Preprogrammed Oscillations Improve Lower Limb Blood Flow and Walking Distance in Patients with Peripheral Arterial Disease

Igor Rabin MD[1], Uri Shpolanski PhD[2], Allon Leibovitz MD[2] and Arie Bass MD[1]

[1]Department of Vascular Surgery, Assaf Harofeh Medical Center, Zerifin, Israel
[2]VascuActive Ltd., Herzliya Pituah, Israel

ABSTRACT: **Background:** Claudication is one of the sequelae of peripheral arterial disease (PAD). To date, no effective treatment has been found for this condition.

Objectives: To investigate a new device to treat PAD. The device administers pre-programmed protocols of oscillations to the foot.

Methods: Fifteen patients aged 40–70 years who suffered from intermittent claudication secondary to PAD were recruited to an open prospective study. Each patient was treated once for 30 minutes. The following parameters were evaluated: pain-free and maximal walking distances, skin blood flux by laser-Doppler, skin temperature, ankle-brachial and toe-brachial indices, transcutaneous oxygen pressure ($tcpO_2$) and transcutaneous carbon dioxide pressure ($tcpCO_2$). Non-parametric signed-rank test was applied for testing differences between baseline assessment and post-treatment assessments for quantitative parameters.

Results: Mean pain-free walking distance was 122 ± 33 m and increased to 277 ± 67 m, after the treatment session ($P = 0.004$). Mean maximal walking distance was 213 ± 37 m and it increased to 603 ± 77 m ($P < 0.001$). Foot skin perfusion also improved, as demonstrated by an increase in $tcpO_2$ by 28.6 ± 4.1 mmHg ($P < 0.001$), a decrease in $tcpCO_2$ by 2.8 ± 1.3 ($P = 0.032$), and up to twofold improvement in blood flux parameters, and an increase in skin temperature by 1.9 ± 0.5°C ($P < 0.001$). Ankle-brachial index increased by 0.06 ± 0.01 ($P = 0.003$) and toe-brachial index by 0.17 ± 0.02 ($P < 0.001$).

Conclusions: Preprogrammed oscillations applied to the foot had a positive effect on microcirculation, tissue oxygenation and CO_2 clearance; they had a smaller though significant effect on arterial blood pressure indices, and the change in the arterial-brachial index correlated with the change in the pain-free walking distance.

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KEY WORDS: claudication, peripheral arterial disease, walking distance, oscillations, blood flow

Different conservative treatment approaches to peripheral arterial disease have been proposed [1]. These include risk factor modification, which includes smoking cessation, weight reduction, cholesterol and triglyceride control, hypertension management, aggressive glucose control in diabetic patients, and anti-platelet therapy. Supervised exercise rehabilitation is also recommended for individuals with PAD. The effectiveness of conservative approaches is limited, and there is a clear need for more effective therapeutic modalities.

Oscillatory phenomena can affect blood flow. Direct skin vibrations at 47 Hz increased skin microcirculatory blood flow in the ears of mice [2]. The skin blood flow in rabbits increased after exposure to vibrations at frequencies ranging from 8 to 250 Hz [3]. This increase is frequency-dependent and peaks at 63 Hz. In the rabbit this effect was modulated by calcium-channel blocker and alpha-1 adrenergic receptor antagonist, indicating the possible involvement of a neurogenic factor, specifically sympathetic nerve activity.

Whole-body vibrations at a frequency of 30 Hz for a period of 3 minutes resulted in an increase in skin blood flow in healthy human subjects [4]. This increase was sustained for at least 10 minutes after vibrations stopped. Two studies compared the effects of 30 Hz and 50 Hz on skin blood flow in the arms of healthy volunteers [5]. Both frequencies resulted in an increase in skin blood flow of similar magnitudes. However, 50 Hz was clinically superior since skin blood flow increased more rapidly and did not result in vasoconstriction during the recovery period, as occurred with 3 0Hz. Whole-body vibrations at 26 Hz was shown to increase the blood volume in the quadriceps and the gastrocnemius [6]. Blood flow velocity within the large arteries leading to these muscles was doubled, and their resistive index decreased significantly.

Based on these data we developed a device (VascuActive®, Israel) for the treatment of intermittent claudication by administering pre-programmed sequences of oscillations at specific frequencies, amplitudes and waveforms. The patient's foot is placed in the device, which administers these oscil-

PAD = peripheral arterial diease

lations for the duration of the treatment. The objectives of this proof-of-concept study were safety and primary efficacy.

PATIENTS AND METHODS

Fifteen patients, aged 40–70 years with arterial claudication (Fontaine II) at the level of the calf, were screened for this open one-arm prospective trial. Patients were included in the study if pulses in both the posterior and the anterior tibial artery were absent in at least one foot, and the ankle-brachial index was < 0.7 by Doppler in at least one of these arteries. In all patients in the study, below-inguinal pulses were not palpable, including the popliteal and dorsalis pedis arteries. We assume that the superficial femoral artery was blocked, but angiography was not conducted. Patients were excluded if their femoral artery pulses were absent, since the effect of the treatment is regional and confined to the lower limb, and the atherosclerotic site must be in relative proximity to the foot. Other exclusion criteria included venous insufficiency evident by Doppler, or a severe cardiac or systemic disease.

The device is shaped like a shoe, in which the foot is placed and gently wrapped. Its base plate is equipped with a set of two vibrators perpendicular to each other, controlled by a programmed controller and operated at frequencies in the range 32–145 Hz. Balloons are inflated and deflated at pre-defined intervals to add a squeezing effect on the foot sole. No heat is generated by the device during its operation.

Each patient was given a single 30 minute treatment with the device after at least 10 minutes rest in the supine position until a stable steady state was achieved. The treatment was administered on one leg, the one that was more severely affected. Treatment was administered under the supervision of a vascular surgeon. The study was performed in an air-conditioned room, temperature 21–22°C, with the window closed and shaded.

Baseline measurements were taken for each patient just prior to the treatment and 1, 15 and 30 minutes after treatment completion. These included skin temperature (thermocouplers and data logger, MMS300, Commtest Instruments, New Zealand) at two points in the leg and a reference point on the hand, transcutaneous partial pressures of O_2 and CO_2 of the foot (TCM4, Radiometer Medical ApS, Denmark), blood flux measurements using both laser-Doppler fluxmetry (DRT4, Moor Instruments Ltd., UK) and infra-red fluxmetry (pulse plethymograph, UFI 1020, USA). Blood pressure was measured using the auscultatory method aided with a piezoelectric pulse transducer (UFI model 1010).

For the purpose of laser-Doppler fluxmetry, two probes were placed, one above the ankle and the other at the dorsum of the foot. Both peak values and amplitudes were documented. An infra-red fluxmetry probe was placed over the plantar surface of the base of the first toe. Skin temperature of the foot was measured at two points – one on the dorsum and one on the medial aspect of the foot; a control electrode was placed on the back of the hand, as reference.

Blood pressure indices – ankle-brachial index and toe-brachial index – were calculated. Pain-free walking distance and maximal walking distance were measured on a treadmill (Vitamaster FF 1267T, USA) which was set to a slope of 10° and speed of 60 m/min. To avoid the possibility of affecting other physiologic measurements, baseline treadmill tests were taken several days (up to a week) prior to the treatment day. Post-treatment measurements were taken 30 minutes after treatment completion.

All participants signed an informed consent form. The study was approved by the institutional Ethics Committee. The clinical study was registered with www.clinicaltrials.gov (NCT01014377).

STATISTICAL ANALYSIS

All measured variables and derived parameters were listed individually and tabulated by descriptive statistics. For descriptive statistics, summary tables were provided giving sample size, absolute and relative frequency for proportions of categorical variables and sample size, arithmetic mean, standard deviation, and median, minimum and maximum for means of continuous variables. The non-parametric signed-rank test was applied for testing differences between baseline assessment and all the post-baseline assessments for quantitative parameters. All tests were two-tailed, and a P value < 0.05 was considered statistically significant. The data were analyzed using the SAS® version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Fifteen patients (14 males and 1 female) were recruited and completed the study. Their mean age was 63.1 ± 8.3 years. Baseline characteristics are presented in Table 1. None of the patients experienced any discomfort during the treatment and no adverse events were recorded. Data are presented in Table 2.

Table 1. Baseline characteristics of the patients in the study

Male:Female ratio	14:1
Age (yr)	63.1 ± 8.3
Diabetes	11 (73%)
Hypertension	12 (80%)
Hypercholesterolemia	6 (40%)
Coronary heart disease	8 (53%)
Stroke	2 (13%)
Smokers	15 (100%)
Present smokers	3 (20%)
Pack-years	35 ± 13

Data are presented as mean ± standard deviation, or as absolute (percentage), as applicable

WALKING DISTANCES

Mean pain-free and mean walking distances before treatment were 122 and 213 m, respectively. The mean change in pain-free and mean walking distances was 155 m ($P = 0.004$) and 391 m ($P < 0.001$) respectively. In two patients the mean walking distance after treatment was more than 1 km [Figure 1].

BLOOD FLOW

Laser-Doppler blood flux peak measurements increased at the dorsum of the foot and at the calf immediately following treatment by 56% and 33%, respectively. Amplitudes approximately doubled, as occurred with infra-red blood flow measurement. Fifteen minutes later, measurements decreased in varying degrees, but all remained at levels significantly higher than baseline.

TISSUE GASES

Transcutaneous oxygen and carbon dioxide pressure were measured over the dorsum of the foot. Mean tissue oxygen levels increased during treatment from 45.8 to 61.7 mmHg and continued to increase steadily during the next 30 minutes, reaching a maximum increase of 28.6 mmHg higher than the baseline levels ($P < 0.001$). Carbon dioxide levels decreased steadily throughout the half hour after treatment, initially only slightly, but reaching a mean decrease of 2.8 mmHg.

BLOOD PRESSURE INDICES

TBI increased from 0.51 to 0.63 ($P < 0.001$) by the end of the treatment, and remained at the same level for the next 15 minutes. In one patient non-measureable toe systolic pressure before treatment increased to almost normal values after the treatment: 49 mmHg at 1 minute after treatment (TBI 0.43) and 71 mmHg 15 minutes later (TBI 0.62). ABI increased in a smaller magnitude, from 0.69 to 0.73 ($P = 0.003$) and returned to slightly below its baseline level 15 minutes afterwards. A positive correlation (Pearson $R = 0.67$, $P = 0.03$) was found between the change in ABI and the change in the pain-free walking distance [Figure 2].

SKIN TEMPERATURE

Skin temperature increased immediately after the treatment by 1.9°C and 1.2 ± 0.3°C in the two locations on the foot. After 15 minutes the temperature decreased, but remained at above-baseline levels. The mean temperature increase of the foot skin was 1.1°C higher than that of the hand skin.

DISCUSSION

This study has shown that the Vasoactive® device is safe and potentially efficacious. The increase in laser-Doppler and infra-red fluxmetry is direct evidence of the improved capillary blood perfusion in the foot. The elevation of foot skin temperature is additional support. These findings concur with those presented by Kershan-Schinndl et al. [6], who documented doubling of popliteal artery blood flow velocity and augmented blood flow in the quadriceps and gastrocnemius, which also responded

TBI = toe-brachial index
ABI = ankle-brachial index

Table 2. Data collected in the study

	N	Baseline	1 min after treatment	15 min after treatment	30 min after treatment	Maximal change from baseline
PFWD (m)	10	122 ± 33	–	–	277 ± 67	155 ± 48 $P = 0.004$
MWD (m)	14	213 ± 37	–	–	603 ± 77	391 ± 63 $P < 0.001$
Blood flux amplitude, above ankle (mV)	15	6.1 ± 1.4	10.9 ± 3.2	8.3 ± 2.9	–	5.0 ± 3.0 $P = 0.007$
Blood flux amplitude, foot (mV)	15	5.6 ± 0.7	10.9 ± 2.4	8.9 ± 1.7	–	6.1 ± 2.0 $P < 001$
Blood flux peak, above ankle (mV)	15	22.4 ± 3.9	26.7 ± 4.4	23.2 ± 4.3	–	7.4 ± 4.3 $P < 0.035$
Blood flux peak, foot (mV)	15	21.3 ± 2.3	30.9 ± 3.5	27.1 ± 3.3	–	12.0 ± 2.7 $P < 0.001$
Blood flow (infra-red) (mV)	15	47 ± 24	67 ± 33	88 ± 59	–	44 ± 31 $P < 0.001$
$tcpO_2$ (mmHg)	13	45.8 ± 4.9	61.7 ± 4.7	63.1 ± 3.4	70.8 ± 4.1	28.6 ± 4.1 $P < 0.001$
$tcpCO_2$ (mmHg)	13	39.7 ± 1.3	39.1 ± 1.1	38.3 ± 1.1	37.8 ± 1.5	-2.8 ± 1.1 $P = 0.032$
Temperature, dorsal aspect of foot (°C), relative to hand	15	29.4 ± 0.7	31.2 ± 0.6 {1.1 ± 0.6}	30.6 ± 0.5 {1.0 ± 0.7}	–	1.9 ± 0.5 $P < 0.001$
Temperature, medial aspect of foot (°C)	15	29.1 ± 0.4	30.3 ± 0.5	29.3 ± 0.4	–	1.2 ± 0.3 $P = 0.003$
ABI	15	0.69 ± 0.03	0.73 ± 0.03	0.67 ± 0.06	–	0.06 ± 0.01 $P = 0.003$
TBI	14	0.51 ± 0.03	0.63 ± 0.04	0.66 ± 0.04	–	0.17 ± 0.02 $P < 0.001$

Data are presented as mean ± standard error

Results are statistically significant if $P \leq 0.05$. Results indicate a trend if $0.05 < P < 0.15$

N=number of subjects, PFWD= pain-free walking distance, MWD=maximal walking distance, mV=millivolt, $tcpO_2$=transcutaneous partial pressure of O_2, $tcpCO_2$= transcutaneous partial pressure of CO_2, ABI=ankle brachial index, TBI=toebrachial index

Figure 1. Pain-free and maximal walking distances

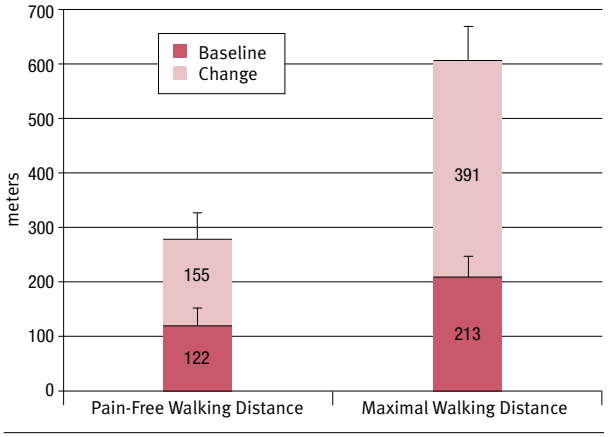
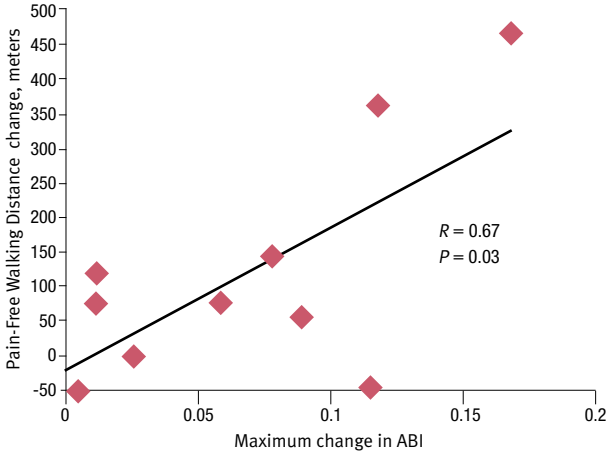


Figure 2. Correlation between changes in ankle brachial index and pain-free walking distance



ABI = ankle-brachial index, PFWD = pain-free walking distance

with rhythmic contractions to the stimulus – 9 minutes of standing on a 26 Hz, 3 mm amplitude vibrating platform.

The concomitant rise in tissue oxygenation and carbon dioxide clearance are probably the major contributors to the clinical effect, mainly the increase in pain-free walking distance. The rise in TBI is likely the result of relaxation and decreased resistance of the small arteries of the foot, proximal to the digital artery, which consequently elevates capillary perfusion. The increase in the ABI is statistically significant; however, its small magnitude calls for further research to determine whether it indicates a true increase in arterial blood flow.

Maximal walking distance and pain-free walking distance increased significantly, indicating a delay in the switch from aerobic to anaerobic metabolism compared to the pre-treatment test. We assume that this is the result of improved oxygen supply to the calf muscles, due to improved blood flow, as evidenced in the foot. Oscillations exerted by the device on the foot propagate proximally through the foot and leg tissues, hence their effect on the foot can be seen further up the leg. The improvement in walking distances may represent a significant improvement in the clinical outcome and quality of life of patients with PAD.

Several of the physiologic changes (i.e., $tcpO_2$, $tcpCO_2$, blood flow by infra-red) were sustained throughout the study duration, while others (e.g., skin temperature and laser-Doppler fluxmetry) showed a partial decline from their maximum value 15 minutes after treatment ended. Further research is required to understand these differences in sustainability of the physiologic effects, unveil the mechanisms underlying these changes, and predict the long-term clinical outcome.

$tcpO_2$ = transcutaneous oxygen pressure
$tcpCO_2$ = transcutaneous carbon oxygen pressure

LIMITATIONS

Since this was a single-arm study, interpretation of the results is limited. A randomized, double-blinded controlled study is required to validate the effectiveness of the device. Another limitation relates to the short period of follow-up, 30 minutes after treatment, which was selected as this was a proof-of-concept study. This short follow-up limits the ability to foresee the long-term effects in these chronic patients.

CONCLUSIONS

In this group of 15 patients with peripheral arterial disease of the lower limbs, a single half-hour treatment session of pre-programmed oscillations applied to the foot significantly increased the maximal and pain-free walking distances. These can be explained by the demonstrated positive effect of the treatment on the various physiological parameters of blood flow to and within the foot: a markedly positive effect on foot microcirculation, a distinctive positive effect on arterial blood pressure indices (ABI and TBI), and a consequent significant increase in tissue oxygenation and a trend of increase in CO_2 clearance.

Further research is needed to reveal the mechanisms by which pre-programmed oscillations cause the physiologic changes demonstrated and the long-term effects on clinical outcome and quality of life. Additional studies are also required to establish the role of this technology in the clinical setting of peripheral arterial disease, diabetic neuropathy and diabetic ulcers.

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Correspondence

Dr. A. Bass

Dept. of Vascular Surgery, Assaf Harofeh Medical Center, Zerifin 60930, Israel

email: arbas@post.tau.ac.il

Fax: (972-8) 977-9186

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