Improving limb salvage in critical ischemia with intermittent pneumatic compression: A controlled study with 18-month follow-up

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Background: Intermittent pneumatic compression (IPC) is an effective method of leg inflow enhancement and amelioration of claudication in patients with peripheral arterial disease. This study evaluated the clinical efficacy of IPC in patients with chronic critical limb ischemia, tissue loss, and nonhealing wounds of the foot after limited foot surgery (toe or transmetatarsal amputation) on whom additional arterial revascularization had been exhausted.

Methods: Performed in a community and multidisciplinary health care clinic (1998 through 2004), this retrospective study comprises 2 groups. Group 1 (IPC group) consisted of 24 consecutive patients, median age 70 years (interquartile range [IQR], 68.7-71.3) years, who received IPC for tissue loss and nonhealing amputation wounds of the foot attributable to critical limb ischemia in addition to wound care. Group 2 (control group) consisted of 24 consecutive patients, median age 69 years (IQR, 65.7-70.3 years), who received wound care for tissue loss and nonhealing amputation wounds of the foot due to critical limb ischemia, without use of IPC. Stringent exclusion criteria applied. Group allocation of patients depended solely on their willingness to undergo IPC therapy. Vascular assessment included determination of the resting ankle-brachial pressure index, transcutaneous oximetry ($TcPO_2$), duplex graft surveillance, and foot radiography. Outcome was considered favorable if complete healing and limb salvage occurred, and adverse if the patient had to undergo a below knee amputation subsequent to failure of wound healing. Follow-up was 18 months. Wound care consisted of weekly débridement and biologic dressings. IPC was delivered at an inflation pressure of 85 to 95 mm Hg, applied for 2 seconds with rapid rise (0.2 seconds), 3 cycles per minute; three 2-hourly sessions per day were requested. Compliance was closely monitored.

Results: Baseline differences in demography, cardiovascular risk factors (diabetes mellitus, smoking, hypertension, dyslipidemia, renal impairment), and severity of peripheral arterial disease (ankle-brachial indices, $TcPO_2$, prior arterial reconstruction) were not significant. The types of local foot amputation that occurred in the two groups were not significantly different. In the control group, foot wounds failed to heal in 20 patients (83%) and they underwent a below knee amputation; the remaining four (17%, 95% confidence interval [CI], 0.59%-32.7%) had complete healing and limb salvage. In the IPC group, 14 patients (58%, 95% CI, 37.1%-79.6%) had complete foot wound healing and limb salvage, and 10 (42%) underwent below knee amputation for nonhealing foot wounds. Wound healing and limb salvage were significantly better in the IPC group ($P < .01$, χ^2). Compared with the IPC group, the odds ratio of limb loss in the control group was 7.0. On study completion, $TcPO_2$ on sitting was higher in the IPC group than in the control group ($P = .0038$).

Conclusion: IPC used as an adjunct to wound care in patients with chronic critical limb ischemia and nonhealing amputation wounds/tissue loss improves the likelihood of wound healing and limb salvage when established treatment alternatives in current practice are lacking. This controlled study adds to the momentum of IPC clinical efficacy in critical limb ischemia set by previously published case series, compelling the pursuit of large scale multicentric level 1 studies to substantiate its actual clinical role, relative indications, and to enhance our insight into the pertinent physiologic mechanisms. (J Vasc Surg 2008;47:543-9.)

In most vascular units, 50% to 60% of patients presenting with critical limb ischemia (CLI) may be considered for some form of revascularization.[1,2] Yet this figure, which may be as high as 90% in specialized tertiary centers, and the contemporary medical and technical advances have resulted in only a modest decrease in the proportion of those with CLI ending in amputation.[1,2] Longitudinal comparisons of the total number of amputations performed during a longer time span indicate an increase, ascribed to the aging population.[1,3,4] It is projected that this may lead to the number of major amputations being doubled within 30 years.[1]

By acutely enhancing the arterial leg inflow,[5] intermittent pneumatic compression (IPC) of the leg has been shown to improve the walking ability, arterial hemodynamics, and quality of life of patients with severe peripheral arterial disease (PAD).[6,7] Well-tolerated in domestic use (compliance >82%), IPC of the leg increased claudication distance by 200% or more while causing the resting and postexercise ankle-brachial pressure index (ABI) to rise by 17% and 64%, respectively, thus implicating collateral circulation enhancement.[6] Further studies have indicated that high-pressure IPC might be able to allow limb salvage in patients with severe infrapopliteal disease[8] and limb-threatening ischemia who are

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Table I. Baseline demography, cardiovascular risk factors and osteomyelitic foot infection in the control group (Group Control) and the group of those who received intermittent pneumatic compression (Group IPC)[a]

Demography, Risk Factors	*Group IPC (n=24)*	*Group Control (n=24)*	*Significance*
Age, median (IQR) years	70 (68.7-71.3)	69 (65.7-70.3)	NS*
Men	18 (75%)	16 (67%)	NS
Women	6 (25%)	8 (33%)	NS
Men / Women Ratio	3	2	—
Cardiovascular Risk Factors			
Coronary Artery Disease	17 (71%)	18 (75%)	NS
Prior Revascularization	19 (79%)	19 (79%)	NS
Diabetes Mellitus	15 (63%)	17 (71%)	NS
Insulin Dependent	13 (62%)	5 (11%)	p<0.02
Non-Insulin Dependent	2 (10%)	12 (20%)	p<0.01
Glycosylated Hemoglobin (≤8%)	18 (75%)	20 (83%)	NS
Median (IQR)	7 (6.72-7.85)	6.9 (6.2-7.98)	NS*
History of Hypertension	14 (58%)	20 (83%)	NS
Dyslipidemia	16 (67%)	20 (83%)	NS
On Statin Therapy	13 (54%)	17 (71%)	NS
Smoking			
Current	3 (13%)	3 (13%)	NS
Former	20 (83%)	14 (58%)	NS
Never	4 (17%)	4 (17%)	NS
Chronic Renal Failure			
Serum Creatinine median (IQR)	1.2 (1.1-1.8)	1.2 (1.17-1.85)	NS*
Hemodialysis	5 (21%)	5 (21%)	NS
Baseline Infection in the Foot			
Osteomyelitis	18 (88%)	24 (100%)	NS

IPC, Intermittent pneumatic compression; *NS*, not statistically different.
[a]Differences in proportions between the two groups are based on the χ^2 with Yates correction unless otherwise stated (* Mann Whiteny test).

not candidates for revascularization.[9-11] Intermittent pneumatic compression increases axial, muscular, collateral, and skin blood flow in patients with PAD[5,12] and CLI.[13] This evidence in the paucity of established methods of treatment when revascularization fails or is not feasible[3] prompted us to evaluate the clinical efficacy of IPC in patients with chronic nonhealing amputation wounds of the foot and tissue loss attributable to CLI on whom all means of additional revascularization had been exhausted.

METHODS

Institutional Review Board approval was granted before data were accumulated and analyzed. This is a retrospective controlled study pursued in a multidisciplinary wound-healing outpatient's clinic comprising orthopedics, vascular surgery, and vascular medicine services. Considered for inclusion were consecutive patients with chronic nonhealing toe or transmetatarsal amputation wounds and tissue loss of the foot attributable to chronic CLI,[3] on whom all means of additional revascularization had been exhausted. Excluded were those with tissue loss of mixed cause (ie, venous, vasculitic, neuropathic, infective, traumatic); those who underwent alternative means of CLI treatment in the course of the study, including vasoactive pharmacotherapy (ie, prostaglandins) and epidural analgesia, as a means of enhancing their healing response to the tissue loss; those with deep vein thrombosis sustained ≤6 months of the study inclusion or during the study course, and finally, those with calf wounds.

Conducted from January 1998 through December 2004, the study comprised two groups managed concurrently. The active treatment group (IPC group) consisted of 24 consecutive patients with a median age of 70 years (interquartile range [IQR], 68.7-71.3 years) who received IPC for tissue loss and nonhealing amputation wounds of the foot attributable to chronic CLI, in addition to a standardized wound care regimen. The control group (control group) also consisted of 24 consecutive patients with a median age of 69 years (IQR: 65.7-70.3) years who received a standardized wound care regimen for tissue loss and nonhealing amputation wounds of the foot due to chronic CLI, without the use of IPC. Group allocation depended solely on the patients' willingness to undergo IPC therapy. Demographic data of the study groups are in Table I. Baseline arterial evaluation of the patients in both study groups is summarized in Table II.

Vascular assessment included measurement of the resting ABI, duplex ultrasound scanning for lower limb arterial examination, graft surveillance, and exclusion of deep vein thrombosis and chronic venous stasis, in addition to leg radiography or magnetic resonance imaging or both. The functional evaluation of cutaneous blood flow was assessed with transcutaneous oximetry ($TcPO_2$) in the supine and dependent (10 minutes) positions performed with electrodes (temperature,

Table II. Baseline arterial status and amputations of patients in the control group (Group Control) and the group of those receiving intermittent pneumatic compression (Group IPC)[a]

Baseline Arterial Status	*Group IPC (n=24)*	*Group Control (n=24)*	*Significance (χ^2)*
Transcutaneous Oximetry ($TcPO_2$)			
0-20 mmHg	10 (42%)	12 (50%)	NS
21-30 mmHg	14 (58%)	12 (50%)	NS
Resting ABPI median (IQR)	0.55 (0.44-0.68)	0.52 (0.45-0.65)	NS**
Prior Arterial Reconstruction	*19 (79%)*	*16 (67%)*	*NS*
Femoro-popliteal Bypass	4 (17%)	6 (25%)	NS
Femoro-distal Bypass	15 (63%)	10 (42%)	NS
Femoro-peroneal	7 (29%)	5 (21%)	NS
Femoro-dorsalis pedis	5 (21%)	3 (13%)	NS
Femoro-medial-plantar artery	3 (13%)	2 (8.5%)	NS
Amputations			
Digit	14 (58%)	15 (63%)	NS
Ray	7 (29%)	6 (25%)	NS
Trans-metatarsal	7 (29%)	3 (13%)	NS

IPC, Intermittent pneumatic compression; *IRQ,* interquartile range; *NS,* not statistically different.
[a]Study patients, all with active foot ulcers, either had a $TcPO_2$ of 30 mmHg or less or had an absolute ankle pressure of less than 70 mmHg, or both, thus meeting contemporary TASCII criteria for critical limb ischemia. Differences in proportions between the two groups are based on the χ^2 with Yates correction, unless otherwise stated (** Mann Whitney test).

45°C) attached to the foot adjacent to the area of tissue loss and in the hindfoot, calf, and thigh (minimum of 4 probes) with airtight adhesive (normal, >45 mm Hg; mild ischemia, 40-45 mm Hg; moderate ischemia, 20-39 mm Hg; severe ischemia <20 mm Hg), Used for the purposes of this study were the lowest $TcPO_2$ values per posture and limb, apparently associated with the foot site of ischemia. The protocol of laboratory assessments performed during the study period is schematically presented in Table III. Patients enrolled in the study were followed up for 18 months. Surgical outcomes were considered favorable if complete healing occurred and the treated limb was salvaged. An unfavorable outcome was noted if the patient had to undergo a below knee amputation (BKA) subsequent to failure of healing and deterioration of the amputation wound.

All patients received a standard wound care regimen consisting of weekly débridement and biologic dressings with cadexomer iodine (Iodosorb, Smith & Nephew, London, UK), provided by a home health care agency under the supervision of the authors, and monthly surveillance at the wound center. Cadexomer iodine gel (Iodosorb), a standard adjunct in wound care, was added for its antimicrobial properties and tissue granulation enhancement.[14]

Intermittent pneumatic compression of the calf was delivered using the ArterialFlow (DJO, Vista, Calif), a mechanical pneumatic pump consisting of a pneumatic impulse generator and a plastic inflatable pad (length, 29 cm; maximum circumference, 48 cm), specially designed to fit the calf. Large-bore elastic tubing connects the unit with the pad. The pump throughout the study was set to operate at a maximum inflation pressure of 85 to 95 mm Hg, delivered for 2 seconds with a rise time of 0.2 seconds, and a deflation pressure of 0 mm Hg of 18 seconds' duration. A minimum of 6 hours of IPC application per day, in three 2-hour sessions, was requested. A 24-hour help-line was offered for pertinent emergencies or medical advice.

Table III. Working protocol of investigations in the two study groups

	Study baseline		*Study completion*[a]	
	IPC group	*Control group*	*IPC group*	*Control group*
Clinical exam	√	√	√	√
ABI determination	√	√	√	√
$TcPO_2$ determination	√	√	√	√

ABI, Ankle-brachial index; *$TcPO_2$,* transcutaneous oximetry.
[a]Follow-up lasted 18 months. In patients who died at 12 months, the assessments made when they were last examined were included.

Patient compliance was monitored by means of a recording device built-in the IPC pump and a patient logbook. As the IPC pumps were regularly inspected for optimal function, the IPC application time reported in the patient logbook was compared with that of the recording device.

Analysis of the study data was performed with nonparametric statistics.[15] Quantitated paired data comparisons between the initial and study completion $TcPO_2$ values were conducted with the Wilcoxon sign ranked test. Comparisons of quantitated nonpaired data for age, ABI, and $TcPO_2$ between the IPC group and the control group, both at baseline and at study completion, were conducted with the Mann-Whitney test. For those who died before study completion at 18 months, the data last accumulated were considered for an intention-to-treat analysis. The 95% confidence interval (CI) of the estimated median difference (Wilcoxon test), point

Table IV. Patency and graft or anastomotic stenosis (≤ 50%) of infrainguinal arterial bypass grafting in the two study groups at the time study patients were recruited[a]

Prior Arterial Grafting/Reconstruction	*IPC Group (n=24)*	
	Patency (%)	*Anastomotic/graft Stenosis ≤ 50%*
Femoro-popliteal Bypass	4 in 4 limbs (100%)	1 in 4 limbs (25%)
Femoro-distal Bypass	13 in 15 limbs (87%)	8 in 13 limbs (62%)
Femoro-peroneal	6 in 7 limbs (86%)	4 in 6 limbs (67%)
Femoro-dorsalis pedis	4 in 5 limbs (80%)	2 in 4 limbs (50%)
Femoro-medial-plantar artery	3 in 3 limbs (100%)	2 in 3 limbs (67%)
Total	**17 in 19 limbs (89%)**	**9 in 17 limbs (53%)**
Prior Arterial Grafting/Reconstruction	*Control Group (n=24)*	
	Patency (%)	*Anastomotic/graft Stenosis ≤ 50%*
Femoro-popliteal Bypass	5 in 6 limbs (83%)	2 in 5 limbs (40%)
Femoro-distal Bypass	9 in 10 limbs (90%)	5 in 9 limbs (56%)
Femoro-peroneal	5 in 5 limbs (100%)	3 in 5 limbs (60%)
Femoro-dorsalis pedis	2 in 3 limbs (67%)	1 in 2 limbs (50%)
Femoro-medial-plantar artery	2 in 2 limbs (100%)	2 in 3 limbs (67%)
Total	**14 in 16 limbs (87.5%)**	**7 in 14 limbs (50%)**

IPC, Intermittent pneumatic compression.
[a]There were no cases of graft or anastomotic stenosis exceeding 50%. Please note that these procedures were not performed in time proximity with the study, but they preceded the study patients' recruitment by several years, often more than 5 years.

estimate (Mann-Whitney test), and select proportions are quoted. Bonferroni correction was applied, if appropriate. Differences in proportion were assessed with the χ^2 test. A $P < .05$ was considered significant. Data are expressed as median and interquartile range (IQR).

RESULTS

Failure to meet the study criteria resulted in the exclusion of 19 potential recruits, leading to a dropout rate of 28.4%. Of those, 7 had mixed etiology ulcers (37%), 5 had received other treatments (ie, vasoactive drugs) for CLI in addition to IPC (26%), another 4 (21%) had sustained deep vein thrombosis in the limb with CLI ≤6 months of their potential recruitment, and 2 (11%) had additional ulcers in the calf.

The baseline differences in the age, the male/female ratio, and the associated cardiovascular risk factors (diabetes, smoking, hypertension, dyslipidemia, renal impairment) were not significantly different between the two study groups (Table I). This was also true for the baseline ABIs, $TcPO_2$, the extent and type of prior arterial reconstruction, and the type of PAD (Table II). The location of tissue loss or foot ulceration, or both, as well as the distribution of the local foot amputation procedures performed in the study course or <3 months before the commencement of the study, are presented in Table II. Study patients, all with active foot ulcers, either had a $TcPO_2$ of ≤30 mm Hg or had an absolute ankle pressure of <70 mm Hg, or both, thus meeting contemporary TransAtlantic Inter-Society Consensus (TASC) II criteria[3] for critical limb ischemia. Two grafts in the IPC group (1 femoral–peroneal and 1 femoral–dorsalis pedis) and 2 grafts in the control group (1 femoral–popliteal and 1 femoral–dorsalis pedis) had been found occluded on graft surveillance with duplex ultrasound imaging ≥12 weeks before the referral of patients for treatment at our institution. Patency or stenoses of the grafts, or both, in patients who had previously (months up to >5 years) undergone arterial revascularization in the two study groups are summarized in Table IV.

The local foot amputation failed to heal in 20 patients (83%) in the control group and they required BKA (Table V). The remaining four (17%, 95% CI, 0.59%-32.7%) had complete healing and limb salvage. However, 14 patients (58%, 95% CI, 37.1%- 79.6%) in the IPC group had complete healing and subsequent limb salvage. The remaining 10 patients (42%) in this group underwent BKA after the foot wound failed to heal. Wound healing and limb salvage were significantly better in the IPC group ($P < .01$).

The $TcPO_2$ in the supine position was similar between the two groups at baseline and remained so upon completion of the study ($P > .5$). The $TcPO_2$ in the sitting position on completion of the study was significantly better in the group receiving IPC (95% CI, 0.001-11.0 mm Hg; $P = .0038$). Comparison of the $TcPO_2$ between the two groups at the end of the study was conducted on the basis of $TcPO_2$ estimations performed before lower extremity amputation occurred. There was no difference in the ABIs between the two groups on study completion, obtained again just before extremity amputations were performed.

More than 83% (20 of 24) of patients in the IPC group complied fully with the allotted IPC treatment schedule. The remaining four used IPC less often than the time originally agreed upon (a minimum of 6 hours of IPC application per day), but no less than 75% of that time. Assisting compliance of IPC application was the clinical improvement that the patients so treated felt they had received.

Table V. Surgical outcomes at 18 months follow up in the group receiving intermittent pneumatic compression (Group IPC) and the control subjects (Group Control)[a]

Surgical Outcomes	*Group IPC (n=24)*	*Group Control (n=24)*	*Significance*
Survivorship at $18_{/12}$ follow up	20 (83%)	18 (75%)	NS
Complete healing - limb intact at $18_{/12}$	14 (58%)	4 (17%)	p<0.001
BKA after a failed local amputation	10 (42%)	20 (83%)	p<0.001
Hemodialysis	2	5	NS
Peripheral Perfusion			
$TcPO_2$ Horizontal <20	9 (37.5%)	12 (50%)	NS
$TcPO_2$ Horizontal 20-30	15 (62.5%)	12 (50%)	NS
$TcPO_2$ on Sitting <10	2 (8.3%)	10 (42%)	p<0.01
$TcPO_2$ on Sitting 10 to <20	4 (16.6%)	7 (29%)	NS
$TcPO_2$ on Sitting 20-40	18 (75%)	7 (29%)	p<0.01

BKA, below knee amputation; *IPC,* Intermittent pneumatic compression; *NS,* nonstatistically significant; *$TcPO_2$,* transcutaneous oximetry.
[a]Differences in proportion analysed with the χ^2 test with Yates correction. Quantitated non-paired data comparison between the two groups performed. Statistical analysis based on the Mann Whitney test.

DISCUSSION

The data from this controlled study revealed that patients with chronic CLI and wounds in the foot, due to a toe or transmetatarsal amputation and tissue loss, refractory to healing, may be significantly aided in improving their healing and the likelihood of limb salvage if IPC is provided as an adjunct to a standard wound care. Within 18 months of therapy commencement, three times as many patients with chronic CLI receiving IPC (6 hours per day) as part of their wound care had their foot ulcers completely healed (58%) and an equal proportion of limbs salvaged ($P < .01$), as those in the control group (17%) undergoing an identical treatment, except IPC, and matching the former in demography, cardiovascular risk factors, and PAD distribution. These findings come to enhance further the clinical momentum associated with the use of IPC in PAD.[6,7,9-11]

Previously, Montori et al[10] (2002) had investigated the effect of IPC among 107 patients (median age, 73 years) with CLI, of whom 94.4% had leg ulcers, 25% had a history of amputation, and 64% had diabetes. The etiology was multifactorial in 64% of wounds, and 60% were associated with $TcPO_2$ <20 mm Hg. Patients used IPC at home on the affected limb for 6 hours daily.[10] Within 6 months, complete wound healing and limb salvage had been achieved in 40% of patients with $TcPO_2$ levels <20 mm Hg, in 48% of those with osteomyelitis or active wound infection, in 46% of those with insulin-dependent diabetes, and in 28% of those who had a previous foot amputation.[10]

These findings are consistent with those by van Bemmelen et al[9] (2001) on 13 consecutive patients (mean age, 76), consisting of 14 legs with CLI (rest pain, 1; tissue loss, 13), who underwent 3-month IPC therapy (4 hours daily), in the absence of revascularization options owing to lack of outflow arteries (n = 7), lack of autogenous vein (n = 5), or poor general medical condition (n = 3).[9] They represented 10% of their referrals for CLI, and 62% were diabetic. In the duration of treatment, nine legs (64%) had a significant increase ($P < .05$) in pulse-volume amplitude, and all of these legs were salvaged.[9] The remaining limbs that failed to show any hemodynamic improvement were amputated. A direct correlation between patient compliance and clinical outcome was documented. Those in whom limb salvage was achieved made use of IPC for longer ($P < .05$) periods of time (mean 2.38 hours daily) compared with those who had limb amputation (mean 1.14 hours daily).[9]

Promising results with IPC for the management of chronic CLI were also reported by Louridas et al[11] (2002) in 25 patients, with tissue loss present in 23 limbs, rest pain in 10, after a failed bypass graft in 9, or with angiographically diagnosed distal disease that could not be reconstructed in the remaining.[11] At a mean follow-up of 3 months, 19 legs (58%) were saved and 14 (42%) were amputated, 11 of which were in patients with chronic renal failure, a known risk factor.[11] Excluding this group, the amputation rate was 13.6% (n = 3). Toe pressures after 3 months of IPC had significantly improved ($P = .03$). The mortality rate was 12% overall. Among those presenting with rest pain, 40% improved with IPC. While on IPC therapy, 26% of the foot ulcers healed.[11]

Assessment of the hemodynamic efficacy of IPC of the leg (120 mm Hg for 4 seconds, three times per minute) at a microcirculatory level with laser Doppler fluxmetry, had been reported to generate a significant increase in the skin blood flux ($P < .001$) at the pulp of the big toe on dependency in patients with critical or subcritical limb ischemia after femoral–popliteal and femoral–distal (18 limbs each) bypass grafting.[12] In a cohort of 20 limbs in 20 patients with CLI, with 14 limbs characterized as inoperable and six considered as marginal for reconstruction, IPC leg application (120 mm Hg, inflation 3 seconds, deflation 17 seconds) caused flow to increase significantly in the popliteal, gastrocnemial, and collateral arterial arteries (18 of 20 limbs) compared with baseline values ($P < .02$).[13] This was associated with a significant skin blood flux increase ($P < .03$). In two limbs without arterial or skin blood flow enhancement with IPC, significant popliteal vein reflux was present and both limbs were amputated shortly thereafter.[13]

Three physiologic mechanisms have been implicated in explanation of the leg inflow enhancement with IPC in PAD:

(1) an increase in the arteriovenous pressure gradient, (2) suspension of peripheral sympathetic autoregulation, and (3) enhanced release of nitric oxide with flow and shear-stress increase.[7,16] Arteriovenous pressure-gradient enhancement with IPC could not be disputed in CLI,[17] forming the substrate empowering ignition of the other two mechanisms.[7,16] 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.[7,16-18] 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.[5,7,16-18]

A direct reduction in peripheral resistance has also been postulated by 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.[5,7,16,19,20] 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 revealed an up-regulation of tissue plasminogen activator and nitric oxide synthase expression.[19,20]

Transient suspension of the venoarteriolar reflex, an axon sympathetic reflex autoregulating arteriolar resistance, is probably an additional mechanism of peripheral resistance attenuation during IPC.[21,22] The unstretched baroreceptors of the emptied venous radicles, immediately after impulse delivery, transiently cease igniting their vasoconstrictor effect through the reflex until priming of the refilling veins causes the baroreceptors to stretch again.[21-26] Peripheral sympathetic autoregulation is considered largely abolished in CLI,[21] yet epidural anesthesia and analgesia[27] and the administration of prostaglandins,[28,29] both causing attenuation of peripheral flow resistance with vasodilatation, have been reported to offer an appreciable clinical improvement, thus contradicting the contention of peripheral vasoparalysis in CLI.

It has been purported that an aggressive approach to arterial revascularization is justified on humanitarian and socioeconomic grounds.[30-32] With the aging population in Western societies and thus the increasing prevalence of CLI with age, the financial implications of limb salvage, revascularization, or otherwise, are most substantial, with savings estimated to exceed US $40 million per annum in the United Kingdom.[33,34] However, repercussions on quality of life are probably of an even higher order, because elderly amputees are less likely be mobile with a prosthesis.[35-37]

Examining the association between limb salvage and reconstruction in patients with CLI aged ≥70 years, Eskelinen et al[38] (2003) reported 1976 major amputations per million inhabitants when infrapopliteal bypass surgery was methodically pursued for severe PAD compared with 3177 per million when infrapopliteal bypass surgery was performed as a last resort to preventing limb loss.[38] In a 20-year perspective of the patient and procedural variables in infrainguinal reconstruction in a tertiary practice (1978-1997), an increasingly complex medical and surgical challenge was documented when compared with the previous decades pertaining to a significant increase in the age, female sex, diabetes mellitus, renal failure, prior coronary artery bypass grafting, technical complexity, tissue necrosis as the indication for surgery, more distal levels of outflow, and the use of ectopic or synthetic graft material.[39] These clearly indicate the need for methods that would be able to reverse perfusion in CLI when arterial reconstruction surgery is exhausted.

On the basis of the data of the current report, adding to those by previous accounts,[9-11] IPC appears to be able to enhance tissue healing and limb salvage in patients with CLI, secondary to perfusion augmentation. Although $TcPO_2$ determination is susceptible to a host of confounding variables, the importance of the information derived is substantial, reflecting cutaneous blood flow, metabolic activity, oxyhemoglobin dissociation, and oxygen diffusion through the tissues.[40] The $TcPO_2$ measurement is most sensitive to higher grades of arterial obstruction and tissue perfusion impairment. The substantial increase of $TcPO_2$ in the IPC group on dependency may indicate a far better balance between oxygen supply and the metabolic demand of the ischemic tissues after therapy with IPC. Severe arterial foot inflow and sympathetic autoregulation impairment is likely implicated in the improvement of $TcPO_2$ on dependency alone among the patients of the IPC group. Other investigators have associated the clinical improvement of CLI after IPC, with pulse-volume amplitude[9] and toe pressure[11] corroborating distal arterial perfusion enhancement.

In addressing plausible limitations of the present study, its retrospective controlled design would certainly not be able to provide the robustness of evidence that a prospective, randomized controlled design could yield. Nonetheless, the study aimed to contribute further to our understanding of the clinical and hemodynamic efficacy of IPC in patients with CLI, with data never previously published to our knowledge. Those who agreed to receive IPC might represent those with a more aggressive or adventurous mindset, or both, seeking resolution of their physical problem more emphatically than those who declined IPC. Conversely, study groups consisted of demographically matched patients of the same geographic region who had sought optimal care at our nonpublic institution before and during the active ulcer period aided in bridging plausible social or economic discrepancies, or both. A better control group would have been put on IPC for 6 hours daily, but without active compression; yet those acting as the control group would not have agreed to such an option. Finally, the clinical efficacy of other IPC modes (ie, IPC of foot, IPC of foot and calf) or optimal duration of IPC use, or both, could not be addressed in the framework and study population of the present study.

CONCLUSION

By enhancing the leg inflow and the metabolic balance of tissue oxygen supply to its demand, IPC has been found to promote the healing process and to improve limb salvage in patients with CLI when revascularization options are unavailable or exhausted and established treatment alternatives in current practice are lacking. These encouraging data are in support of large-scale multicentric studies aiming not only to substantiate the exact indications and the actual clinical benefit but also to

promote our insight into the underlying physiologic mechanisms that facilitate these IPC-dependent outcomes.

AUTHOR CONTRIBUTIONS

Conception and design: SJK, KTD
Analysis and interpretation: SJK, KTD
Data collection: SJK
Writing the article: KTD, SJK
Critical revision of the article: KTD
Final approval of the article: JK, KTD, NST, AEV, DAL, PG, TWR
Statistical analysis: KTD
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Overall responsibility: SJK, KTD

REFERENCES

1. Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. Semin Vasc Surg 1999;12:142-7.
2. The Westcoast Vascular Surgeons (WVS) Study Group. Variations of rates of vascular surgical procedures for chronic critical limb ischaemia and lower limb amputation rates in western Swedish counties. Eur J Vasc Endovasc Surg 1997;14:310-4.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al; and the TASC II Working Group. Consensus Statement Inter-society consensus for the management of peripheral arterial disease. Int Angiol 2007;26:81-158.
4. Pohjolainen T, Alaranta H. Lower limb amputations in southern Finland 1984-1985. Prosthet Orthot Int 1988;12:9-18.
5. Delis KT, Nicolaides AN, Labropoulos N, Stansby G. The acute effect of intermittent pneumatic foot vs calf vs simultaneous foot and calf compression on popliteal artery hemodynamics: a comparative study. J Vasc Surg 2000;32:284-92.
6. Delis KT, Nicolaides AN. 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. Ann Surg 2005;241:431-41.
7. Delis KT. The case for intermittent pneumatic compression of the leg as a novel treatment in patients with intermittent claudication. Persp Vasc Surg Endovasc Ther 2005;17:29-42.
8. van Bemmelen PS, Weiss-Olmanni J, Ricotta JJ. Rapid intermittent compression increases skin circulation in chronically ischemic legs with infra-popliteal arterial obstruction. Vasa 2000;29:47-52.
9. 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;136:1280-5.
10. Montori VM, Kavros SJ, Walsh EE, Rooke TW. Intermittent compression pump for nonhealing wounds in patients with limb ischemia. The Mayo Clinic experience (1998-2000). Int Angiol 2002;21:360-6.
11. Louridas G, Saadia R, Spelay 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.
12. Delis KT, Husmann MJ, Nicolaides AN, Wolfe JH, Cheshire NJ. Enhancing foot skin blood flux in peripheral vascular disease using intermittent pneumatic compression: controlled study on claudicants and grafted arteriopaths. World J Surg 2002;26:861-6.
13. Labropoulos N, Leon LR Jr, Bhatti A, Melton S, Kang SS, Mansour AM, et al. Hemodynamic effects of intermittent pneumatic compression in patients with critical limb ischemia. J Vasc Surg 2005;42:710-6.
14. Skog E, Arnesjö B, Troëng T, Gjöres JE, Bergljung L, Gundersen J, et al. A randomized multicenter trail comparing cadexomer iodine and standard treatment in the out patient management of chronic venous ulcers. Br J Dermatol 1983;109:77-83.
15. Altman DG. Practical statistics for medical research. Boca Raton, FL: Chapman and Hall/CRC; 1999.
16. Delis KT, Knaggs AL. Duration and amplitude decay of acute arterial leg inflow enhancement with intermittent pneumatic leg compression: an insight into the implicated physiologic mechanisms. J Vasc Surg 2005;42:717-25.
17. Delis KT, Azizi ZA, Stevens RGJ, Wolfe JHN, Nicolaides AN. Determining the optimum intermittent pneumatic compression stimulus for lower limb venous emptying using direct pressure measurements. Eur J Vasc Endovasc Surg 2000;19:261-70.
18. Delis KT, Slimani G, Hafez HM, Nicolaides AN. Enhancing venous outflow in the lower limb with intermittent pneumatic compression. A comparative haemodynamic analysis on the effect of foot vs. calf vs. foot and calf compression. Eur J Vasc Endovasc Surg 2000;19:250-60.
19. Dai GD, Tsukurov O, Orkin RW, Abbott WM, Kamm RD, Gertler JP. An in vitro cell culture system to study the influence of external pneumatic compression on endothelial function. J Vasc Surg 2000;32:977-87.
20. Dai G, Tsukurov O, Chen M, Gertler JP, Kamm RD. Endothelial nitric oxide production during in vitro simulation of external limb compression. Am J Physiol Heart Circ Physiol 2002;282:H2066-75.
21. Delis KT, Lennox AF, Nicolaides AN, Wolfe JH. Sympathetic autoregulation in peripheral vascular disease. Br J Surg 2001;88:523-8.
22. Delis KT, Nicolaides AN, Wolfe JHN. Peripheral sympathetic autoregulation in arterial calf inflow enhancement with intermittent pneumatic compression. Eur J Vasc Endovasc Surg 2001;22:317-25.
23. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. Scand J Clin Lab Invest 1974;34:103-9.
24. Henriksen O. Local nervous mechanism in regulation of blood flow in human subcutaneous tissue. Acta Physiol Scand 1976;97:385-91.
25. Michel CC. Microcirculation in the limbs in venous hypertension. Medicographia 1989;11:40-2.
26. Levick JR, Michel CC. The effects of position and skin temperature on the capillary pressures in the fingers and toes. J Physiol 1978;274:97-109.
27. Hickey NC, Wilkes MP, Howes D, Watt J, Shearman CP. The effect of epidural anaesthesia on peripheral resistance and graft flow following femorodistal reconstruction. Eur J Vasc Endovasc Surg 1995;9:93-6.
28. The ICAI Study Group. Prostanoids for chronic critical leg ischemia. A randomized, controlled, open-label trial with prostaglandin E1. Ann Intern Med 1999;130:412-21.
29. The Iloprost Bypass International Study Group. Effects of perioperative ilioprost on patency of femorodistal bypass grafts. Eur J Vasc Endovasc Surg 1996;12:363-71.
30. Johnson BF, Evans L, Drury R, Datta D, Morris-Jones W, Beard JD. Surgery for limb threatening ischaemia: a reappraisal of the costs and benefits. Eur J Vasc Endovasc Surg 1995;9:181-8.
31. Vascular Surgical Society of Great Britain and Ireland. Critical limb ischemia: management and outcome. Report of a national survey. Eur J Vasc Endovasc Surg 1995;10:108-113.
32. Luther M. Treatment of chronic critical leg ischaemia–a cost benefit analysis. Ann Chir Gynaecol 1997;213:1-142.
33. Cheshire NJW, Noone MA, Wolfe JHN. Re-intervention after vascular surgery for critical leg ischaemia. Eur J Vasc Surg 1992;6:545-50.
34. Sayers RD, Thompson MM, Hartshorn T, Budd JS, Bell PRF. Treatment and outcome of severe lower limb ischaemia. Br J Surg 1994;81:521-3.
35. Houghton AD, Taylor PR, Thurlow S, Rootes E, McColl I. Success rates for rehabilitation of vascular amputees: implications for preopretaive assessment and amputation level. Br J Surg 1992;79:753-5.
36. McWhinnie DL, Gordon AC, Collin J, Gray DWR, Morrison JD. Rehabilitation outcome 5 years after 100 lower limb amputations. Br J Surg 1994;81:1596-9.
37. Pohjolainen T, Alaranta H, Karkkainen M. Prosthetic use and functional and social outcome following major lower limb amputation. Prosthet Orthot Int 1990;14:75-9.
38. Eskelinen E, Luther M, Eskelinen A, Lepantalo M. Infrapopliteal bypass reduces amputation incidence in elderly patients: a population based study. Eur J Vasc Endovasc Surg 2003;26:65-8.
39. Conte MS, Belkin M, Upchurch GR, Mannick JA, Whittemore AD, Donaldson MC. Impact of increasing comorbidity on infrainguinal reconstruction: a 20-year perspective. Ann Surg 2001;233:445-52.
40. Zwicky S, Mahler F, Baumgartner I. Evaluation of clinical tests to assess perfusion in chronic critical limb ischemia. Vasa 2002;31:173-8.

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