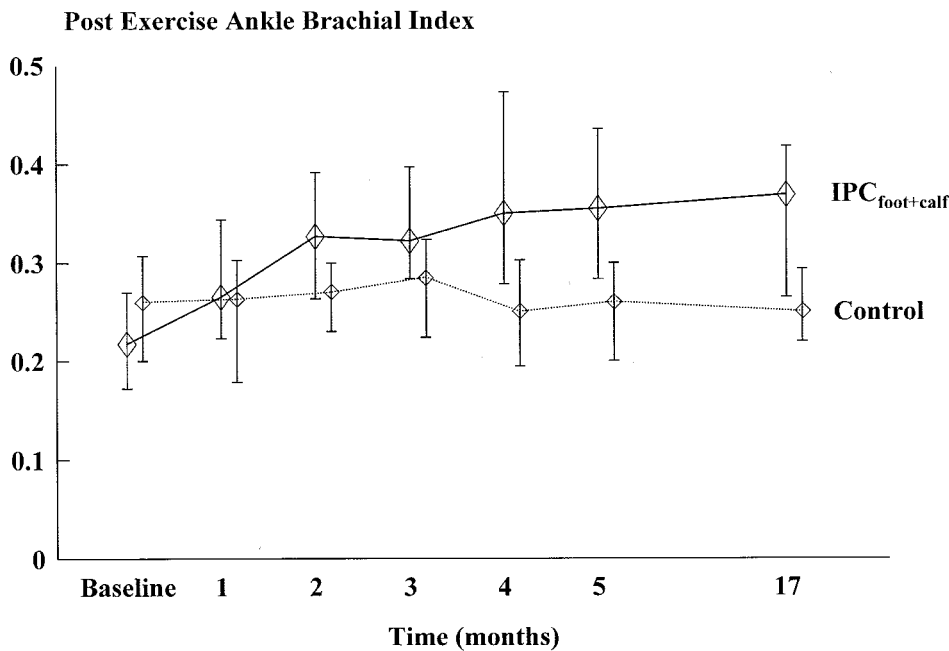
Post Exercise Ankle Brachial Index

FIGURE 4. Postexercise ankle brachial index (p-eABI) in Groups 1 (IPC$_{foot+calf}$) and 2 (control). Increases in the p-eABI over the first and second months among those on IPC$_{foot+calf}$ were both significant ($P < 0.01^*$). Changes in the control patients were not significant. Group 1 had a higher p-eABI than Group 2 ($P = 0.04$) as early as the second month; this also applied on the fifth month ($P = 0.0026$). At 12 months' follow-up, the p-eABI in Group 1 was not different statistically from that at 5 months ($P = 0.45^*$) (*Bonferroni correction).

A and B). There was no significant change in the control group in any of the evaluated parameters. Intragroup differences at baseline were not significant; however, at 5 months group 1 had a better quality of life than the control one in all evaluated aspects ($P < 0.01$).

Patient Compliance

IPC$_{foot+calf}$ compliance defined as ≥ 2.5 hours of pneumatic compression therapy per day exceeded 82% in the first month in Group 1, and was greater than 85% both in the third and fifth months.

DISCUSSION

The daily application of IPC$_{foot+calf}$ for a period of 5 consecutive months in this study, added to aspirin (75 mg) and unsupervised exercise, was found to improve significantly the walking ability of patients with stable claudication.
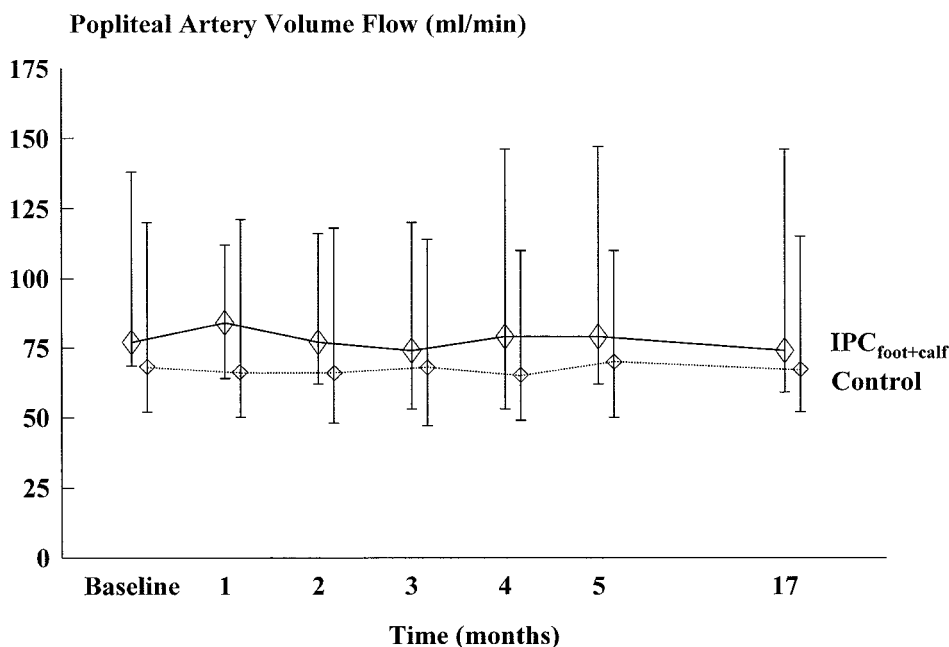
Popliteal Artery Volume Flow (ml/min)

FIGURE 5. Popliteal artery volume flow (median and interquartile range) in Groups 1 (IPC$_{foot+calf}$) and 2 (control). Differences within and between groups were not statistically significant.
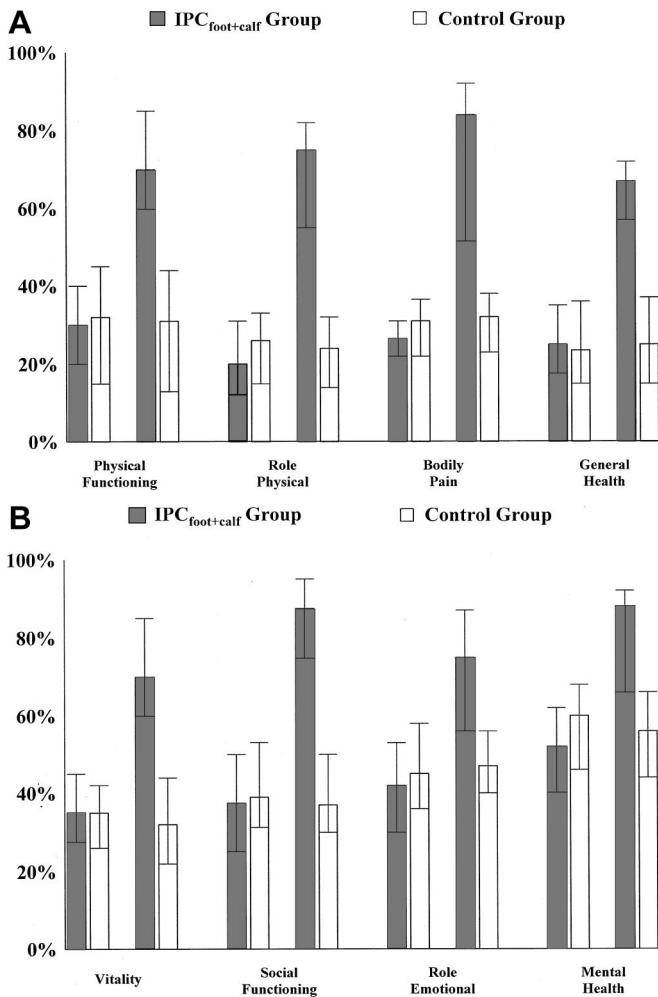
FIGURE 6. Perception of physical functioning, role physical, bodily pain, and general health (A), and perception of vitality, social functioning, emotional role, and mental health (B), evaluated with the SF-36 health survey questionnaire in Groups 1 (IPC$_{foot+calf}$) (shaded bars) and 2 (control) (white bars), at baseline (left), and at 5 months (right). Performance in all these domains of quality of life increased significantly ($P < 0.001$) within 5 months of treatment with IPC$_{foot+calf}$. Changes in the control patients were not statistically significant. Although differences were small ($P > 0.1$) at baseline, Group 1 was better than the controls at 5 months ($P < 0.01$) in all these domains.

The pain-free walking distance increased by a median of 197%, which was associated with an equal improvement in the ACD by 212%. By comparison, the control group, consisting of patients who received aspirin (75 mg) and exercised unsupervised, did not have a significant improvement in their walking ability (ICD and ACD) overall. When the control individuals were compared with those receiving IPC$_{foot+calf}$, the latter had a significantly better ICD as early as the first

month of treatment and a better ACD by the end of the second month. These findings lend support to the data of the single previously conducted prospective (pilot) study on the clinical effects of IPC, reporting a 100% increase in the ICD and ACD of patients with long-standing claudication after 3 months of treatment with impulse foot compression.[3] However, the clinical effects of IPC$_{foot+calf}$ are superior to those achieved with IPC of the foot. This could be justified by consideration of the reported immediate hemodynamic superiority of IPC$_{foot+calf}$ in virtually all arterial and venous flow velocity parameters, including the mean, peak systolic and end diastolic velocities, volume flow, pulsatility index, and venous pressure.[5–7,9,11]

Explanation of the mechanisms involved in the improvement of walking ability of claudicants undergoing IPC therapy implicates the development of collateral circulation in light of concomitant increases in the pressure indices. Four main theories have so far been proposed regarding the stimuli for the development of collateral circulation: a) increase in the pressure gradient around the arterial block;[19] b) increase in the volume flow and the flow velocity around the block;[20] c) attenuation of the vasoconstrictor tone in collateral vessels;[21] and d) the accumulation of metabolites in tissues distal to the occluded segment.[22] IPC$_{foot+calf}$ has not been associated with release of the collateral vessel wall tone, and it is unlikely that it increases the concentration of metabolites in the tissues distal to the arterial block. However, IPC$_{foot+calf}$ enhances the arteriovenous pressure gradient by decreasing the venous pressure in the leg[2,6] and augments the (median) resting arterial leg inflow and mean flow velocity 2- to 3-fold.[7,9] Application of IPC$_{foot+calf}$ therefore could be considered as a stimulus for the development of collateral circulation.

The immediate enhancement of arterial leg inflow on the application of IPC has been attributed to an increase in the arteriovenous pressure gradient,[2,4,5,7,9,23] and a decrease in peripheral resistance to arterial flow.[6,7,9,23] As interstitial pressure in the leg increases with the delivery of a pneumatic impulse, the walls of underlying veins collapse, ejecting venous blood up in the thigh and causing venous pressure to decrease transiently, until veins are refilled by forward flow from the arteries. An increase in the hydrostatic pressure gradient during this brief transitional period postcompression is thought to be a major mechanism for the enhancement of the arterial leg inflow.[4,5,7,9,23] A direct reduction in peripheral resistance has also been postulated via release of nitric oxide, secondary to shear stress increase in the venous radicles with IPC, the action of which on the adjacent arteriolar resistance vessels, by local diffusion, causes them to dilate transiently with concurrent flow enhancement.[4,7,23–25] In an in vitro cell culture system designed to simulate blood flow and vessel collapse conditions during IPC, Northern blot analysis of messenger RNA in endothelial cells showed an up-regulation

of tissue plasminogen activator and nitric oxide synthase expression.[26] Transient suspension of the venoarteriolar reflex, an axon sympathetic reflex autoregulating arteriolar resistance,[7,10,27–29] is probably an additional mechanism of peripheral resistance attenuation during IPC.[7,10,27] The unstretched baroreceptors of the emptied venous radicles immediately after impulse delivery transiently cease igniting their vasoconstrictor effect via the reflex, until priming of the refilling veins causes the baroreceptors to stretch again.[28,29]

Assessment of the quality of life status at baseline and on completion of the 5-month active study period using the SF-36 generic health survey questionnaire showed that IPC$_{foot+calf}$, by enhancing the walking ability of claudicants, can also improve significantly their quality of life. Physical functioning, bodily pain, vitality, social functioning, the perception of general and mental health, and the physical and emotional role all improved significantly within 5 months of treatment with IPC$_{foot+calf}$. Virtually all aspects of quality of life (SF-36) are known to be impaired in patients with claudication.[30–33] Physical functioning, physical role, bodily pain, vitality, and social functioning are affected the most,[32] but emotional reaction and sleep are also impaired.[33] Angioplasty and surgical reconstruction with bypass grafting or thromboendarterectomy improve the energy, pain, emotional reactions, sleep, and physical mobility of claudicants at 6 months.[34] Patients' sleep, social contact, paid employment, and family relationships are restored completely; however, pain, emotional reactions, physical mobility, energy, housework, hobbies, holidays, sex, and social life, despite improvement, remain impaired.[34] Unsupervised exercise brings about only minimal changes in quality of life.[35] Pharmacotherapy treatments have not been assessed in terms of quality of life, except cilostazol, which is reported to improve physical functioning parallel to an increase in the ACD by 47% versus a 13% increase in the placebo group.[36,37]

Follow-up studies performed 12 months after completion of treatment with IPC$_{foot+calf}$ revealed that the significant benefits in the claudication distance and hemodynamics gained during the period of active therapy are sustainable. Moreover, a third (33%) of the patients who had received IPC$_{foot+calf}$ previously increased either their ICD or ACD during the 12-month follow-up. The sustained or improved clinical performance of patients well after cessation of IPC$_{foot+calf}$ therapy could be attributable to their motivation for physical exercise and an appropriate lifestyle in general, reinforced by our continuing personal support and encouragement, and the appreciation of the difference that these improvements had made to their life. In a recent report by Menard et al,[38] only those who continued to exercise were able to maintain the benefits of improved walking capacity and health-related quality of life gained previously with a 12-week program of supervised exercise.

The clinical implications of the results of this study are essential, considering the incidence and prevalence of arterial claudication in the adult population, the natural history, and its effect on the quality of life. Based on objective criteria, 0.6–1.5% of males less than 50 years old and 3–7.5% of men more than 50 years old have symptomatic PAD.[17,39] Soon after its onset, PAD stabilizes clinically in 65–75% of patients, with only 25–35% deteriorating significantly.[17,40–42] The amputation rate in hospital patients with PAD is 7% in 6 years;[41,43] however, in large population studies[17,44,45] among patients with claudication the rate is lower (2%). Although the impact of atherosclerosis on the life span of claudicants is high (5–30% 5-year cumulative mortality rate in males),[17,46] only 3–22% of those who seek medical advice for their PAD will ever require revascularization.[42] On the other hand, the impact of claudication on the quality of life is severe.[30–33,35] Unfortunately, the treatment options available currently are limited and are in practice applicable only to a fraction of those with claudication.

Surgical bypass reconstruction is indicated for severe claudication only after other forms of conservative therapy have been applied and have failed or have been rejected for a good reason.[17] Cumulative primary patency even in straightforward femoropopliteal bypass grafting is on average 75% in 2 years and 60–70% in 5 years, depending on the graft, the level of distal anastomosis, the run-off, and the team.[47,48] Operative mortality is 2% or less,[49] but the cost effectiveness of surgical reconstruction is disputed in view of the impaired long-term survival of these patients. For each year of normal life quality gained using strategies that include both bypass surgery and balloon angioplasty the cost is $202,700–779,000, compared with $37,000–82,000 for strategies based on balloon angioplasty alone.[17,50]

Balloon angioplasty may be effective in selected iliac artery lesions, yet results are less promising in femoropopliteal disease, with a 5-year patency of 17–68%.[51,52] Furthermore, the actual long-term benefit in claudication distance and quality of life is limited.[53,54]

Current drug therapy provides a rather marginal level of improvement.[17] Meta-analyses of all randomized studies on the effect of pentoxifylline, the best-studied agent, revealed an improvement in claudication by 20–44 m.[55,56] Similar or worse results are reported on the effect of other medications.[17,57,58]

Supervised exercise emerges as the most effective noninvasive treatment option in claudication.[17] A meta-analysis of 21 English-language articles on exercise rehabilitation programs reported a mean increase in ICD by 179% and in ACD by 122%.[59] These findings are confirmed by another meta-analysis of all level 2 studies ($n = 5$) verifying a substantial increase in both the ICD and ACD (139 m and 179 m, respectively).[56] However, programs of supervised exercise are expensive, time consuming, and most often

unavailable;[56] regular attendance may be impractical, limiting long-term compliance to 65%.[60]

IPC$_{foot+calf}$ treatment, on the other hand, may be domiciliary, flexible to meet patients' variable time schedules, and is brief in duration, requiring no supervision after an initial brief period of familiarization. Because physical exertion is not required, the pain of claudication, so often experienced in supervised exercise programs, is avoided. IPC treatment has contraindications such as recent venous thrombosis and congestive cardiac failure,[61] yet, if properly administered, IPC$_{foot+calf}$ is virtually complication free, producing a sustainable beneficial effect within a brief period. For these reasons, monitored patient compliance ($\geq$2.5 hours per day) in the current study was high, exceeding 82% in the first month of treatment, and 85% both in the third and fifth months of IPC. In terms of cost effectiveness, an IPC$_{foot+calf}$ unit ($4900) could be used by 4 claudicants annually over a number of years, assuming 3 months of treatment per patient and equipment serviceability, thus offering effective treatment at only a very small fraction of the minimal cost of a treatment strategy involving bypass surgery and balloon angioplasty.[17,50]

In conclusion, IPC$_{foot+calf}$ emerged as an effective treatment in the management of intermittent claudication, offering a clinically significant improvement of both the walking ability (ICD and ACD) and peripheral arterial hemodynamics. These benefits were paralleled by significant improvements in all evaluated aspects of life quality. Follow-up studies a year after cessation of IPC$_{foot+calf}$ treatment showed that the benefits gained are also sustainable. The study data indicate that IPC$_{foot+calf}$ treatment achieves a level of improvement that is equal to that reported for supervised exercise, and better than that accounted for by drug therapies. In addition, IPC$_{foot+calf}$ offers the benefits of an uncomplicated domestic treatment, flexibility, avoidance of physical suffering, and high compliance at a fraction of the cost of most currently available therapies.

ACKNOWLEDGMENTS

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