Sequential Pneumatic Compression Biomechanical Home Therapy Device in the Management of Critical Lower Limb Ischemia for No-Option Patients

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ABSTRACT: Critical limb ischemia (CLI) causes pain, skin ulcers, and sores, and it leads to an unacceptable quality of life. Sequential pneumatic compression (SPC) has been proposed as an adjunct to best medical care, aimed at preventing amputation, relieving pain, and promoting wound healing by recruiting the nonfunctional capillary bed and increasing blood flow in distal limbs. Our tertiary referral center conducted a study to determine the efficacy of SPC in patients with CLI between 2005 and 2015, where patients were commenced on a 12-week treatment protocol. Sustained clinical improvement was 68% at 1 year. Thirty-day mortality was 0.6%. Limb salvage was 94% at 5 years. Freedom from major adverse clinical events was 62.5% at 5 years. All-cause survival was 69% at 4 years. From 2010 to 2015, 20 limbs (7.6%) underwent major amputation out of the 262 limbs studied. Amputation-free survival was 98% for those who acquired the device and 90% for those who did not at 6 months, and 96% and 84% at 1 year, respectively. SPC is a valuable tool in the armamentarium for CLI therapy. It achieves rapid relief of rest pain without any intervention in patients with limited life expectancy. It reduces minor amputations and adjourns major amputations, although it does not significantly lessen the incidence of inevitable limb loss.

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Critical limb ischemia (CLI) causes pain, skin ulcers, and sores, and it leads to an unacceptable quality of life. The 5-year mortality for patients with CLI is 70%. Of those, 35% are cardiovascular deaths.1-4 Previous studies have signalled an increase in the incidence of amputations, which may be attributed to cardiovascular atherosclerotic burden, the pandemic of diabetes mellitus, and an aging population.5-7 This predicts an increase in the number of major amputations
over the coming decades. CLI is a serious condition with dire consequences. After 1 year, only half of the patients diagnosed with CLI will be alive without a major amputation. Approximately 25% would have undergone a major amputation, and the remaining 25% would have died. Unmanaged patients with CLI are associated with high subsequent morbidity and mortality due to the associated prohibitive cardiovascular risk factors.

Revascularization is not always a viable treatment option, either due to the poor general condition of the patient or due to the absence of reconstructable vessels. Despite advances in vascular surgical and interventional radiologic techniques, up to 14% to 20% of patients with CLI are not suitable for distal arterial reconstruction, owing to occlusion of crural and pedal vessels. Subsequently, up to 70% of all patients with CLI are amputation bound.

Sequential pneumatic compression (SPC) has been proposed as an adjunct to best medical care, aimed at preventing amputation, relieving pain, and promoting wound healing by increasing arterial blood flow.

Figure 1. The ArtAssist unit (ACI Medical).
in distal limbs. It has been shown to achieve wound healing and limb salvage in patients with severe infrapopliteal disease and limb–threatening ischemia who are not suitable for revascularization. SPC increases flow to the lower limbs. It generates up to a 4-fold improvement in popliteal artery blood flow, with modulation and recruiting of the capillary bed and collateral circulation enhancement.

TECHNIQUE

Sequential Pneumatic Compression

The device described is the ArtAssist (Figure 1; ACI Medical). The mechanism of action of the ArtAssist is to increase arterial blood flow. It applies a massage-like compression to the foot, ankle, and calf to circulate blood flow at a maximum inflation pressure of 120 mmHg, minimum deflation pressure of 0 mmHg, inflation rise time of 0.3 seconds, and inflation time of 4 seconds followed by 16 seconds of deflation, resulting in 3 compression cycles each minute. This compression regimen simulates the beneficial effects of brisk walking, without pain. Firstly, the device compresses the foot and ankle. One second later, the calf is compressed. As a result, the foot, ankle and calf veins are almost completely emptied. In return, the arterial blood is more easily pushed down to the toes and blood-deprived tissues. Because of this mechanism, blood flow to the skin of the feet can be tripled.

A second mechanism of action that accounts for the large blood flow increase involves the endothelium. Endothelial cells release important biochemical factors, such as nitric oxide that aid circulation of the blood. Rapid cyclic blood flow induces high shear stress that promotes the endothelial cells to generate and release nitric oxide, tissue factor pathway inhibitor, and endogenous tissue plasminogen activator. Since these biochemical factors dissipate after approximately 17 seconds, the device repeats the compression sequence three times per minute. This means that in a one-hour session, the patient’s arteries will be expanded almost 200 times.

Numerous postulated theories in relation to the mechanism of action of SPC include emptying of the plantar venous plexus and reduction of the venous leg pressure, increasing the arteriovenous pressure gradient, and increasing shear stress in endothelial cells of the lower limb vascular beds. An additional mechanism is the momentary delay in the local vasoregulation resistance of the venoarteriolar response and the transient suspension of the arteriovenous reflex hyperaemia, which both improves endothelial function and induces collateral arterial formation. Improved endothelial function and formation of collaterals enhance capillary recruitment and decreases peripheral resistance. Moreover, long-term effects were provided from the enhanced angiogenesis and collateral formation in response to the generation and release of nitric oxide, tissue factor pathway inhibitor (TFPI), and endogenous tissue plasminogen activator (tPA), secondary to increased shear stress following rapid cyclic blood flow.

MATERIALS AND METHODS

To date, 2 studies have been conducted by our tertiary referral center to determine the efficacy of SPC in patients with CLI. The first study was conducted between 2005 and 2012, in which 171...
patients with severe CLI who were not suitable for revascularization were enrolled in the program. A matched control group of 75 patients with primary amputation was used. Primary endpoints were limb salvage, sustained clinical improvement, and 90-day mortality. Secondary endpoints were hemodynamic outcomes with increase in popliteal artery flow and toe pressure, and cost effectiveness.

The second study was conducted between 2010 and 2015, in which a total number 187 patients (262 limbs) were enrolled in the SPC program. These patients were retrospectively scrutinized to investigate the overall role of SPC in limb salvage. Statistical analysis was used to compare demographics, preintervention Rutherford categories, major and minor amputation, and improvement in rest pain among 2 groups of patients; those who acquired the device and those who did not.

Criteria for Use

Patients included in this study were those with CLI (Rutherford categories IV, V, and VI) defined as the presence of rest pain, tissue loss, or gangrene along with an ankle brachial pressure index of less than 0.5 and a systolic ankle pressure less than 50 mmHg. Patients included in this study were required to have a nonreconstructable arterial tree either due to absence of anatomically suitable outflow (Figure 2) as agreed upon by at least 2 vascular surgeons, or due to unacceptable operative risk by the patient after adequate explanation by a consultant anaesthetist.

Patients excluded from this study were those who had intermittent claudication, and those who were fit both anatomically and functionally for operative or endovascular revascularization. In addition, patients with extensive foot gangrene precluding attempts at limb salvage, recently confirmed deep venous thrombosis, or an inability to tolerate compression were excluded.

Protocol for Use

Patients were commenced on a 12-week home treatment protocol that consisted of a minimum of 6 to 8 hours per day of use. Treatment was spread throughout the day at 2 intervals. The device was
applied to the symptomatic legs while the patient was sitting upright in a chair. Some patients purchased the machine and continued daily use in their homes. Additional medical treatment was maintained in the form of a dual antiplatelet (acetyl salicylic acid 75 mg once daily and clopidogrel 75 mg once daily), naftidrofuryl 200 mg three times daily, and a statin according to blood lipid levels, in addition to diabetic control. Patients with infected foot ulcers were admitted, started on intravenous antibiotics, empirical broad spectrum initially, then according to culture. Necessary drainage and debridement were done and exposed wounds were managed using negative pressure wound therapy. Patients with congestive heart failure were managed with diuretics, fluid restriction, and optimization of their cardiac status.

Statistical Methods
Statistical analysis was conducted using SPSS v.6. Evaluation of data such as Rutherford categories, toe pressures, blood flow velocities, limb salvage, amputation, and rest pain was conducted with the paired t test or chi-square test, where appropriate. Spearman’s correlation was used to investigate the relationship between the duration of use of the device and amputation free survival. A P value <.05 was considered statistically significant.

RESULTS
Seventy-five of the patients in the control group had a Rutherford category of V and VI. Seventy-four percent (n=171) of patients in the SPC group had a Rutherford category of V and VI. Patients from both groups were comparable, resulting in a Rutherford P value of .138 (chi-square). Findings from the patient group between 2005 to 2012 showed that sustained clinical improvement was 68% at 1 year. Mean toe pressure increased from 19.90 to 35.42 mmHg (P<.0001). Ulceration healed in all but 12 patients over the course of follow-up in the SPC group. Mean popliteal flow increased from 35.44 to 55.91 cm/sec (P<.0001), and 30-day mortality was 0.6%. Limb salvage was 94% at 5 years. Freedom from major adverse clinical events was 62.5%, compared to 32% in patients with amputation at 5 years. All-cause survival was 69%, compared to 38% for primary amputation at 4 years. Median cost of managing a primary amputation patient is €29,815 compared to €3,985 for SPC. We treated 171 patients with the ArtAssist unit at a cost of €681,965. In comparison, primary amputation for 75 patients cost €2,236,125 (€3,988 vs €29,815 per patient respectively, a difference of €25,827, or approximately $29,205).

From 2010 to 2015, 20 limbs (7.6%) underwent major amputation out of the 262 limbs studied. On evaluat-
ing the performance of the SPC device in the prevention of amputation, there was no statistically significant association between using the device and limb salvage ($P = .714$). There was a statistically significant correlation between minor amputation and inability to obtain the device, suggesting evidence to support the efficacy of SPC in preventing minor amputation and improve healing of ulcers ($P = .023$) (Table 1).

Amputation-free survival at 6 months was 98% for those who acquired the device and 90% for those who did not, and at 1 year it was 96% and 84%, respectively. There was a strong positive correlation in toe pressures before and after application of the device ($P = .072$) (Table 2). On exploring the effect of the device application on rest pain, there was a statistically significant likelihood that using the device would improve rest pain ($P < .0001$). Average baseline pain numeric scale results were 7 out of 10 prior to usage of the device, 5 out of 10 at 3 months ($P = .049$), and 4 out of 10 at both 6 months and 2 years after use.

Spearman’s correlation was used to investigate the relationship between the duration of use of the device and amputation-free survival, and indicated a weak negative correlation between the 2 variables ($P = -.07$), however this proved to be statistically insignificant ($P = .39$). The postulated hypothesis that the longer the device is used, the more likely the limb is salvaged was rejected.

### Discussion

Incidence of CLI has been exponentially increasing over the last decade, especially with the graying of nations and increased prevalence of diabetes.\(^{25}\) There is also a lack of clarity regarding optimum management when revascularization had been exhausted or is not practical. This motivated us to evaluate the clinical efficacy of SPC in amputation-bound patients with CLI. Limb salvage with an improved quality of life will continue to be the paramount ambition for most patients referred to a vascular surgery practice. Given the grave impact of amputation on social, vocational, and economic factors with regard to both the patient and the community, any therapy that has the potential to save a limb is worth evaluation.

Our experience shows that 10% of patients with peripheral artery disease older than 50 years will develop CLI within 5 years. The fact that more than 90% of those will never progress to CLI makes it apparent that there is something particularly indolent about the minority with CLI that makes them susceptible to limb loss and therefore a priority for therapy. Equally there may be an innately protective mechanism in those with claudication that defends them from the risk of limb loss.

Despite a modest improvement in medical therapies since 1997, 1 in 5 patients still die or lose their leg within a year and wounds and ulcers are more likely to worsen.\(^{26-28}\) Although the exact reason for

### Table 2 Comparison of Toe Pressures Before and After Device Use

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Mean difference</th>
<th>Correlation coefficient</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>61.4 mmHg</td>
<td>29.7</td>
<td>-3.53</td>
<td>0.72</td>
<td>0.071</td>
</tr>
<tr>
<td>After</td>
<td>65.0 mmHg</td>
<td>31.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $P$ value and 95% confidence interval were calculated using paired $t$ test.
improvement is unclear, it is likely related to improved medical care for patients with CLI as well as improved clinical care of the comorbidities associated or existing with CLI. This translates to indirect improvements in survival from comorbidities rather than direct and so justifies an attempt at revascularization whenever possible.

The TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) recommends revascularization as the optimal treatment for patients with CLI, but the type of revascularization for patients with CLI, whether surgical or endovascular, remains a subject of debate. The evidence comparing the effect of these two main interventions on mortality, morbidity, and limb function remains inconclusive.

A recent systematic review and meta-analysis concluded that until there are more robust data, the choice of revascularization strategy depends on the surgeon’s expertise as well as on the patients’ values and preferences, expected perioperative risk, and anticipated long-term survival. Given the broad heterogeneity of this clinical syndrome, future studies should appropriately stratify patients to improve the fidelity of outcomes, reporting, and methodology of comparative effectiveness studies in this field. In any case, revascularization, regardless of the method, does not guarantee limb salvage. Therefore, a definitive cure for CLI remains an unmet clinical need.

The ArtAssist is a valuable tool in the armamentarium for CLI therapy. It achieves rapid relief of rest pain without any intervention in patients with limited life expectancy. Delis et al noted that SPC increased blood flow, relieved rest pain, and limited tissue damage in patients with CLI by generating a 3- to 4-fold augmentation in popliteal artery blood flow, and verified that blood flow improvement was sustained following cessation of SPC usage.

Although limb salvage is essentially the utmost aspiration for all patients referred for vascular surgery services, unfortunately, some patients with CLI are indisputably superiorly managed with primary amputation. Regrettably, it is not always apparent beforehand which patients will benefit from primary amputation vs an attempt at limb salvage. In our case-control study conducted between 2010 and 2015, we could not formulate any association or added risk of any of the patients’ comorbidities to major amputation and subsequent limb loss. Hence, we could not predict likelihood of limb salvage through patients’ demographic or preintervention patient comorbidities.

On investigating the efficacy of SPC as a treatment modality to avoid limb loss and amputation in patients with nonreconstructable CLI, the results were divisive. We could not find a statistically significant correlation between duration of usage of the device and limb salvage, and consequently rejected the hypothesis that longer durations of device usage could alter outcome. Although we could not deduce a statistically significant difference in limb salvage rates between those who utilized the device and those who did not, SPC application significantly moderates minor amputation in addition to significantly protracting amputation-free survival. Moreover, in patients presenting only with rest pain (Rutherford category IV), there was a statistically significant improvement in rest pain, and consequently the quality of life.
CONCLUSION

SPC is a valuable tool in the armamentarium for CLI therapy. It achieves rapid relief of rest pain without any intervention in patients with limited life expectancy. It reduces minor amputations and adjourns major amputations, although it does not significantly lessen the incidence of inevitable limb loss.

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REFERENCES
22. Tawfick WA, Hamada N, Soylu E, Fahy A, Hynes N, Sul-


