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The Effectiveness of Calf Muscle Electrostimulation on Vascular Perfusion and Walking Capacity in Patients Living With Type 2 Diabetes Mellitus and Peripheral Artery Disease

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Abstract

The aim of the study was to explore calf muscle electrostimulation on arterial inflow and walking capacity in claudicants with peripheral artery disease and diabetes mellitus. A prospective, 1-group, pretest-posttest study design was used on 40 high-risk participants (n = 40) who exhibited bilateral limb ischemia (ankle brachial pressure index [ABPI] <0.90), diabetes mellitus, and calf muscle claudication. A program of calf muscle electrical stimulation with varying frequency (1-250 Hz) was prescribed for 1 hour per day for 12 weeks. Spectral waveforms analysis, ABPI, absolute claudication distance (ACD), and thermographic temperature patterns across 4 specified regions of interest (hallux, medial forefoot, lateral forefoot, heel) at rest and after exercise, were recorded at baseline and following intervention to evaluate for therapeutic outcomes. A significant improvement in ACD and ABPI was registered following the intervention (P = .000 and P = .001, respectively). Resting foot temperatures increased significantly (P = .000) while the postexercise temperature drops were halved across all regions at follow-up, with hallux (P = .005) and lateral forefoot (P = .038) reaching statistical significance. Spectral Doppler waveforms were comparable (P = .304) between both serial assessments. Electrical stimulation of varying frequency for 1 hour per day for 12 consecutive weeks registered statistically significant improvement in outcome measures that assess arterial inflow and walking capacity in claudicants with diabetes mellitus. These results favor the use of electrostimulation as a therapeutic measure in this high-risk population.

Keywords

electrical stimulation, diabetes mellitus, peripheral artery disease, intermittent claudication

Exercise has been the cornerstone of noninvasive management of peripheral arterial disease (PAD) for the past 40 years.[1] Indeed, several collaborative authorities, including the Trans-Atlantic Inter-Society Consensus (TASC) II PAD management working group,[2] the American Heart Association/American College of Cardiology,[3] and the Society of Vascular Surgery,[1] recommend exercise as a first-line therapy in claudicants.

Despite the known efficacy of exercise in patients living with PAD, not all patients can follow a prescribed exercise regime. A number of physical and psychosocial factors may preclude adherence of patients to any form of exercise program.[1] Comorbid conditions like osteoarthritis, musculoskeletal problems, foot/limb pain, foot ulcers, and other factors like bad weather, age, and lack of motivation may all discourage any form of cardiovascular exercise.[4] Another significant barrier to exercise is intermittent claudication, which is experienced by 25% to 35% of patients with PAD. Furthermore, in the context of diabetes, a cross-sectional study[5] on a multigender cohort of 460 patients with PAD (147 with diabetes) aged 55 years and older with medical histories consistent of PAD (ankle brachial pressure index [ABPI] <0.90) demonstrated that patients with diabetes and PAD have poorer lower extremity functions than patients presenting with PAD only.

All these factors preclude adherence to exercise therapy creating a lacuna for the effective management of this vulnerable population. In this context, electrical stimulation

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(ES) targeted on ischemic muscles has been proposed as a potential passive alternative to exercise training. However, to date, only a few studies have evaluated the sustained effectiveness of this therapeutic modality on patients living with diabetes and PAD.[6,7] Moreover, those studies that provide evidence on the effects of intermittent ES have been conducted on laboratory ischemic animal models[8-11] while those including PAD patients had methodological limitations, including poor sample sizes, fixed low frequency of stimulation, and short duration of intervention.[6,7]

Therefore, the aim of this study was to explore the efficacy of longer term variable frequency (1-250 Hz) calf muscle ES on arterial inflow and walking capacity in claudicants with PAD and diabetes mellitus.

Materials and Methods

A prospective, 1-group, pretest-posttest study design was used on 40 participants (n = 40) with bilateral limb ischemia, diabetes mellitus, and PAD (ABPI < 0.90). Subjects were recruited for the study by a convenience sampling method and had to meet the following key inclusion criteria: high-risk subjects aged 55 years and older, defined by the presentation of type 2 diabetes mellitus, presenting with PAD with ABPI < 0.90 in both legs and abnormal spectral pedal waveforms at the ankle arteries. Patients had to experience calf claudication symptoms that were reproducible on a graded treadmill protocol and willing to follow the prescribed intervention regime. Patients were excluded if they presented with neuropathy, renal disease, uncompressible ankle arteries (ABPI > 1.30), neurological disease, spinal stenosis, or sciatic nerve impingement. Those reporting a history of angina pectoris, cardiac arrhythmias and those with a pacemaker were also excluded for safety reasons since testing would involve a form of relatively strenuous exercise. Furthermore, patients who could not follow a treadmill program, those who were following supervised treadmill exercise programs, those with previous lower limb amputations and subjects with a history of oral claudication therapies such as cilostazol and/or pentoxifylline were also excluded. Ethical approval was sought and granted by the University Ethics Research Committee. All participants provided informed consent to participate in this study. The reported investigations were carried out in accordance with the Declaration of Helsinki as revised in 2008.[12]

Demographic data were recorded for each participant along with anthropometric measurements (weight and height). A full medical history, including current and former pharmacological treatment done within the past year was recorded. Pretest and posttest assessments were carried out by an experienced clinician in a temperature- and humidity-controlled hospital laboratory (pretest, 22.52°C; SD, 0.2°C; posttest, 22.35°C; SD, 0.3°C) and monitored using a calibrated digital thermometer between January and June 2015.

Testing Protocol

Five outcome measures were employed, including resting ABPI, spectral Doppler waveform analysis, resting and exercise temperature change (eTC), and maximal walking distance on a treadmill. Measurements from each tool were obtained at pretest to establish a baseline and repeated at a 12-week follow-up (posttest).

ABPI Measurements and Spectral Waveform Analysis

Measurement of ABPI was performed using the Huntleigh Dopplex Assist Vascular Package (Cardiff, UK) and blood pressure cuffs. The systolic pressure at bilateral posterior tibial and brachial arteries was measured as per standard practice.[13] Additionally, qualitative pedal waveform analyses of the dorsalis pedis and posterior tibial artery were reported according to standards of the literature, classified as triphasic, biphasic, monophasic, or monophasic continuous.[14] Triphasic waveforms were excluded from the study as they denote absence of PAD.

Resting Thermographic Analysis

Resting foot temperatures on soles of the feet were acquired utilizing a thermographic camera with a thermal sensitivity of 0.1°C (Flir i3, Wilsonville, OR, USA). The camera was fixed to a tripod placed at a uniform distance of 1 m away from the end of the couch (Figure 1). Each subject was placed in the supine position with both feet exposed up to the shin and utilizing clamps to maintain the foot at a perpendicular position relative to the couch[15] (Figure 1). All thermographic images were taken after a minimum of 10 minutes to acclimatize to the surrounding environment, ensuring that angles between the camera and the plane of view were within 20° to maximize reliability of temperature readings.[16] Each thermogram was processed using the proprietary Flir Tools software whereby regions of interest (ROI) that included hallux, medial forefoot, lateral forefoot, and heel were defined. The mean temperature in degrees Celsius within each ROI was extracted. Previous research reported suitability and reliability of these regions for the quantification of temperatures in soles of the feet.[15]

Treadmill Test

The maximal walking distance defined as the absolute claudication distance (ACD), that is, the distance at which claudication becomes so severe that the participant is forced to

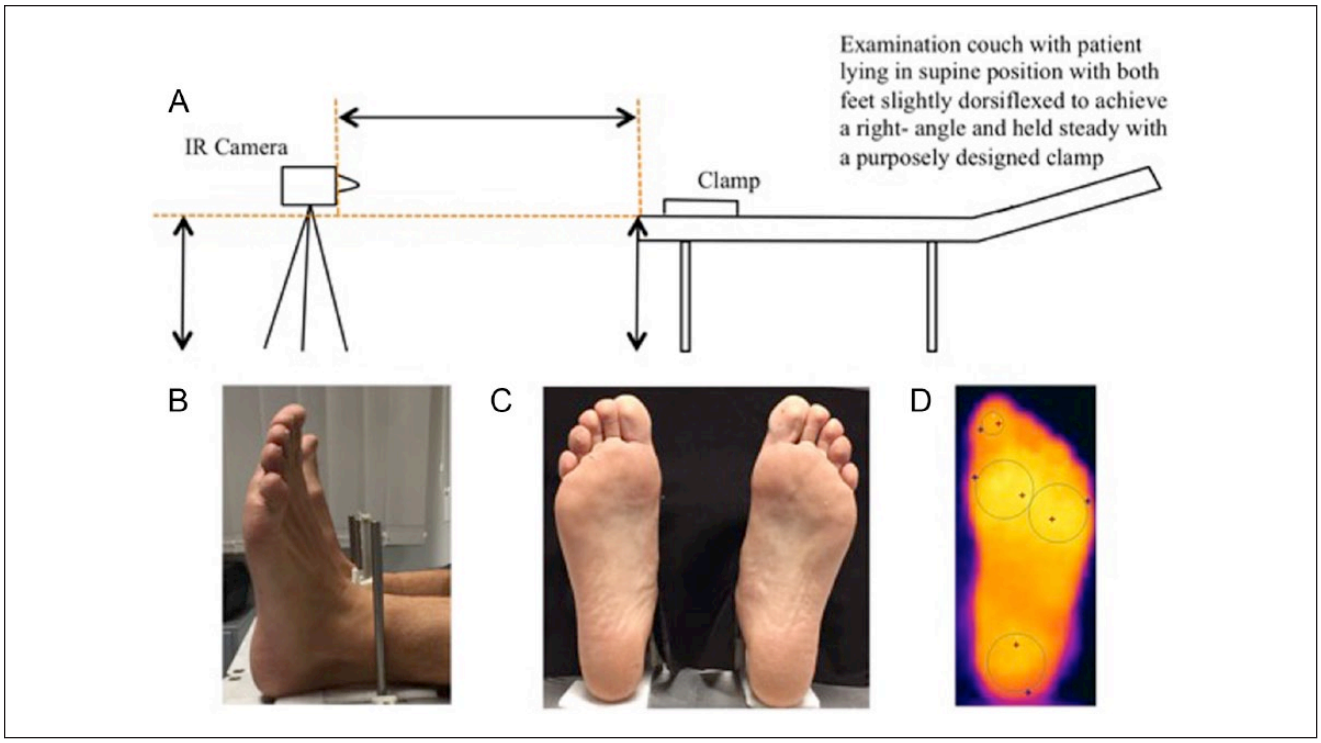

Figure 1. (A) Protocol for thermogram capture. A uniform distance of 1 m between the foot and the camera was maintained during thermogram capture while the participants were asked to maintain their ankles at a 90° position perpendicular to the couch. (B) A clamp was used to avoid leg and foot movement during thermogram acquisition. (C) A uniform black back drop was placed in the transverse plane just below the malleoli to create a contrast between the foot and surrounding environment. (D) Regions of interest were derived from each thermogram of each foot using the proprietary Flir Tools software. These regions (represented with a circle) included hallux, medial/lateral forefoot, and heel.

stop walking,[17] was measured. This method has been reported as the most reliable measure of claudication severity and response to therapy.[18]

The graded treadmill protocol employed to acquire ACD included initiating treadmill speed at a fixed 3.2 km/h, while the inclination was increased gradually by 2° every 2 minutes from an initial inclination of 0° up to a maximum of 10°.[18,19] This method has been reported to be more reproducible and reliable than the fixed treadmill protocol.[20] The recorded ACD was not disclosed to the participant to ensure blinding. On the other hand, those participants who did not show typical signs and symptoms of intermittent claudication during the treadmill protocol within 30 minutes or 1500 m at baseline were excluded from the study.

Exercise Thermography

Within 1 minute from exercise cessation at the point of ACD, a recapture of thermograms ensued using the same method described earlier for the resting thermograms. This allowed for the quantification of variations in temperature in each region of interest before and after exercise.

The equation

$$\left[\text{Temp}(^{\circ}\text{C})_{\text{exercise}} - \text{Temp}(^{\circ}\text{C})_{\text{resting}}\right]$$

was used to derive the exercise temperature change (eTC)[21] for each region of interest.

The method employed for each outcome measure was repeated at baseline and 12-week follow-up after intervention with ES for each participant to identify variations in the readings that may be attributed to the intervention prescribed. The researcher was blinded to all previous measurement results.

Intervention Tool

The Veinoplus Arterial model 2.1 (Ad Rem Technologies, France) was used to generate the electromuscular contractions on ischemic calf muscles as per manufacturer's instructions. This battery-operated device consisted of a central unit with 2 adhesive electrodes attached to the calf muscle, that generated electrical stimulation at varying frequencies (1-250 Hz) through a series of rectangular pulses of low energy (<25 μC) and low voltage (50 V peak) within a fixed 1-hour session.

Following a demonstration session in which participants were familiarized with the device to be used at home, they were given an instruction manual and log sheets to record daily use so as to quantify adherence at follow-up. Participants were instructed to use the device on a daily basis for 12 consecutive weeks in the seated position with the legs hanging down, setting the intensity of stimulation from the control unit at the beginning of each session. With prolonged use, the required intensity of stimulation in order to achieve a visible contraction increases due to muscle adaptations that are able to sustain higher intensities. Participants were therefore advised to set the optimal intensity of stimulation at the beginning of each session manually, increasing it gradually along the intervention period instead of maintaining a fixed intensity of stimulation throughout the intervention period. The optimal intensity for each session was defined as the point at which a visible but comfortable calf contraction occurred on both limbs as per manufacturer's instructions. This method, as advised by the manufacturer, has been used previously in the literature.[22]

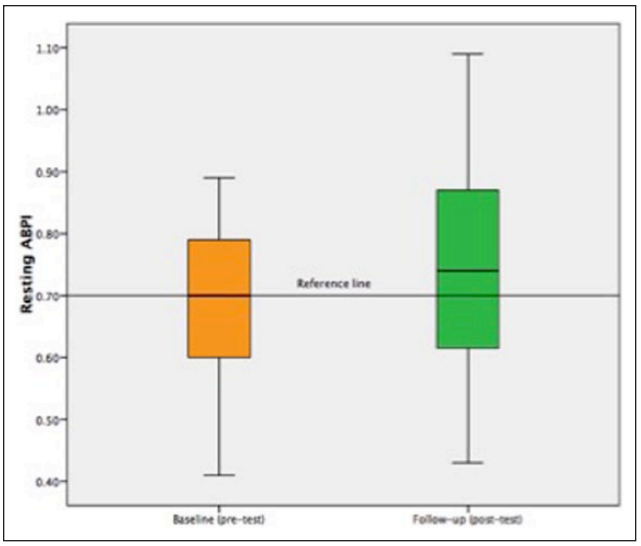

Figure 2. Baseline versus follow-up resting ankle brachial pressure index (ABPI) with means (N = 80). Reference lines indicate baseline and follow-up means.

Results

Out of a total of 71 prospective participants, 40 participants (30 males; 10 females) with a mean age of 70.83 years (SD 7); mean body mass index 28.88 kg/m^2 (SD 3.7); mean diabetes duration 15 years (SD 6); mean HbA1c 8.2% (SD 1.56) (66 mmol/mol), were included in the study. Thirty-one participants were excluded during screening due to elevated ABPI readings or because they did not reach claudication distance within the maximal walking distance or timeframe stipulated in the protocol. The Veinoplus Arterial device (Ad Rem Technologies, France) was used for a consecutive mean duration of 91.68 days (SD 6.23) as quantified through the patient log-sheets. Seventy-five percent of participants were on aspirin, 10% on clopidogrel, and 22.5% on dipyridamole.

Table 1. Comparison of Spectral Doppler Waveforms at Preintervention and Postintervention.

Anatomical Artery	Waveform Type	Baseline n (% Frequency)	Follow-up n (% Frequency)
Posterior tibial	Monophasic continuous	15 (18.8)	16 (20)
	Monophasic	60 (75)	59 (73.8)
	Biphasic	5 (6.3)	5 (6.3)
Dorsalis pedis	Monophasic continuous	26 (32.5)	24 (30)
	Monophasic	49 (61.3)	52 (65)
	Biphasic	5 (6.3)	4 (5.1)

Arterial Flow

The ABPIs of 80 limbs were recorded with each limb scored separately for each participant at baseline (mean 0.702, SD 0.12) and follow-up (0.743, SD 0.16). Following intervention, a statistically significant increase in ABPI was detected (paired sample *t* test, $P = .001$; 95% CI, 0.02-0.07). Figure 2 presents the mean baseline and follow-up ABPI scores.

Qualitative spectral waveforms of the posterior tibial and dorsalis pedis arteries of both limbs (N = 80) were also evaluated. Table 1 illustrates the waveform classification for each artery. Spectral waveform changes at follow-up relative to baseline are comparable (McNemar test, posterior tibial, $P = .304$; dorsalis pedis, $P = .117$).

Walking Capacity

The mean ACD at baseline was 333.71 m (SD, 208.44), which increased to 470.73 m (SD, 278.75) at 12-week follow-up. This translated to a mean walking capacity that was 41% better at follow-up relative to baseline. This mean improvement (137 m, SD = 136) in ACD was found to be statistically significant (Wilcoxon signed rank test, $P = .000$).

The post hoc power analysis of the ABPI and ACD result was 90% and 94%, respectively, exceeding the minimum level of power required of 80%.[23]

Resting Temperature and Postexercise Temperature Change

The resting temperatures and eTC derived from the regions of interest at baseline and follow-up are presented in Table 2. In both measures, the mean resting temperature was lowest in the hallux ROI and highest in the medial forefoot ROI; however, these differences were not found to be statistically significant (baseline, $P = .451$; follow-up, $P = .259$, one-way analysis of variance).

Table 2. Comparison of Infrared Thermal Temperatures at Baseline and at 12 Weeks Following Intervention.

		Baseline (N = 80), °C		Follow-up (N = 80), °C	
Description	Region of Interest	Mean	SD	Mean	SD
Resting temperatures	Hallux	27.71	3.19	30.14[a]	2.45
	Medial	28.38	2.59	30.74[a]	2.07
	Lateral	28.19	2.58	30.66[a]	2.04
	Heel	28.06	2.21	30.43[a]	1.75
Exercise temperature change (eTC)	Hallux	−0.82	1.35	−0.41[a]	1.22
	Medial	−0.50	1.38	−0.25	1.16
	Lateral	−0.57	1.42	−0.29[a]	1.08
	Heel	−0.30	1.26	−0.11	1.05

[a]$P < .05$, relative to baseline.

At the follow-up, a statistically significant increase (paired-sample *t* test) in resting temperature of around 2°C was recorded across all ROIs for the hallux ($P = .000$, 95% CI, 1.86-2.99), medial ($P = .000$, 95% CI = 1.89-2.84), lateral ($P = .000$, 95% CI, 2.00-2.95), and heel ROI ($P = .000$, 95% CI 1.93-2.82).

Following exercise, drops in temperatures were registered across all ROIs at both baseline and follow-up as presented in Table 2. The reduction in temperature drops following the 12-week intervention was approximately halved in all regions and found to be statistically significant in the hallux ($P = .005$, 95% CI, −0.10 to −0.72) and lateral forefoot ($P = .038$, 95% CI, 0.03 to −0.58) ROI. In the medial ($P = .063$, 95% CI, 0.07 to −0.56) and heel ($P = .091$, 95% CI, 0.09 to −0.47), no statistical significance was found.

Discussion

Electrical stimulation of varying frequency for 1 hour per day for 12 consecutive weeks registered statistically significant improvement in outcome measures that assess arterial inflow and walking capacity in claudicants with diabetes mellitus.

This result is novel in nature since previously reported studies have failed to show an improvement in arterial flow and walking capacity simultaneously following ES.[6,7]

Arterial Perfusion

Improvements in arterial perfusion could be attributable to the variable frequency of stimulation employed in this study along with duration of the intervention, which is the longest period reported to-date when compared with other similar studies that used fixed low frequency of stimulation (<40 Hz) and a shorter intervention period (<8 weeks).[6,7] Laboratory experiments have shown that improvements in collateral circulation in response to sustained ES are frequency dependent, with higher frequencies of stimulation likely to augment collateral growth thereby improving blood flow.[24]

Although it has been cited that the optimal frequency of stimulation to improve blood flow is not yet recognized,[24] experimental models have shown that endogenous growth factors such as vascular endothelial growth factor expression in response to ES increase with higher frequencies.[24,25]

Underlying benefits of higher frequencies also include an increase in mechanical stretch in the vessel attributed to increased shear stress,[24] which are essential for true arterial collateral development and maturation (arteriogenesis).[26] Consequently, it could be postulated that higher frequencies of stimulation could create the right environment for patent collateral vessel growth, resulting in clinically detectable improvement in blood flow[26] measurable through the ABPI.[27]

Furthermore, a long duration of ES as reported in this study beyond previously reported literature[6,7] may be required to augment patent collateral artery growth. In fact, duration of ES has been reported to be of primary importance in arteriogenesis. Studies have reported intermittent stimulation of between 20 and 40 days before significant arteriogenic effects are obtained.[26]

While Doppler spectral waveforms at follow-up did not improve relative to baseline as was the case in ABPI measurements, this is not said to be a contradictory finding since spectral Doppler waveforms distal to a stenosis only estimates the extent of stenosis.[28] This suggests that spectral waveform analysis cannot discriminate between the presence or absence of collateral vessels at a poststenotic location in contrast to the ABPI.[27] Based on this result, the authors conclude that no changes in stenosis severity occurred following this intervention, since the effects of electrical stimulation on limb ischemia are attributed to the development and maturation of patent collaterals and not to recovery of stenosed arteries.[25,26]

The significant improvement in ABPI in response to ES is an important finding suggesting that this form of passive exercise therapy may have therapeutic effects on a disease that is often described as a progressive disease resulting in gradual deterioration in limb perfusion and the ABPI.[13,29] Moreover, lower ABPI readings have been associated with a significant increased risk of morbidity and mortality,[30] so that the registered improvements may not only improve prognosis of the limb but also the general prognosis of the patient.

Walking Capacity

Results from this study show significant improvement in absolute walking distance in patients with intermittent claudication. Improvements in walking capacity have been reported to be due to angiogenesis and muscle fiber recruitment in response to ES. Angiogenesis in ischemic muscles

increases capillary density, capillary to fiber ratio, arteriolar growth, and dilatory capacity thereby increasing oxygen supply to the muscle. ES has been shown to augment angiogenesis by increasing growth factors, shear stress, and nitrous oxide (NO) bioavailability.[6,8-11,31]

Furthermore, ES is thought to have positive therapeutic effects on muscle fibers. In contrast to traditional physical exercise, all muscle fiber types are activated simultaneously in response to ES,[32] resulting in a more intensive work level than normal low-intensity physical activity,[6] otherwise only achievable through high-intensity endurance training, resulting in increased strength and muscle bulk.[6,31,32] Concomitant angiogenesis increases oxidative capacity within the ischemic muscle, thereby increasing oxidative enzyme activity and reduction in glycolytic activity, favoring the recruitment of oxidative fatigue resistant type I muscle fibers over fast-twitch glycolytic type II muscle fibers, thereby increasing resistance to fatigue.[31,33,34]

As a result, apart from sustained improvement in blood flow in the ischemic limb, potential benefits behind ES in claudicants is the reduction of ischemic muscle symptoms, which are often a major impediment to any form of active exercise. A more intensive muscle workout as a result of simultaneous recruitment of all muscle fibres in response to ES is also a major advantage of this treatment method in contrast to the traditional low-intensity active exercise, in which type II muscle fibers associated with strength and endurance are rarely recruited.

Thermography

This study reports improvement in mean resting temperatures following intervention (hallux, 30.14°C; medial, 30.74°C; lateral, 30.66°C; heel, 30.43°C) that are similar to other normative data reported in a type II diabetic cohort without arterial disease.[35] These results complement the results of the ABPI, that is, following intervention with ES, better blood perfusion was achieved to the ischemic limbs possibly even due to increased arterial compliance. Following the intervention, mean exercise temperature drops (eTC) experienced across all ROI at baseline were practically halved in all regions (Table 2).

The innovative employment of multiple outcome measures clearly suggest that ES maybe recommended as an effective therapy that improves symptoms, and may potentially reverse derangements associated with PAD, including muscular ischemia and poor arterial perfusion. It is felt that this often neglected and highly underutilized treatment modality should be disseminated among clinicians so that wider usage is employed in those patients whose PAD management is challenged with decreased mobility. Additionally, the authors suggest further research incorporating an appropriately matched control group with blinding, which was considered as the main methodological limitation of this study.

Electrical stimulation of varying frequency for 1 hour per day for 12 consecutive weeks registered statistically significant improvement in outcome measures that assess arterial inflow and walking capacity in claudicants with diabetes mellitus. These results favor the use of ES in this high-risk population as defined by ischemia (ABPI < 0.9), type 2 diabetes mellitus, and intermittent claudication, increasing the prospects for this method to become a standardized therapeutic measure in the diabetic population with symptomatic PAD. Further dissemination of this adjunct treatment modality is required among clinicians who often underutilize ES therapy.

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Declaration of Conflicting Interests

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