Hemodynamic effects of intermittent pneumatic compression in patients with critical limb ischemia

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Background: Traditional teaching assumes that the distal arterial tree is maximally dilated in patients with critical limb ischemia (CLI). Endovascular or arterial bypass procedures are the commonly used interventions to increase distal perfusion. However, other forms of treatment such as spinal cord stimulation or intermittent pneumatic compression (IPC) have been shown to improve limb salvage rates. This prospective study was designed to determine if the use of IPC increases popliteal, gastrocnemial, collateral arterial, and skin blood flow in patients with CLI.

Methods: Twenty limbs with CLI in 20 patients (mean age, 74 years) were evaluated with duplex ultrasound scans and laser Doppler fluxmetry in the semi-erect position before, during, and after IPC. One pneumatic cuff was applied on the foot and the other on the calf. The maximum inflation pressure was 120 mm Hg and was applied for 3 seconds at three cycles per minute. All patients had at least two-level disease by arteriography. Fourteen limbs were characterized as inoperable, and six were considered marginal for reconstruction. Flow volumes were measured in the popliteal, medial gastrocnemial, and a genicular collateral artery. Skin blood flux was measured on the dorsum of the foot at the same time.

Results: Significant flow increase during the application of IPC was found in all three arteries (18/20 limbs) compared with baseline values (P < .02). The highest change was seen in the popliteal, followed by the gastrocnemial and the collateral artery. After the cessation of IPC, the flow returned to baseline. This was attributed to the elevation of time average velocity, as the diameter of the arteries remained unchanged. The skin blood flux increased significantly as well (P < .03). In the two limbs without an increase in the arterial or skin blood flow, significant popliteal vein reflux was found. Both limbs were amputated shortly after.

Conclusions: IPC increases axial, muscular, collateral, and skin blood flow in patients with CLI and may be beneficial to those who are not candidates for revascularization. Patients with significant venous reflux may not benefit from IPC. This supports the theory that one of the mechanisms by which IPC enhances flow is by increasing the arteriovenous pressure gradient. (J Vasc Surg 2005;42:710-6.)

Intermittent pneumatic compression (IPC) is widely used as prophylaxis for deep venous thrombosis (DVT). In the early 1930s, IPC was shown to have a positive effect on lower-extremity blood flow of the calf and foot. Later, clinical benefits in patients with various degrees of limb ischemia were demonstrated, including those with critical limb ischemia (CLI).

CLI occurs when the blood supply to the capillary beds is less than that necessary to maintain tissue viability. Arteriolar vasodilation, resulting in a reduction of peripheral vascular resistance, is a compensatory response to CLI. Peripheral arterioles in CLI are relatively insensitive to vasodilator stimuli compared with those in control subjects. Consequently, arterioles in CLI patients are thought to be “maximally dilated,” a phenomenon known as vasomotor paralysis, which has become a traditional assumption.

Significant evidence suggests that IPC increases temporarily the arterial blood flow in healthy subjects, in patients with intermittent claudication, and in those with peripheral arterial disease with prior successful surgical revascularization. However, Duplex ultrasound (DU) or laser Doppler blood flow (LDF) evaluation of the lower extremities in patients with CLI has not been yet reported. We postulate that the demonstrated clinical effect of IPC on limbs with CLI is due to further increases in the arterial blood flow at all levels, either because of a reversal of vasomotor paralysis or an increase in the lower-extremity arteriovenous gradient caused by venous emptying from intermittent compression.

This prospective study was designed to measure the hemodynamic effects of IPC in patients with CLI in the systemic, muscular, and collateral circulation as well as in the foot skin blood flow.

PATIENTS AND METHODS

Limbs of patients with CLI were evaluated with DU and LDF in the semi-erect position before, during, and after IPC. CLI was defined according to the TransAtlantic Inter-Society Consensus document as those patients whose arterial disease has resulted in a breakdown of the skin (ulcer or gangrene) or pain in the foot at rest. It corresponds to stages III and IV of the Fontaine classification. The semi-erect position was chosen to study these limbs for two reasons: it was the natural position adopted by these patients because of severe discomfort while lying supine, and to increase the arterio-venous gradient. The ArtAssist device (model AA-1000; ACI Medical Inc., San Marcos, California) was used in all cases. Inflatable 12- and 22-cm bladders in a single cuff structure were
applied on the foot and calf, respectively. The maximum inflation pressure of 120 mm Hg was applied for 3 seconds at three cycles per minute. The foot bladder was inflated first, and the calf bladder, 2 seconds later. This is a rapid inflation device, with a time of 300 to 360 milliseconds to reach peak pressure.

All patients underwent digital subtraction arteriography to optimize visualization and vessel conspicuity with maximum contrast of the potential distal target arteries. The images were obtained with the target limb gently but securely immobilized to limit patient motion, which would cause misregistration artifact on the digital subtraction images. Whenever possible, the target area was imaged in an anatomic position (either anteroposterior or lateral) to optimize correct identification of distal target vessels.

Nonionic and isosmolar contrast agents were used to minimize patient discomfort. Appropriate collimation, filtering and catheter positioning were used to optimize radiographic exposure in the target area. Whenever possible, contrast was injected from the ipsilateral side to maximize contrast opacification. Long, 5- to 10-second infusion times and delay were used to allow for complete filling of any patent channels in the target extremity. Peripheral vasodilators (tolazoline, nitroglycerine) or hot compress warming were often used to maximize peripheral vasodilation.

The images were reviewed by an interventional radiologist (M. B.) and by two vascular surgeons (A. M., S. S. K.). They were classified as inoperable if no target vessels were identified for revascularization and marginal for reconstruction if the target vessels had a small caliber or diffuse disease that made them not suitable for a durable bypass procedure or intervention.

For the purpose of this study, patients selected had a patent popliteal artery. Before each measurement, the subjects were acclimatized in supine position on a couch for at least 10 minutes. Flow volumes were measured in the popliteal, medial gastrocnemius, and a genicular collateral artery. Artery blood flow was measured by using a 4- to 7-MHz linear array transducer (ATL-Ultramark 9; Advanced Tech Laboratory, Bothell, Wash). The internal arterial diameter was measured by imaging the vessel longitudinally with real time B-mode. The average of three repeated measurements was obtained. Velocity measurements were performed at an angle of 60°, with the gate of the sample volume matching the internal diameter of the artery. The mean volume flow was calculated from the time average mean velocity of at least five cycles.

At the same time, skin blood flow was measured at the dorsum of the foot by using LDF (Laserflo model BPM 403A, TSI Inc, St Paul, Minn) and recorded in flux units. The BPM 403A has a semiconductor gallium-aluminum-arsenide diode that emits a laser beam with a 780-nm wavelength. For all studies, a right angle probe was used. The probe was fixed on the skin by means of a double adhesive ring and adhesive tape. LDF readings at rest, before the initiation of the pump, were stabilized over a 5-minute period. The average resting skin blood flow was calculated over 30 seconds. The skin blood flow during the pump application was not measured because of significant motion artifact and was averaged for 10 seconds immediately after.

No attempts were made to correlate the hemodynamic findings with transcutaneous oxygen pressure measurements (TcPO2), as they were not performed simultaneously with the other two methods.

The degree of discomfort produced by the application of the pump was graded as none, mild, moderate, and severe. In cases of severe discomfort, the pump was discontinued and the patient was excluded from the study.

Statistical analysis. Descriptive statistics were used for patient demographic characteristics. A paired t test was used to compare the arterial flows and diameters before, during, and after the application of IPC. Data were expressed as a mean and 95% confidence intervals (CI). The Wilcoxon sum-rank test was used for the LDF data, as their distribution was nonparametric. These data were expressed as median and interquartile range (IQR). The level for statistical significance was set at P = .05.

RESULTS

Twenty limbs with CLI in 20 patients (mean age, 74 years) were evaluated. The demographic characteristics are summarized in Table I. An additional patient was excluded because of inability to tolerate the foot component of the pump due to severe pain. All other patients tolerated it well, with mild-to-moderate discomfort that disappeared after a few pump cycles. All of the patients in our study had rest pain, and nine had tissue loss. All had an ankle-brachial index (ABI) of <0.3, and the mean TcPO2 was 21.6. All patients had at least two-level disease by arteriography. Stenosis or occlusion in the aortoiliac segment was found in 17 patients, common femoral in 6, deep femoral in 6, superficial femoral in 18, and all patients had infrapopliteal disease. Fourteen limbs were inoperable, and six were marginal for reconstruction.

Significant flow increase during the application of IPC was found in all three arteries (18/20 limbs) compared

Table I. Demographic characteristics of the study population before intervention

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>74 (65–83)</td>
</tr>
<tr>
<td>Males</td>
<td>13</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
</tr>
<tr>
<td>Mean ABI (range)</td>
<td>0.25 (0.1–0.29)</td>
</tr>
<tr>
<td>Mean TcPO2 (range)</td>
<td>21.6 (12–31)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13</td>
</tr>
<tr>
<td>Smoking</td>
<td>12</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11</td>
</tr>
<tr>
<td>Rest pain</td>
<td>20</td>
</tr>
<tr>
<td>Tissue loss</td>
<td>9</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2</td>
</tr>
<tr>
<td>History of prior bypass</td>
<td>8</td>
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</tbody>
</table>

ABI, Ankle-brachial index; TcPO2, transcutaneous oxygen pressure measurements.
with baseline values ($P < .02$) (Table II). The highest change was seen in the popliteal (104.5%), followed by the gastrocnemial (70%) and the collateral artery (55.6%). After the cessation of IPC, the flow returned to baseline. This was attributed to the elevation of time average velocity as the diameter of the arteries remained unchanged (Fig 1 and Table III). The skin blood flux increased significantly as well (3.5 flux units, IQR 2 to 4.2 vs 5.2 flux units, IQR 3.8 to 6.2, $P < .03$) (Fig 2).

In the two limbs without an increase in the arterial or skin blood flow, significant popliteal vein reflux was found (Fig 3). This reflux was of high velocity and >5 seconds in duration in both cases. Both limbs were amputated shortly after. The remaining 18 patients did not have popliteal reflux. The rest of the veins were not examined, but none of them had clinically evident varicose veins or a history of venous thrombosis. Two patients were lost at a 6-month follow-up. Four patients underwent amputations at 10, 14, 30, and 60 days after the experiment.

**DISCUSSION**

Several trials on the effects of IPC on the arterial system in the lower limbs have been reported. A meta-analysis of studies between 1966 and 2001 identified several limitations.19 There were differences in the type of devices used (sequential vs simultaneous compression), protocols of cycle length, and duration of treatment, severity of limb ischemia, flow measurement techniques, and end points for analysis. Moreover, only three prospective randomized studies were found, all with small sample sizes. Despite those limitations, a clear trend toward a favorable effect on limb hemodynamics was observed.

The first prospective, randomized, controlled evidence for an increase in arterial blood flow with IPC in patients with intermittent claudication was reported in 1993,20 and that was followed by three additional trials.5,21,22 They showed significant beneficial effects on walking distance, symptoms, and systolic blood pressure measurements on the upper and lower limbs with therapy. However, studies on CLI and IPC have been limited to clinical outcomes4,23-25 and case reports.26 The case series are mostly retrospective.23,24

Montori et al23 retrospectively analyzed IPC in 107 patients with arterial ulcers. With a median follow-up of 6 months, wound healing was seen in 40% of patients with TcPO2 levels $<$20 mm Hg. Vella et al24 retrospectively analyzed IPC in 96 patients with ischemic ulcers and found benefit in their treatment at all TcPO2 levels. Van Bemmel et al25 studied 14 consecutive ischemic legs in a Veterans Administration hospital. The patients were deemed poor candidates for surgery and were treated with IPC for 4 hours per day at home for 3 months. Clinical outcomes and calibrated pulse-volume amplitudes were recorded. Nine legs were salvaged.

The only prospective trial was a pilot study of clinical outcomes involving IPC therapy of 33 limbs with CLI.1 At a mean follow-up of 3 months, 58% of legs were saved. Rest pain improved in 40% of patients, 26% of foot ulcers healed, and toe pressures significantly improved.

Several studies have shown increased popliteal artery blood flow during IPC application in healthy subjects and in patients with claudication.13,14,32,34 However, our study
is the first to demonstrate significant improvements in the popliteal artery blood flow in patients with CLI. It is also the first study to demonstrate significant flow increases in muscular and collateral arteries. The previous reports and the current study support arteriovenous pressure gradient augmentation as the main mechanism for the flow increase. This has been shown by the reduction of the venous pressure during IPC application. In the sitting position, the venous pressure in the foot is about 60 mm Hg. The application of IPC reduces this pressure and therefore increases the arteriovenous pressure gradient.

The resting blood flow in the popliteal artery in patients with CLI is reported for the first time in the literature. Compared with previous publications, the resting blood flow in the sitting position in claudicants is significantly higher than in our patients with CLI. This can be explained by the multiple levels of the occlusive disease as depicted by the angiograms and the very low ABI values. The relative increase of blood flow volumes in patients with CLI was significant for all three arteries during IPC. However, the magnitude of change was significantly less compared with previous studies that evaluated patients with claudication. With increasing levels of disease, more vasodilatation is likely present, and therefore, the margin for flow enhancement is less.

Vasodilatation is one of the mechanisms by which limbs with non-CLI obtain an increase in their blood flow. This is through the production of nitric oxide during mechanical stimulation (device inflation). It has been recently proposed that the application of IPC causes a forward pulsatile flow, resulting in emptying of blood at that site. The increase of blood volume and velocity exerts a compressive strain and enhances the shear stress on the venous endothelial cells. IPC has also an effect on the arterial system, as the sudden drop in the venous pressure causes an increase in the arteriovenous gradient that augments the arterial blood velocity. As a consequence, the shear stress on arterial endothelial cells is increased. Cell cultures and animal models have shown that the mechanical forces of shear and strain may elicit vasodilatory, antithrombotic, and fibrinolytic responses in endothelial cells.

Patients with CLI are assumed to have maximal vessel dilatation caused by the critical lack of oxygen. Our findings bring the possibility of a submaximal level of dilatation, which could be raised with compression. Such vasodilatation should occur in the arteriolar level, as we showed that there is no change in the diameter of the popliteal, gastrocnemial, and collateral arteries during IPC. Other studies have also shown no change in the diameter of the popliteal artery in healthy subjects and in patients with claudication during IPC. This is also substantiated by the increased LDF in our patients, which measures flow in the microcirculation. Further research is required to elucidate this matter.

Another question is related to the magnitude of the blood flow increase. We hypothesize that collaterals showed the lowest increase in blood flow because vessel dilatation in these arteries is likely almost maximum. The same theory may be applicable to muscular arteries, smaller in size and probably fully dilated because of muscle ischemia. The popliteal artery had the greatest flow increase. This was possibly because of the additive effect of the diminished peripheral resistance in collateral and muscular branches that the main popliteal artery supplies.

It is of interest to observe two occurrences of popliteal vein reflux in patients who ultimately underwent limb amputation shortly after the study. No reports have addressed the causes for failure to achieve beneficial arterial hemodynamic effects with IPC. Malone et al demonstrated that patients with post-thrombotic venous disease have a compromised venous hemodynamic response to all IPC devices. Furthermore, they showed an increased velocity response to high-pressure, rapid-inflation IPC machines. But this has only been evaluated in the context of DVT prophylaxis. Van Bemmelen et al did not see any hemodynamic improvement in limbs that were amputated after IPC therapy. No comments are made as to the reasons for failure and no documentation of reflux made.

Conceivably, significant axial vein reflux will impede a clinically significant arteriovenous gradient, limiting flow augmentation in the arterial system, supporting further this theory as the underlying mechanism for the success of IPC devices. The introduction of novel IPC designs could po-
potentially improve venous emptying and arterial flow in these subjects.29 Commercially available IPC devices have constant cycles of compression and deflation. It has been shown that vein refilling times vary with limb position and with different venous pathologies.29,30 Relatively new systems have been designed with the ability to detect venous volume changes and to respond by initiating the subsequent cycle when the veins are again full. So far, this technology has not been tested from the arterial flow point of view but appears feasible and promising.

No studies have been designed to identify the ideal compression sequence to enhance arterial blood flow maximally in the lower limbs of patients with ischemia. However, following the premise that IPC acts through enhancement of venous flow and increasing the arteriovenous gradient, we chose our treatment strategy by selecting the optimal way for venous emptying. This was based on a study that showed that foot and calf compression of 120 to 140 mm Hg with a frequency of 3 to 4 impulses per minute and 1-second delay was the optimum stimulus, as it had the maximal reduction in the venous pressure.16

LDF has been used to assess blood flow at the foot skin level in patients with different levels of limb ischemia.12,35 However, foot skin level assessment of blood flow has never been reported in patients with CLI. Our study is the first evidence of an improvement of blood flow at the skin level in this subgroup, which once more is against the presumed clinical dictum of maximal dilatation. This supports further the theory of a submaximal level of dilatation even at the skin capillary level, which is ultimately required for the healing of ulcers caused by arterial disease.

Nailfold capillary video microscopy has shown that the arteriolar postural vasoconstriction is abolished in patients with CLI.36 It has also demonstrated that the capillary density increases significantly from the supine to the dependent position. These phenomena explain why patients with CLI prefer to have their limbs in the dependent position.

As previously mentioned, the application of IPC is effective in reducing the venous pressure, further increasing the limb blood flow. The increase in LDF at the foot supports these findings and implies significant changes at the arteriolar level. The marked increase of blood flow at the systemic, muscular, collateral, and skin levels provide useful evidence for the application of IPC in this cohort of patients when no other options for limb salvage are available.

Only one patient in our series had severe pain due to IPC application. Seven of 107 patients in the Montori et al series23 discontinued the device because of pain experienced with its use. These results suggest that this machine is well tolerated by most patients. Clinically, these devices can still be used on those few patients that experience pain by omitting the bladder that compresses the sensitive area. Later, the bladder may be reintroduced into therapy if tolerated.

Limitations. We did not analyze the effect of patient position during the test to see how much of the improvement was due to arteriovenous gradient vs vasodilatation. All of our patients were tested in the semi-erect position because they tolerated the application of IPC better and because it has been proven to be optimal for venous emptying and arterial flow enhancement.1,3,16

Volume flow measurements were performed by using the internal diameter of the arteries, assuming that these vessels were perfect cylinders. However, they were often
irregular, which further increased the inherent errors of this measurement. Since the location of the measurement was kept constant and each vessel as its own control, this should not have a significant effect in the results of the study. No correlation was made with TcPO2 measurements. Even though all of our patients had this test performed, they were not simultaneously done with DU or LDF. These, added to the inherent variability and limited reliability of this exam, were reasons not to include TcPO2 results in the final analysis.

It is important to mention that all 20 patients had a patent popliteal artery; therefore, our findings apply only to CLI patients with such an anatomic configuration. Patients with CLI who have this condition may be selectively advantaged compared with those with popliteal artery occlusion. IPC may be beneficial for this subgroup of patients, however, as the collateral and muscular artery flow were shown to improve as well.

Conclusively, no long-term clinical follow-up was available to address the clinical impact of the hemodynamic changes in this subset of patients. As this was an acute-phase experiment, no detailed follow-up was available other than the amputations performed within 6 months. However, several clinical trials have suggested that this technique is associated with an improved rate of limb salvage, wound healing, and improvement in ischemic symptoms.

**CONCLUSIONS**

This is the first evidence to show IPC improvements at all levels: axial, muscular, and collateral arteries as well as in skin blood flow in patients with CLI. This treatment is well tolerated and may be beneficial to those who are not candidates for revascularization. Patients with significant venous reflux may not benefit from IPC. This supports the theory that IPC enhances flow by increasing the arteriovenous pressure gradient. Our findings also support the theory that distal vasodilation is not maximal in areas of ischemia and that further decreases in their vascular resistance can be achieved with IPC. As one of the most skeptical surgeons have acknowledged, the time for a multicenter randomized trial has come.

**REFERENCES**


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