

# Effects of transcutaneous electrical nerve stimulation via peroneal nerve or soleus muscle on venous flow

## A randomized cross-over study in healthy subjects

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### Abstract

**Background:** Transcutaneous electrical nerve stimulation (TENS) is used to prevent venous stasis and thromboembolism. However, best electrostimulation parameters have yet to be established. The aim of the study was to compare the hemodynamic effects and the participants' relative discomfort of 3 TENS sequences at the maximum tolerated intensity stimulus.

**Methods:** Twenty-four healthy university students (50% male) participated in a cross-over, randomized study. Each participant received 2 TENS sequences on peroneal nerve at 1 and 5 Hz, and the third one on soleus muscle at 5 Hz. Popliteal flow volume (FV) and peak velocity (PV) were measured using Doppler ultrasound and the relative change from basal values was recorded. Discomfort questionnaires -visual analogue scale (VAS) and verbal rating scale (VRS)- were also administered to compare sensations among the three applications.

**Results:** All interventions produced significant hemodynamic responses compared to baseline. Both 5 Hz applications obtained higher FV increments than 1 Hz TENS ( $P < .001$ ). The muscle application resulted in the lowest PV increment ( $P < .001$ ). TENS at 5 Hz on nerve location was the worst tolerated, with higher values in VRS ( $P = .056$ ) and VAS ( $P = .11$ ), although not significant.

**Conclusion:** TENS at 5 Hz on soleus site may be the most appropriate protocol for enhancing venous return.

**Abbreviations:** ANOVA = analysis of variance, BMI = body mass index, DVT = deep vein thrombosis, ES = electrical stimulation, FV = flow volume, IPC = intermittent pneumatic compression, Musc = muscle, NMES = neuromuscular electrical stimulation, PE = pulmonary embolism, PV = peak velocity, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, TENS = transcutaneous electrical nerve stimulation, VAS = visual analogue scale, VRS = verbal rating scale, VTE = venous thromboembolism.

**Keywords:** hemodynamics, muscle, peroneal nerve, skeletal, transcutaneous electric nerve stimulation

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## 1. Introduction

Many individuals are at risk for developing venous thromboembolism (VTE), defined as deep vein thrombosis (DVT), pulmonary embolism (PE), or both. Three factors have been addressed (Virchow triad) as causing VTE owing to immobilization, surgery, or trauma injury: venous stasis, endothelial damage or increased coagulation. There are 2 main types for preventing VTE: chemical and physical. Despite chemical prophylaxis being the preferred method, it has a high risk of bleeding and must be avoided in some patients. There is also increasing evidence supporting the use of mechanical devices as intermittent pneumatic compression (IPC) and compression stockings in surgical patients at high risk of developing VTE.<sup>[1,2]</sup> These options can still have certain limitations such as patient discomfort, tissue injury, improper fitting,<sup>[2,3]</sup> or arterial insufficiency in patients with peripheral arterial disease,<sup>[4]</sup> so alternative physical strategies like electrical stimulation (ES) are being investigated. ES has been shown to have an additive effect to compression stockings<sup>[5]</sup> and to be at least as effective as IPC in terms of the venous hemodynamic response,<sup>[6,7]</sup> and besides, to show some other advantages such as arterial and microcirculatory flux enhancement.<sup>[8,9]</sup> In addition, ES can also play a specific role by stimulating or replacing the neural supply to the veins, which has been proposed recently as the fourth factor in thrombus pathogenesis.<sup>[10]</sup> ES may be even more necessary when early active motion is difficult or unavailable as in traumatology patients because of an immobilized extremity or muscle inhibition after surgery, and in critically ill patients.

Electrical stimulation devices, like transcutaneous electrical nerve stimulation (TENS) and neuromuscular electrical stimulation (NMES), have been used to enhance venous hemodynamics via motor nerves or via skeletal muscles. NMES and TENS are different ES modalities, but there is confusion regarding the description of the ES forms among researchers and clinicians.<sup>[11]</sup> As both ES modalities can be delivered by surface electrodes for stimulating muscles and nerves, the differences are related to their original purpose. TENS has been primarily developed for pain relief, whereas NMES has been primarily developed for the improvement of muscle strength eliciting smooth tetanic muscle contraction and relaxation, similar to an exercise therapy session.<sup>[12]</sup> Therefore, an on-off time in seconds (duty-cycle) is necessary in NMES for minimizing muscular fatigue and discomfort,<sup>[13]</sup> a parameter not considered in TENS applications.<sup>[12]</sup>

Despite ES having been experimentally proved to be effective in improving venous flow and velocity,<sup>[14]</sup> the stimulation parameters vary greatly and it is necessary to clarify which parameters are optimal for venous return.<sup>[15]</sup> Frequencies from 1 to 10 Hz have been tested at nerve locations.<sup>[8,16]</sup> To the best of the authors' knowledge, only one study has compared nerve to muscle stimulation, but used different ES frequencies and intensities for each placement.<sup>[16]</sup>

The primary objective of this study was to compare the effect of frequency and electrode placement among 3 ES applications at the maximum tolerated intensity on hemodynamic popliteal venous flow and peak velocity (PV) using Doppler ultrasound in healthy volunteers. A further objective was to compare the participants' relative discomfort among the 3 applications using a visual analogue scale and verbal rating scoring index.

## 2. Materials and methods

### 2.1. Design and sample

A large variation in hemodynamic response to ES has been found in healthy population.<sup>[17]</sup> Therefore, a within-subjects cross-over design was used to determine differences in hemodynamic effects and discomfort. A random assignment of the ES was used to avoid possible systematic effects of order (6 possible sequences). The order of testing was introduced in opaque envelopes to be randomly selected by each participant, who was not aware of it. Study protocol was reviewed and approved by the regional Clinical Research Ethics Committee of Galicia (Spain) in accordance with the Helsinki Declaration. Informed consent was obtained from each subject before enrollment. This study is registered in the Research Registry (researchregistry3380).

The optimal sample size was determined from a pilot sample of 12 subjects (6 men). The venous flow volume (FV), in milliliter per minute, was measured 3 times and the mean was considered, both basal and after the ES protocol. The FV increment was computed relatively with respect to basal levels, and given as percentage. A 1-way analysis of variance (ANOVA) with repeated-measures was used to compare the difference among the 3 ES results. From the estimated correlation among repeated-measures of 0.7 and a standard deviation within each group of 90%, we obtained that, with a sample size of 24 subjects, the test would have a power of 0.8 to detect significant differences in the relative FV increments if they were 40%, 175%, and 150%, with a type I error of 0.05.

### 2.2. Participants

Students from the Faculty of Physical Therapy (Universidad da Coruña, Spain) were initially invited to participate in a screening session. A university notice board was used to recruit the volunteers. The specific inclusion criteria were: healthy subjects aged between 18 and 39 years. Exclusion criteria included factors that might affect venous return or current flow: body mass index (BMI) <18 or >30 kg/m<sup>2</sup>, smokers, oral contraceptive use, recent surgery/trauma to lower limbs, any diagnosed disease that could affect hemodynamics, clinically significant varicose veins, or ulceration of the lower limbs. Among 27 volunteers assessed for eligibility, 2 women and 1 man were excluded for meeting some exclusion criteria. The pilot sample was included within the final sample of 24 subjects (12 men) selected for evaluation. All of them completed the experimental session.

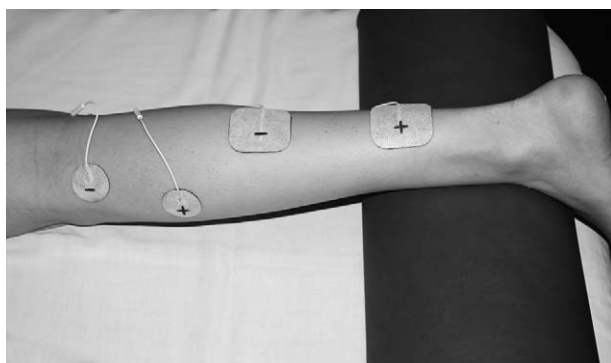
### 2.3. Experimental procedure

All examinations were performed in the same room, in which the temperature was controlled (22°C–24°C). Environmental data were recorded with a weather station (Oregon Scientific, Madrid, Spain). Data collection occurred in March and April 2017.

The subjects lay in the prone position 15 to 20 minutes before the experiment with their feet off the table and a soft cushion beneath the ankle. Stimulation electrodes sites were previously clipped of hairs. Three ES protocols were applied using a 2-channel portable stimulator (TENS MED S82, ENRAF-NON-IUS, Rotterdam, The Netherlands) and matching self-adhesive electrodes. All the ES protocols selected were delivered without a duty cycle (on-off time). Therefore, all of them were considered TENS. Electrode placements (Fig. 1) were the left common peroneal nerve,<sup>[16,18]</sup> and the motor points of the soleus muscle,<sup>[19]</sup> where skin area was most responsive to ES.<sup>[20]</sup> A charge-balanced biphasic square wave with phase duration of 0.35 milliseconds was applied at 1 and 5 Hz over the nerve and at 5 Hz over the muscle to obtain a twitch contraction. The frequency of 5 Hz<sup>[8]</sup> was chosen instead of 10 Hz,<sup>[16]</sup> as 10 Hz was felt uncomfortable and fatiguing because of the almost tetanic muscle response it originated without a resting time. Stimulation amplitude was increased gradually, 0.5 mA per second to find the pain threshold for each application in the random order assigned. The stimulation intensity was set 10% below the pain threshold, and the values (median, first–third quartiles) were 30.5 (22.1–43) mA, 20.0 (14.5–24.3) mA, and 37.0 (25.5–51.5) mA when applying 1 Hz and 5 Hz on nerve location, and 5 Hz at muscle site, respectively.

### 2.4. Outcome measurements

**2.4.1. Primary outcome.** A baseline duplex venous ultrasound scan was performed at least 5 minutes after the last pain threshold determination. The popliteal vein of the nondominant leg was examined with a 6 to 13 MHz linear transducer (LOGIQ e BT12 General Electric Medical Systems). It was placed at the back of the knee by a fixed-arm, once the optimal location was reached. Vein diameter was measured using B-mode. The venous FV (millimeters per minute) was calculated by the Doppler unit's software. The venous PV (centimeters per second) was recorded from the Doppler waveform. The electrical stimulation sequences were applied for 1 minute before recording echographic measures during stimulation. They were followed by a 5-minute recovery phase and a new baseline ultrasound was examined. Measurements were taken over a period of 16 seconds, to obtain several



**Figure 1.** Electrodes sites for nerve (left) and muscle (right) electrical stimulation. Two 3.2 cm round self-adhesive electrodes were placed over the left common peroneal nerve, close to the fibula head. The other pair of 5 × 5 cm self-adhesive electrodes was located at the motor points of the soleus muscle.

endogenous or ES-superimposed blood movement cycles. Three measurements were made for each condition and the mean of them was used for analysis. The same well-trained examiner with >6 years of experience performed all measurements and asked the subjects to remain stationary and maintain a stable breathing pattern during data collection.

**2.4.2. Secondary outcome.** Participants compared discomfort after the 3 TENS applications using a 100-mm visual analogue score (VAS). This scale was modified from traditional pain VAS with 0 mm denoting no sensation, and 100 mm indicating pain onset. Subjects' relative comfort perception was also assessed by a verbal rating score (VRS): 1, no sensation; 2, minimal discomfort; 3, mild discomfort; 4, moderate discomfort; and 5, severe discomfort.

### 2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD); if the distribution is asymmetrical, median and first and third quartiles (Q1 and Q3) are also given. The Kolmogorov-Smirnov-Lilliefors test was used to test for normal distribution of the data. Univariate effects of the ES with respect to baseline values were studied with a paired *t* test, as all the differences were normally distributed. To compare the effects in hemodynamics and discomfort the 3 TENS applications, a 1-way ANOVA with repeated-measures, or Friedman test was carried out. To identify differences in the ES results, post hoc pairwise comparisons were considered with Bonferroni correction. To ensure comparability, standardized effect sizes were calculated by the partial eta-squared  $\eta^2_p$  (partial variance explained in ANOVA). A *P* value <.05 was assumed to denote statistical significance. Statistical analyses were carried out using IBM SPSS for Windows, version 21.0 (IBM Corporation).

## 3. Results

Table 1 presents the physical baseline characteristics of the participants. Typical Doppler waveforms of baseline and the 3 TENS protocols (1 and 5 Hz via nerve and 5 Hz muscle) are shown in Figure 2. The effect of the different TENS programs on both FV and PV was statistically significant (Table 2). The increment of hemodynamics responses has been computed

**Table 1**

### Subject physical characteristics.

	Male (n=12)	Female (n=12)
Age, y	22.50 ± 3.23	19.42 ± 0.90
BMI, kg/m <sup>2</sup>	24.17 ± 2.41	22.17 ± 1.90
Calf perimeter, cm	37.05 ± 1.74	32.93 ± 2.64

Data are presented as means ± standard deviation.

relatively from baseline and given as a percentage (Table 3). The relative increments of the hemodynamic responses (in %) varied significantly with the ES interventions for FV ( $P < .001$ ) and PV ( $P < .001$ ). FV was higher with TENS applications of 5 Hz than of 1 Hz ( $P < .001$ ). TENS protocols at 5 Hz on peroneal nerve and on soleus muscle were not significantly different ( $P = 1.00$ ). Regarding PV, TENS 5 Hz on soleus muscle produced the lowest changes. These changes were significantly lower than for TENS 1 Hz ( $P < .001$ ) and for 5 Hz on peroneal nerve ( $P = .002$ ). Furthermore, no significant difference on PV was found between both applications on peroneal nerve ( $P = .22$ ).

Comparative values of VAS and VRS for discomfort after finishing the 3 protocols are presented in Table 4. TENS applied at 5 Hz on nerve site was the worst tolerated with highest VRS and VAS, although not significantly with respect to the other ES protocol ( $P = .056$  and  $P = .11$ , respectively).

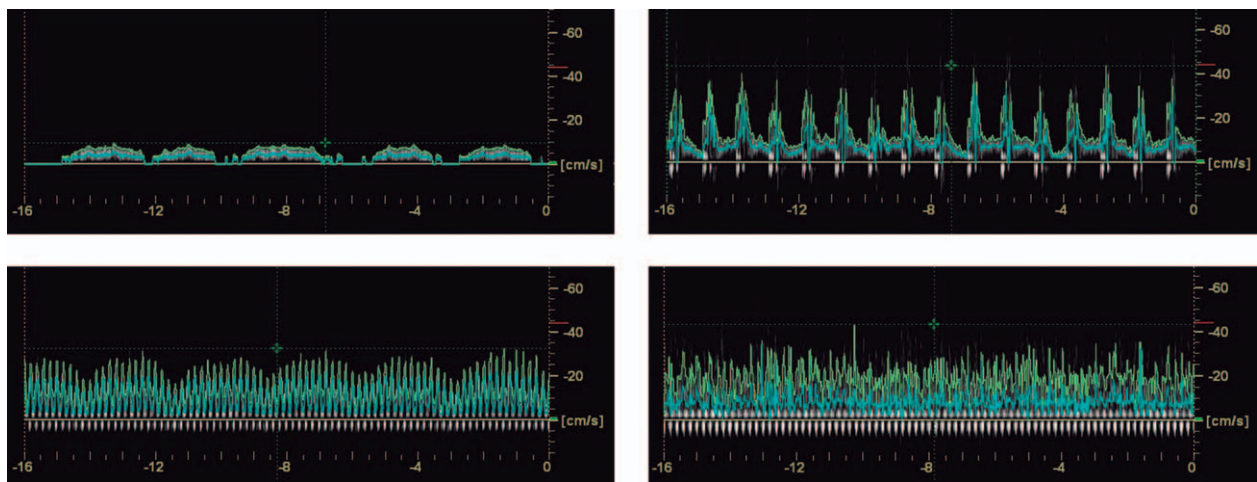
There were no adverse effects at the end of the intervention or reported afterwards by the subjects.

## 4. Discussion

This study compared the efficacy of 3 TENS applications. Increased FV and PV in the ipsilateral popliteal vein were seen both in nerve and muscle stimulation, and using 1 and 5 Hz. This is concordant with the existing literature, despite ES parameters' differences and missing data or discrepancies when reporting it. A review provided a range of 60% to 615% FV increasing from baseline and 25% to 650% for PV.<sup>[15]</sup> The much higher values were from studies in operated on and healthy people at bed rest using NMES.<sup>[21,22]</sup> This can be explained by 2 factors: bed rest causes a decline in venous blood flow, so a higher increase compared to resting values can be expected; in addition, in these researches only the NMES "on time" was compared to baseline, not considering off time where a subsequent cessation in blood flow might happen. Few studies have considered percentage of change, and lower range values have been reported stimulating common peroneal nerve<sup>[9,23]</sup> or different muscle locations<sup>[17]</sup> in healthy volunteers. In these studies a long-lasting hemodynamic recording of 15 seconds was used, as has been also recorded in the present study, to deal with cardiac and respiratory variations.

When looking for the differences among the 3 TENS protocols, TENS at 5 Hz (both nerve and muscle) obtained a higher FV than at 1 Hz on nerve site. However, applying TENS on nerve site (both 1 and 5 Hz) achieved higher PV than on muscle location (with 5 Hz). The latter has not been shown in the previous study comparing nerve and muscle ES, but significantly lower VAS was achieved in nerve site.<sup>[16]</sup> Likely, the discrepancies may be attributed to the distinctive current densities, muscle sites, and frequencies tested.

Current density is estimated as intensity per electrode area.<sup>[24]</sup> Whereas in the mentioned study<sup>[16]</sup> identical current densities were applied (same intensity and small sized electrodes for both locations), in the present study the highest tolerated intensity for



**Figure 2.** Duplex Doppler ultrasound recordings used for blood flow analysis. Representative capture window measuring popliteal blood flow waveform in basal condition is displayed at the top left of the image. The response to transcutaneous electrical nerve stimulation at 1 Hz applied on nerve site is seen at the top right of the figure. The spikes reflect the altered flow pattern at the frequency delivered. Effect on waveform of transcutaneous electrical nerve stimulation at 5 Hz on nerve site is located at the bottom left of the picture. More spikes are seen as frequency is increased 5 times. Finally, at the bottom right corner there is the ultrasound capture window from transcutaneous electrical nerve stimulation at 5 Hz with electrodes placed over the soleus muscle. The flow pattern obtained is different from previous electrical applications as the spikes are less pronounced and there is more regularity in the venous blood flow.

**Table 2**

Comparison of FV and PV, at baseline and at different protocols of electrical stimulation (n=24).

	Baseline Median (Q1–Q3)	Stimulation Median (Q1–Q3)	Difference Mean (95% CI)	Effect size	P*
FV, mL/min					
1 Hz	80.1 (65.3–100.6)	97.8 (73.9–153.1)	24.49 (9.08, 39.91)	0.320	.003
5 Hz	75.1 (55.5–114.7)	174.0 (120.1–251.2)	115.26 (74.74, 155.79)	0.601	<.001
5 Hz musc	74.0 (60.1–114.8)	182.9 (139.9–266.6)	115.05 (86.10, 144.00)	0.746	<.001
PV, cm/s					
1 Hz	13.4 (10.5–18.3)	55.1 (45.4–67.7)	39.93 (34.01, 45.86)	0.894	<.001
5 Hz	13.1 (9.9–17.6)	48.9 (39.4–62.2)	34.61 (28.08, 41.13)	0.839	<.001
5 Hz musc	13.2 (11.2–20.4)	39.2 (29.1–49.4)	23.13 (18.74, 27.53)	0.837	<.001

CI=confidence interval, FV=flow volume, musc=muscle, PV=peak velocity, Q1=first quartile, Q3=third quartile.

\* t test for paired samples.

**Table 3**

Comparison of the relative increment of FV and PV among the different protocols of electrical stimulation (n=24).

	1 Hz	5 Hz	5 Hz musc	Effect size	P*
FV (%)	32.6 ± 46.1 25.2 (–3.5, 62.1) P <sup>**</sup> <sub>1Hz-5Hz</sub> ‡ <.001	146.8 ± 115.9 125.8 (70.4, 193.5) P <sup>**</sup> <sub>1Hz-5Hzmusc</sub> ‡ <.001	147.9 ± 99.1 128.6 (77.4, 208.3) P <sup>**</sup> <sub>5Hz-5Hz musc</sub> ‡ = 1.00	0.482	<.001 <sup>†</sup>
PV (%)	291.9 ± 136.2 299.5 (171.1, 367.6) P <sup>**</sup> <sub>1Hz-5Hz</sub> ‡ = .22	258.6 ± 126.8 257.5 (188.9, 352.7) P <sup>**</sup> <sub>1Hz-5Hz musc</sub> ‡ <.001	169.7 ± 95.1 166.3 (85.6, 229.6) P <sup>**</sup> <sub>5Hz-5Hz musc</sub> ‡ = .002	0.585	<.001 <sup>†</sup>

Data are presented as mean ± SD and median (Q1, Q3).

FV=flow volume, musc=muscle, PV=peak velocity, Q1=first quartile, Q3=third quartile, SD=standard deviation.

\* P for differences among ES protocols.

\*\* P (1 Hz vs. 5 Hz), (1 Hz vs. 5 Hz muscle), and (5 Hz vs. 5 Hz muscle) using Bonferroni correction.

† ANOVA for repeated measures.

‡ Paired t test.



**Table 4****Comparison of discomfort ratings after finishing the three applications of electrical stimulation (n=24).**

	1 Hz	5 Hz	5 Hz musc	Effect size	P*
VAS	68.3 ± 20.9	72.8 ± 18.7	60.4 ± 22.0	0.094	.11 <sup>†</sup>
VRS	3 (3,4)	4 (3,5)	3 (3,4)	0.074	.056 <sup>‡</sup>

Data are presented as mean ± SD or median and Q1-Q3. musc = muscle, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, VAS = visual analogue scale from 0 (no sensation) to 100 (pain onset), VRS = verbal rating scale from 1 (no sensation) to 5 (severe discomfort).

\* P for differences among electrical stimulations.

<sup>†</sup> ANOVA for repeated measures.

<sup>‡</sup> Friedman test.

each protocol was selected. Indeed, in consonance with ES-recommended parameters, greater electrode size was chosen for muscle than for nerve location. Common peroneal nerve was stimulated at a site where good accessibility is considered<sup>[25]</sup> and small electrodes have been found more comfortable and selective for thin fat layers and superficial nerves.<sup>[24]</sup>

Tibialis anterior was the chosen muscle site in Izumi et al's study,<sup>[16]</sup> whereas soleus was the stimulated muscle in the present research. When comparing tibialis anterior and soleus, soleus expelled higher volume and achieved lower peak velocities, which were on average 35% lower than tibialis anterior.<sup>[19]</sup> In another study testing different muscles (soleus was not included), gastrocnemius medial was the only muscle where, besides an increased PV from baseline, a higher FV was detected.<sup>[17]</sup> Explanations from the authors in both researches are in connection with the intimate relationship among the muscles and plexus of deep veins. The leg pump—located in the veins of the soleus muscle—and the popliteal pump—located in the gastrocnemius muscle—are considered together as the calf muscle pump, which is the most important pump in the lower limb. The medial gastrocnemius veins play a major role pushing the blood column upwards and creating an aspiration effect in the popliteal roots below.<sup>[26]</sup> These muscles are innervated from the tibial nerve. Stimulation of the tibial nerve produced nearly identical hemodynamics responses as voluntary contractions when controlling force, duty cycle, and active muscle mass.<sup>[27]</sup>

Regarding the frequency, the previous study used 10 Hz on nerve and 50 Hz on muscle site,<sup>[16]</sup> whereas in this study, 5 Hz was used in both nerve and muscle locations. Other studies have examined the effect of frequency on venous hemodynamics, with diverse results. Stimulating the common peroneal nerve (1–40 mA, 1–5 Hz), venous FV and PV have been enhanced, with both intensity and frequency showing moderate to strong positive correlations.<sup>[8]</sup> In the present research, increased FV at higher frequency was also found, but the same relationship between frequency and PV was not. Different factors can be responsible for the differences. Likely, the most relevant is using the highest tolerated intensity, which was lower at 5 Hz than at 1 Hz, whereas the same intensities were selected by Izumi et al.<sup>[16]</sup> Another study testing 0.13 to 2 Hz in a muscle location on the calf showed that different rates of stimulation had a different effect on PV and FV, as PV decreased and FV increased.<sup>[28]</sup> Perhaps the effect of diminishing PV at increasing frequency is most patent when comparing to frequencies below 1 Hz, as seems to happen in the graphic data presented in this work.

Basically, 2 factors can be argued to support TENS at 5 Hz on soleus muscle rather than TENS at 5 Hz on common peroneal nerve. First, 5 Hz on nerve site originated higher PV increment and it has been noted that an excessive increase in PV can be dangerous. TENS has obtained even higher PV than voluntary

exercise when applied at high intensity and pulse duration.<sup>[29]</sup> In IPC devices, a decline in blood flow velocity has been found in the first section of deflation phase. A negative pressure is generated in the inner vessel, and it pulls blood into the decompressed vessels. There is a possibility of a nondesirable backward flow when a strong negative pressure—related to a high PV—is generated.<sup>[30]</sup> This can be amplified when partial venous obstruction with stenosis or malfunctioning venous valves exists, as it creates the conditions for eddy blood flow.<sup>[31]</sup> For this reason, other factors related to venous volume have been proposed to test the different applications.<sup>[7,19]</sup> Second, when subjects compared the applications using VRS, 5 Hz on muscle was felt more comfortable than 5 Hz on nerve site (close to statistical significance). Discomfort assessment by VRS showed mild discomfort in 1 Hz and 5 Hz muscle. This level of discomfort is in consonance with the application of 1 Hz TENS device (Geko T-1) at normal clinical use setting.<sup>[23]</sup> Despite healthy subjects have been assessed in the present study, it would be useful for collecting normative data to help with better treatment choices in patient population.

## 5. Limitations

There are 2 main limitations to this study. First, although increasing venous flow is assumed to correlate with reduction of thrombosis risk, the data obtained from young healthy people might not be directly translated to patients with a vascular disease or at high risk of suffering it. Second, the medium- and long-term effects of ES can differ from immediate-effects of a brief intervention investigated in this study.

## 6. Conclusions

In conclusion, when considering the highest venous FV increase, the lowest peak venous velocity change, and comparative tolerance, TENS at 5 Hz on soleus muscle is the most beneficial protocol. Stimulation of the common peroneal nerve reached a higher increase in peak venous velocity than in muscle location. Future studies may investigate the ES of tibial nerve and compare it to common peroneal nerve effects on hemodynamics. Furthermore, the influence of frequency and electrode location parameters on population at high risk from suffering DVT has to be established.

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## Author contributions

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## References

- [1] Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. In: The Cochrane Collaboration, ed. *Cochrane Database Syst Rev*. Chichester, UK: John Wiley & Sons, Ltd; 2008.
- [2] Sachdeva A, Dalton M, Amaragiri SV, et al. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* 2014;12:CD001484.
- [3] Hanison E, Corbett K. Non-pharmacological interventions for the prevention of venous thromboembolism: a literature review. *Nurs Stand* 2016;31:48–57.
- [4] Paydar S, Sabetian G, Khalili H, et al. Management of deep vein thrombosis (DVT) prophylaxis in trauma patients. *Bull Emerg Trauma* 2016;4:1–7.
- [5] Lyons GM, Leane GE, Grace PA. The effect of electrical stimulation of the calf muscle and compression stocking on venous blood flow velocity. *Eur J Vasc Endovasc Surg* 2002;23:564–6.
- [6] Czyrny JJ, Kaplan RE, Wilding GE, et al. Electrical foot stimulation: a potential new method of deep venous thrombosis prophylaxis. *Vascular* 2010;18:20–7.
- [7] Broderick BJ, O'Connell S, Moloney S, et al. Comparative lower limb hemodynamics using neuromuscular electrical stimulation (NMES) versus intermittent pneumatic compression (IPC). *Physiol Meas* 2014;35:1849–59.
- [8] Tucker A, Maass A, Bain D, et al. Augmentation of venous, arterial and microvascular blood supply in the leg by isometric neuromuscular stimulation via the peroneal nerve. *Int J Angiol* 2010;19:e31–7.
- [9] Williams KJ, Moore HM, Davies AH. Haemodynamic changes with the use of neuromuscular electrical stimulation compared to intermittent pneumatic compression. *Phlebology* 2015;30:365–72.
- [10] Stefanou C. Electrical muscle stimulation in thromboprophylaxis: review and a derived hypothesis about thrombogenesis—the 4th factor. SpringerPlus 2016;5:884.
- [11] Maffioletti NA. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. *Eur J Appl Physiol* 2010;110:223–34.
- [12] Nussbaum EL, Houghton P, Anthony J, et al. Neuromuscular electrical stimulation for treatment of muscle impairment: critical review and recommendations for clinical practice. *Physiother Can* 2017;69:1–76.
- [13] Glaviano NR, Saliba S. Can the use of neuromuscular electrical stimulation be improved to optimize quadriceps strengthening? *Sports Health* 2016;8:79–85.
- [14] Hajibandeh S, Hajibandeh S, Antoniou GA, et al. Neuromuscular electrical stimulation for thromboprophylaxis: a systematic review. *Phlebology* 2015;30:589–602.
- [15] Williams KJ, Ravikumar R, Gaweesh AS, et al. A review of the evidence to support neuromuscular electrical stimulation in the prevention and management of venous disease. *Adv Exp Med Biol* 2017;906:377–86.
- [16] Izumi M, Ikeuchi M, Mitani T, et al. Prevention of venous stasis in the lower limb by transcutaneous electrical nerve stimulation. *Eur J Vasc Ceryny Endovasc Surg* 2010;39:642–5.
- [17] Evans DRS, Williams KJ, Strutton PH, et al. The comparative hemodynamic efficacy of lower limb muscles using transcutaneous electrical stimulation. *J Vasc Surg Venous Lymphat Disord* 2016;4:206–14.
- [18] Izumi M, Ikeuchi M, Aso K, et al. Less deep vein thrombosis due to transcutaneous fibular nerve stimulation in total knee arthroplasty: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2015;23:3317–23.
- [19] Breen PP, Galvin O, Quondamatteo F, et al. Comparison of single- and two-channel neuromuscular electrical stimulation sites for enhancing venous return. *IEEE Trans Neural Syst Rehabil Eng* 2012;20:389–94.
- [20] Gobbo M, Maffioletti NA, Orizio C, et al. Muscle motor point identification is essential for optimizing neuromuscular electrical stimulation use. *J NeuroEngineering Rehabil* 2014;11:17.
- [21] Broderick BJ, Breathnach O, Condon F, et al. Haemodynamic performance of neuromuscular electrical stimulation (NMES) during recovery from total hip arthroplasty. *J Orthop Surg* 2013;8:3.
- [22] Broderick BJ, O'Brian DE, Breen PP, et al. A pilot evaluation of a neuromuscular electrical stimulation (NMES) based methodology for the prevention of venous stasis during bed rest. *Med Eng Phys* 2010;32:349–55.
- [23] Jawad H, Bain DS, Dawson H, et al. The effectiveness of a novel neuromuscular electrostimulation method versus intermittent pneumatic compression in enhancing lower limb blood flow. *J Vasc Surg Venous Lymphat Disord* 2014;2:160–5.
- [24] Kuhn A, Keller T, Lawrence M, et al. The influence of electrode size on selectivity and comfort in transcutaneous electrical stimulation of the forearm. *IEEE Trans Neural Syst Rehabil Eng Publ IEEE Eng Med Biol Soc* 2010;18:255–62.
- [25] Van den Bergh FRA, Vanhoenacker FM, De Smet E, et al. Peroneal nerve: Normal anatomy and pathologic findings on routine MRI of the knee. *Insights Imaging* 2013;4:287–99.
- [26] Uhl J-F, Gillot C. Anatomy of the veno-muscular pumps of the lower limb. *Phlebology* 2014;30:180–93.
- [27] Miller BF, Gruben KG, Morgan BJ. Circulatory responses to voluntary and electrically induced muscle contractions in humans. *Phys Ther* 2000;80:53–60.
- [28] Griffin M, Nicolaidis AN, Bond D, et al. The efficacy of a new stimulation technology to increase venous flow and prevent venous stasis. *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg* 2010;40:766–71.
- [29] Yang S, Gong X, Wei S, et al. A hemodynamic study of the effect of neuromuscular electrical stimulation on enhancing popliteal venous flow. *J Shanghai Jiaotong Univ Sci* 2014;19:706–11.
- [30] Lee W, Seo JH, Kim HB, et al. Investigation of blood flow during intermittent pneumatic compression and proposal of a new compression protocol. *Clin Appl Thromb Hemost* 2018;24:338–47.
- [31] Bajd F, Vidmar J, Fabjan A, et al. Impact of altered venous hemodynamic conditions on the formation of platelet layers in thromboemboli. *Thromb Res* 2012;129:158–63.