Calf muscle stimulation with the Veinoplus device results in a significant increase in lower limb inflow without generating limb ischemia or pain in patients with peripheral artery disease

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Objective: **Increase in arterial inflow to the lower limbs is important to obtain functional improvement in peripheral artery disease (PAD) patients with claudication. The aim of this study was to assess the effect of electrical stimulation of calf muscles on arterial inflow and tissue oxygen content in PAD in the area of stimulation.**

Methods: **Fifteen adult patients [mean (standard deviation) age, 62 (12) years; height, 165 (8) cm; weight, 76 (13) kg; lowest ankle-brachial index 0.66 (0.19)] with stable arterial claudication were recruited. All patients performed a treadmill test (3.2 km/h, 10% slope) associated with a transcutaneous oximetry test expressed as decrease from rest of oxygen pressure (DROP) index values (calf changes minus chest changes from rest) with a maximum walking distance (median [25th/75th percentiles]) of 295 [133-881] m. The DROP index on the symptomatic side was −25 [−18/−34] mm Hg. On another day the patients underwent electrical stimulation in the seated position on the leg that was the most symptomatic on the treadmill. After resting values were recorded, the gastrocnemius was stimulated for 20 minutes at increasing contraction rates at 5-minute steps of 60, 75, 86, and 100 bpm on the most symptomatic side. Arterial blood inflow with duplex Doppler ultrasound scanning of the femoral artery, DROP transcutaneous oxygen pressure value, and oxygen concentration (O_2Hb) from the near-infrared spectroscopic signal of the calf were recorded on both sides. Patients were instructed to report eventual contraction-induced pain in the stimulated calf. Results are given as mean (standard deviation) or median [25th/75th percentiles] according to distribution, and the level of statistical significance was set at $P < .05$ on two-tailed tests.**

Results: **Lower limb inflow (mL/min) was 64 [48/86] vs 63 [57/81] ($P > .05$) before stimulation, 123 [75/156] vs 57 [44/92] ($P < .01$) at 60 bpm, 127 [91/207] vs 49 [43/68] ($P < .01$) at 75 bpm, 140 [84/200] vs 57 [45/71] ($P < .01$) at 86 bpm, and 154 [86/185] vs 55 [46/94] ($P < .01$) at 100 bpm on the stimulated vs nonstimulated limb, respectively. No apparent decrease or significant leg difference was observed in DROP index or O_2Hb values. None of the patients reported contraction-induced pain in the leg.**

Conclusions: **Electrical stimulation of calf muscle with the Veinoplus device results in a significant increase of arterial inflow without measurable muscle ischemia or pain. Potential use of this device as an adjuvant treatment to improve walking capacity in PAD patients remains to be evaluated. (J Vasc Surg 2013;57:714-9.)**

Walking limitation is one of the first clinical complications of peripheral artery disease (PAD). Stimulating muscle contraction is the major method of increasing limb blood flow and improving walking capacity in patients with claudication resulting from PAD.[1] Regular walking has a beneficial effect,[2] but many events may preclude the adherence of patients to this recommendation,[3] including comorbid conditions, low motivation to exercise,[4] and bad weather conditions. As an adjuvant to walking or for patients who cannot walk, methods to induce passive increase of limb inflow, such as external intermittent compression or direct electrical muscle stimulation (EMS), have been proposed.[5-8]

The fact that EMS-induced contraction can improve blood flow and decrease muscle fatigue in the ischemic muscle has been previously suggested in animals[9] and humans.[5] Among commercially available devices, the Veinoplus (Ad Rem Technology, Paris, France) has been proposed to increase venous outflow for prevention of deep venous thrombosis.[10-12] Nevertheless, direct evidence of the tolerance of electrical-induced contractions in terms of EMS-induced ischemia and of the amplitude of inflow to the stimulated limb in PAD patients is lacking. Our primary hypothesis was that self-selected intensity of EMS with the Veinoplus system could induce a significant

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increase in arterial inflow in PAD patients. Second, whether direct muscle stimulation results in calf ischemia comparable with that observed during walking has never been assessed.

The aim of this study was to confirm the tolerance and clinical effects of electrical stimulation of muscle in patients with PAD, that is, to determine whether self-selected EMS with the Veinoplus apparatus is feasible and safe in PAD patients.

METHODS

Study population. Adult patients were recruited among the patients referred for treadmill evaluation of arterial claudication at the exercise unit of the Department of Vascular and Exercise Investigations of the University Hospital in Angers.

Treadmill tests and exercise transcutaneous partial pressure of oxygen. The routine exercise procedure has been extensively described elsewhere.[13-15] In brief, we used a 10% slope and speed of 3.2 km/h for 15 minutes, followed by an incremental phase in case of nonlimiting claudication during the constant load phase. Exercise was stopped on patient request. For all transcutaneous partial pressure of oxygen ($tcPO_2$) tests, as a routine we used at least three transcutaneous oxygen pressure probes (TCM400 Radiometer, Copenhagen, Denmark), one on the chest and one on each calf. Each probe was carefully calibrated according to the manufacturer's recommendations. The $tcPO_2$ values were recorded for 2 minutes in the standing position before the treadmill was started, during the walking period, and for 10 minutes in the standing position after the end of the exercise test. The $tcPO_2$ values were automatically stored every 2 seconds by a homemade computer program and converted to decrease from rest of oxygen pressure (DROP) indices. The DROP index was calculated as $tcPO_2$ absolute changes from rest at the limb level corrected with the absolute value of the chest $tcPO_2$ changes, with chest changes subtracted (if increased from rest) or added (if decreased from rest) from the changes observed at the limb level. The DROP index has been shown to be a reliable and accurate index for exercise-induced regional blood flow impairment at the calf and buttock level because it is independent from absolute starting values.[13-15]

Patient selection and inclusion. Patients were eligible to the study if they had stable Fontaine stage 2 PAD for at least 1 month, an ankle-to-brachial systolic pressure index <0.90 on at least one side, a patent femoral artery on the mid-third of both thighs, and no femoropopliteal bypass. If proof of femoral patency was not available from the patient file, it was checked by ultrasound scanning before inclusion. The study was performed according to the recommendation of the Declaration of Helsinki and Register Number was NCT01592812 in the clinicaltrial.gov database. Patients provided written informed consent before inclusion in the study.

Investigations. Investigations were performed in the vascular unit of the department within two to 30 days of the treadmill test and the stimulation performed on the most symptomatic leg. The contralateral leg of each patient was not stimulated and thus was used as a control. Investigations were conducted in an air-conditioned room (22°C ± 2°C), with the patient comfortably seated on an armchair. A minimum period of 20 minutes in the seated position was allowed to avoid any possible influence of a previous walk over recordings. Thereafter, measurements were started at rest, performed throughout the 20-minute period of stimulation, and for 10 minutes after the end of the stimulation.

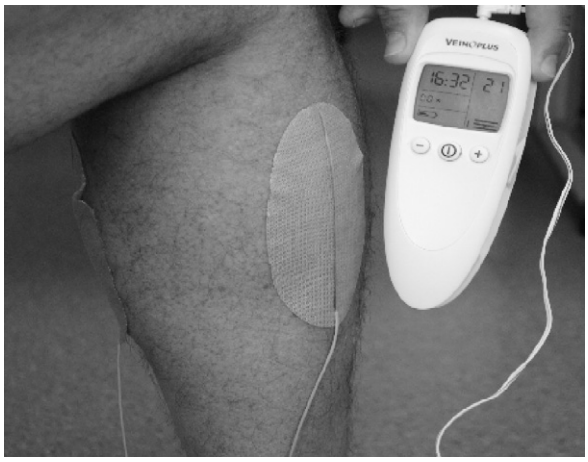

Fig 1. The Veinoplus device placed on a patient.

Electrical muscle stimulation. The stimulation from Veinoplus consists of a series of rectangular pulses of low energy (<25 μC), low voltage (50 V_{peak}), low frequency (1-250 Hz), and maximum duration of impulse 240 μs; intensity can be changed manually. The effective output voltage ranges from 0.1 to 5 V root mean square (RMS), with each intensity unit corresponding to approximately 0.1-V RMS increment. The shape of the current wave is biphasic, leading to nearly symmetric contractions of the muscles of the calf muscle in each leg. The device consists of a handheld central unit that works on a battery, connected to two ovoid skin adhesive electrodes. Each electrode is ~8 cm wide and 13 cm long. The two electrodes of the device are positioned symmetrically on the mediocentral part of the calf (Fig 1). A switch on the central unit starts the preset EMS program, and, thereafter, the intensity of stimulation can be increased (or decreased) manually. There is a wide interindividual difference in the intensity required to reach muscle contraction as well as the intensity to reach stimulation-induced pain. When switched on, the device automatically delivers a stimulation of preset incremental rate, starting with 60 bursts of stimulation per minute (bpm) and changing to approximately 75, 86, and 100 bpm every 5 minutes. At the end of the 20 minutes of stimulation, the device stops automatically.

For the present study, the electrodes were positioned on the most symptomatic leg. Patients were instructed that the intensity of stimulation would slowly increase, that they

should stop this increase before the feeling became uncomfortable, and that thereafter the intensity of stimulation would remain stable throughout the test. For the protocol, after 2 minutes of rest, the Veinoplus device was started and the intensity of stimulation was increased to reach the optimal intensity level within 1 minute. Thereafter, electrical stimulation could be stopped at the patient's request in case of ischemic pain or if the $tcPO_2$ in the calf of the stimulated leg (expressed as DROP index) fell by >5 mm Hg beyond the decline observed in the same calf during the walking test. A minimal level of intensity was required, corresponding to a visible contraction of the calf muscles with comfortable sensation. If the self-selected intensity did not result in visible contractions, the patient was excluded from the study.

Systemic hemodynamic parameters. Systemic and diastolic arterial pressures and heart rate were recorded every 2 minutes using Dynamap V100 (General Electric, Buc, France), before, during, and in the 10 minutes after EMS.

Ultrasound measurements. Arterial leg inflow was examined in the femoral artery with real-time gated Doppler sonography (Sequoia 512, 8-MHz linear array probe; Siemens SAS, Saint Denis, France). The sites to be measured on both sides were searched on the superficial femoral artery (SFA), 3 to 15 cm from the femoral bifurcation in order to avoid luminal irregularities, and marked with a permanent marker on the skin to allow repeated measurements on both sides. The diameter of the SFA was measured at rest on both sides before each protocol by viewing the artery longitudinally and by placing the tracker ball–guided calipers across the intimal–luminal interphases of the near and far walls. An average of five measurements was used to calculate cross-sectional area. This average value of cross-sectional area was used for calculating arterial inflow. Spectral velocity data were obtained at a maximum of 45° insonization angle with the sample volume gate encompassing the entire lumen of the vessel and the position of the probe marked on the skin to allow repeated measurements at the same place. Doppler waveforms were enveloped automatically using dedicated software for flow estimation. The mean integrated velocity (VTI) over three cardiac cycles (three peaks systolic velocity) was measured to calculate arterial inflow to the leg and performed as often as possible, changing the side of measurement for every three measurements of VTI. The goal was to average at least two, optimally three, measurements on each side and for each rate of stimulation in order to decrease measurement variability. Arterial inflow was calculated from VTI by the cross-sectional area of the femoral artery (L/min), before, during, and in the 10 minutes after EMS.

The $tcPO_2$ recording during EMS. The $tcPO_2$ was measured at the chest and on both calves close to the area where they were measured for the exercise treadmill test. Values were recorded manually every 2 minutes, before, during, and in the 10 minutes after EMS. Results are expressed as DROP values (mm Hg).

Near-infrared spectroscopy during EMS. Gastrocnemius muscle oxygenation was monitored by two pairs of continuous-wave near-infrared spectroscopy (NIRS) probes (Oxymon Mk III; Artinis Medical Systems, Zetten, The Netherlands). The NIRS light consisted of two wavelengths (780 and 850 nm). Oxygen content (O_2Hb) was calculated from the age-dependent differential path-length factors (range, 4.95-6.12). The theory, limitations, and reliability of measurement obtained with this device during exercise have been reported previously.[16,17] The probes consisted of one emitter and one detector (3.5 cm one from the other) housed in a black, plastic holder affixed over the belly of the gastrocnemius lateralis. A bandage covered and stabilized each probe holder in order to reduce the intrusion of external light and the loss of transmitted NIRS light from the measuring area. NIRS data were continually acquired at 5 Hz and transferred online from the Oxymon Mk III to a personal computer. Data were averaged over the last 30 seconds of each seven measurement periods. Results were analyzed before, during, and in the 10 minutes after EMS.

Table I. Demographic characteristics

Gender	12 males, 3 females
Age, years	62 (12)
Height, cm	165 (8)
Weight, kg	76 (13)
Systolic arterial pressure, mm Hg	139 (15)
Diastolic arterial pressure, mm Hg	81 (11)
Lowest ankle-brachial index	0.66 (0.19)
Maximal walking distance on treadmill, m	295 [133/881]
Heart rate before the walking test, bpm	75 (14)
Heart rate at peak exercise, bpm	120 (22)

Results are given mean (standard deviation) or median [25th/75th percentiles].

Calculation of the number of participants. From preliminary results we expected that the increase in arterial inflow to be at least 50% at the end of muscle stimulation compared with the contralateral limb (0%) with a variability of 15%, and that the decrease in the DROP index during EMS would remain smaller than the drop observed during treadmill for the same patient. Fifteen patients were included in order to assess the difference between the stimulated and control limb inflow, with $P < .01$ and power >80%.

Statistical analysis. Statistical calculations were performed using SPSS 16.0.1 (IBM, Bois-Colombes, France). Mean (standard deviation) values are presented for normal distributed variable and median [25/75 percentiles] for non-Gaussian distributions. Statistical tests for comparison of flow values between stimulated and nonstimulated limb were performed using Wilcoxon r-paired *t*-test as appropriate. For each test, the level of statistical significance was set at $P < .05$ on two-tailed test.

RESULTS

Characteristics of the patients are listed in Table I. All of the patients had PAD and claudication for 1 to 20 years, and five had undergone a lower limb revascularization. In brief, two patients had aortic stenosis, four had infrapopliteal lesions, five had bilateral iliofemoral lesions, and four

Table II. Decrease from rest of oxygen pressure index (median [25°/75° percentiles]) during treadmill test on the most symptomatic side (side of stimulation) and contralateral (control) side

	At minute 1	*At minute 2*	*Minimal value*
Side of stimulation, mm Hg	−5 [−3/−10]	−10 [−4/−15]	−25 [−18/−34]
Control side, mm Hg	−3 [−1/−5]	−5 [−3/−8]	−14 [−10/−25]

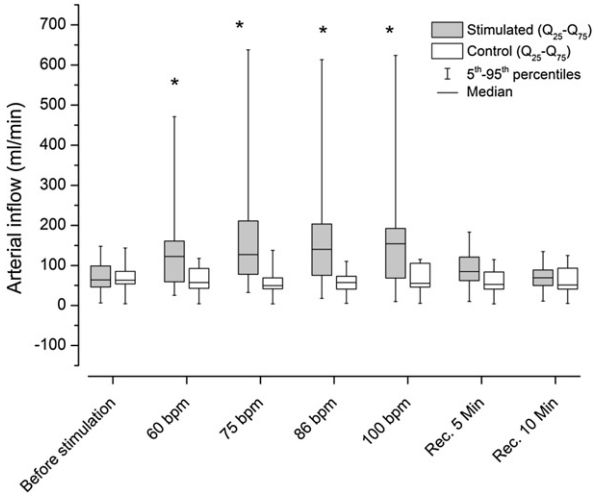

Fig 2. Median arterial inflow with 25-75 percentiles in the stimulated and control limb, at rest, during stimulation, and in the 10 minutes of recovery (*Rec*) after stimulation. Differences are significant between stimulated and control throughout the stimulated period. $*P < .05$.

unilateral iliofemoral lesions. In case of femoral lesions or occlusion, the femoral artery was always patent on both sides down to the lower third of the thigh. Three patients reported having type 2 diabetes, although only two were treated with antidiabetic drugs. All but one patient received antiplatelet agents. All but three patients were taking cholesterol-lowering drugs. Treadmill tests reproduced usual limb symptoms, and limitation was due to limb pain on the treadmill except in one patient. This patient had a self-reported maximal walking distance > 1 km at usual walking speed. Although his symptoms were present while he was on the treadmill, he stopped the test because of exhaustion during the incremental phase of the treadmill (speed 4 km/h, slope 12%). As expected, the DROP index decreased progressively during exercise and tended to be lower in the most symptomatic side (the one used for muscle stimulation) than on the other side (Table II).

The stimulation was performed on the right side in eight patients and left side in seven patients. The level of stimulation reached ranged from 12 to 20 units (1.2-2 V RMS) for all patients on the device selector, allowing for visible calf muscle contraction in all cases. Calf EMS was well tolerated by all patients, and 20-minutes EMS could be completed in all cases without contraction-induced muscle ischemic pain, even for the seven patients with a maximal walking time on the treadmill <5 minutes.

No significant systemic hemodynamic changes were observed throughout the experiment, although systolic pressure tended to decrease moderately with time as a result of the patient being comfortably seated at rest for 30 minutes. Systolic and diastolic arterial pressures and heart rate were 139 (10) mm Hg, 76 (11) mm Hg, and 69 (13) bpm at rest, 136 (10) mm Hg, 75 (10) mm Hg, and 69 (14) bpm at 20 minutes of stimulation, and 134 (10) mm Hg, 76 (11) mm Hg, and 69 (12) bpm at the end of the experiments, respectively.

Stimulation induced a significant increase in arterial inflow in the stimulated limb, whereas the inflow remained stable on the control side (Fig 2). The coefficient of variation of repeated measurements during the test calculated in the nonstimulated leg was on average 18.3% (8.8%) for the 15 subjects. In the stimulated leg, we found a wide variability of inflow increase among subjects, ranging from 27% to >700% of resting values. The highest flow value increase was observed in a patient who had a severe stenosis at the origin of the profunda femoris artery with multiple but nonsignificant lesions on the SFA on the stimulated side. The lowest value was observed in a patient with distal occlusion of the SFA.

No relationship was found between the intensities of stimulation and flow ($r = 0.20$; $P > .05$). No difference in flow increase was found in perspective of treatments. Flow increase was 192% among the six patients who did not receive a vasodilating drug (nitrate, angiotensin-converting enzyme inhibitor, naftidrofuril, angiotensin-receptor antagonists) vs 181% in patients who did receive a treatment.

Although stimulation significantly increased arterial inflow, there was no apparent decrease in $tcPO_2$ (DROP index) during and in the 10 minutes after stimulation (Fig 3). Specifically, the lowest value observed during all sessions of 20 minutes of EMS was −10 mm Hg. This lowest value was found in a patient whose value after 6-minute walk on the treadmill (~300 m) was −25 mm Hg. Consistently, no significant difference was found on the NIRS signal between the right and left legs during and after EMS (Fig 4).

DISCUSSION

Muscle contraction induced by EMS seems to be well tolerated by PAD patients with claudication. EMS induced no pain due to the stimulation itself and no ischemic pain even though the total duration of EMS by far exceeded the duration of treadmill tests, limited by walking-induced pain in the same patients. This observation likely is a result of the moderate intensity of muscle contraction

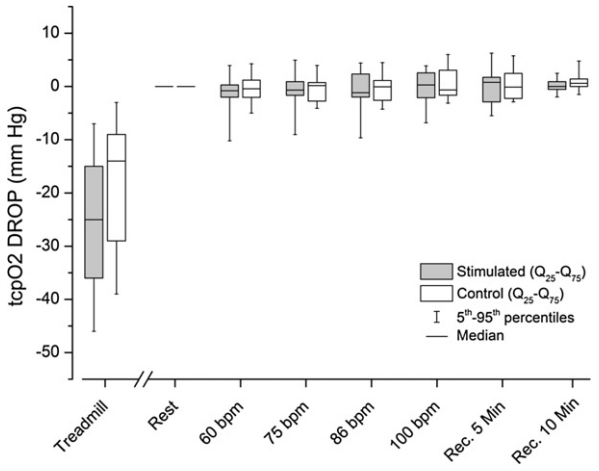

Fig 3. Median decrease from rest of the transcutaneous oxygen pressure (*tcPO*$_2$) decrease from rest of oxygen pressure (*DROP*) index with 25-75 percentiles observed during and in the 10 minutes of recovery (*Rec*) after stimulation. The minimum values observed on treadmill are shown as references.

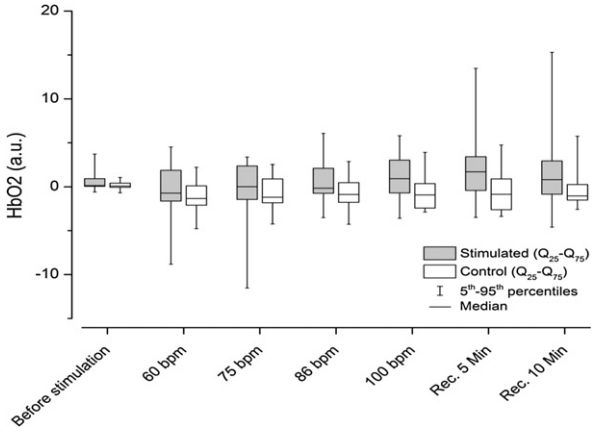

Fig 4. Near-infrared spectroscopy oxygen content (*HbO*$_2$) of the gastrocnemius lateralis muscle observed before, during, and in the 10 minutes of recovery (*Rec*) after stimulation.

and thus of oxygen demand. This hypothesis seems consistent with the absence of significant O_2Hb or $tcPO_2$ DROP index decrease on the stimulated leg compared with the nonstimulated leg. The NIRS changes during EMS were very small and extremely limited compared with the changes reported in the literature during walking tests.[18] Furthermore, $tcPO_2$ changes during EMS were much smaller than the changes observed during walking tests in the same patients. Consistently, the inflow increase found in this study remains moderate compared with the estimated limb flow increase observed during walking in healthy subjects. Indeed, blood flow to the anterior tibial compartment increased three- to fourfold during muscle contraction in healthy humans[19] and is dependent of age and exercise intensity.[20] The inflow values observed in the present study for the SFA were quite low compared with values in some previous reports.[8,20-22] It is likely that calculating limb inflow from the sole SFA underestimated the total leg inflow increase due to collateral circulation through the profunda femoris artery at the thigh level. The distribution of flow between the SFA and the profunda femoris artery is highly variable, and inflow in the SFA is decreased in the presence of lesions in this artery and is increased after angioplasty.[21,22] We believe that the inflow differences we observed likely resulted from the distribution of vessel lesions between the profunda femoris and the SFA. In the patient who showed the highest increase in inflow, we assume that all of the inflow increase was driven by the SFA, whereas in all other patients, the variable percentage of leg inflow was derived toward the profunda femoris artery. It is clear that total limb flow is, roughly, the sum of the inflow through the SFA and the profunda femoris arteries. The leg inflow that we measured likely was underestimated compared with the total flow of the limb. Thermodilution and xenon scintigraphy are invasive and not easily performed with patients in the seated position, and plethysmography results are influenced by the position of the limb from the heart.[23] It was not possible to measure both arteries on both sides with ultrasound in our experimental conditions. It could be suggested that measurement of arterial inflow at the level of the common femoral or popliteal arteries would have been preferable, but these arteries are difficult to access with patients in the seated position. Another point is that the absence of repeated diameter measurements may have interfered with our results, which could have underestimated arterial inflow changes.

There are other limitations to the present study. First, because the treadmill tests and EMS experiments were not performed in the same unit of the department, we could not record NIRS changes during exercise. Second, it is likely that greater changes could be attained if the intensity of stimulation, and the resulting force of muscle contraction, was increased. Nevertheless, the aim was to test the effect of tolerable (comfortable) use of the device in the setting of repetitive use "at home" without medical supervision, which we aim to study in the future. The intensity required to reach stimulation-induced muscle contraction was variable among subjects. Reasons for these differences (eg, electrode position, subcutaneous fat thickness, water content of the tissues) remain unknown. Third, the population studied showed relatively moderate severe claudication. This finding probably relies on the fact that we studied only patients with a patent SFA (at least of the first third) on both sides to allow ultrasound measurements. Clinical tolerance of EMS in patients with severe claudication or critical limb ischemia should be studied in another population. Finally, it could be suggested that the variability of flow increase resulted from the fact that arterial lesions were either proximal (aortoiliac) or distal. We believe this was not the case, but future experiments might be required to determine a difference in leg inflow between patients with suprainguinal and those with infrageniculate disease.

Clinical applications. Our results are important in view of potential use of EMS as an adjuvant treatment in PAD patients with claudication but remain to be evaluated. The absence of significant muscle ischemia on tissue saturation and DROP index is of major interest to prevent pain and for safety reasons if the device were to be used by the patient at home without medical supervision. Nevertheless, although the absence of pain and measurable ischemia during EMS may be beneficial from a compliance standpoint, it cannot be excluded that the oxidative stress of ischemia is as important as inducing increased arterial inflow in improving walking capacity, in which case, electrical stimulation would be less beneficial. We assume this is not the case because low-intensity treadmill walking exercise seems to be effective in improving maximum walking distance, even within a 6-week period for patients with intermittent claudication due to PAD.[24]

CONCLUSIONS

All study patients were able to self-select a level of intensity from the Veinoplus device that resulted in visible muscle contraction. The EMS of calf muscle resulted in a significant increase of arterial inflow in the SFA, without inducing ischemic pain in patients with PAD and a patent SFA. The decrease in $tcPO_2$ DROP index during and in the 10 minutes after EMS was extremely limited compared with the DROP index observed in the same leg and in the same patients during a treadmill walking test. Similarly, the NIRS O_2Hb values remained almost unchanged on the stimulated gastrocnemius muscle, suggesting that no measurable calf muscle ischemia occurred during or after EMS.

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AUTHOR CONTRIBUTIONS

Conception and design: PA, FB
Analysis and interpretation: VM, NO, FC, GL
Data collection: PA, VM, FB, FC
Writing the article: PA, FB
Critical revision of the article: VM, NO, FC, GL
Final approval of the article: PA, VM, FB, NO, FC, GL
Statistical analysis: PA, FB
Obtained funding: PA, FC
Overall responsibility: PA

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