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Interferential electrical stimulation improves peripheral vasodilatation in healthy individuals

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ABSTRACT | **Background:** Interferential electrical stimulation (IES), which may be linked to greater penetration of deep tissue, may restore blood flow by sympathetic nervous modulation; however, studies have found no association between the frequency and duration of the application and blood flow. We hypothesized that 30 min of IES applied to the ganglion stellate region might improve blood flow redistribution. **Objectives:** The purpose of this study was to determine the effect of IES on metaboreflex activation in healthy individuals. **Method:** Interferential electrical stimulation or a placebo stimulus (same protocol without electrical output) was applied to the stellate ganglion region in eleven healthy subjects (age 25±1.3 years) prior to exercise. Mean blood pressure (MBP), heart rate (HR), calf blood flow (CBF) and calf vascular resistance (CVR) were measured throughout exercise protocols (submaximal static handgrip exercise) and with recovery periods with or without postexercise circulatory occlusion (PECO+ and PECO -, respectively). Muscle metaboreflex control of calf vascular resistance was estimated by subtracting the area under the curve when circulation was occluded from the area under the curve from the AUC without circulatory occlusion. **Results:** At peak exercise, increases in mean blood pressure were attenuated by IES ($p<0.05$), and the effect persisted under both the PECO+ and PECO- treatments. IES promoted higher CBF and lower CVR during exercise and recovery. Likewise, IES induced a reduction in the estimated muscle metaboreflex control (placebo, 21±5 units *vs.* IES, 6±3, $p<0.01$). **Conclusion:** Acute application of IES prior to exercise attenuates the increase in blood pressure and vasoconstriction during exercise and metaboreflex activation in healthy subjects.

Keywords: neuromodulation; blood flow control; physical therapy; rehabilitation.
Clinical Trial Registration Number: NCT 01450371.

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Introduction

The study of electrical current stimulation has been subdivided into analgesic and non-analgesic effects. Most studies have evaluated its effect on conditions such as low back pain, refractory angina and post-operative pain[1-5]. Compared to other methods of transcutaneous electrical nerve stimulation (TENS, a low frequency current), *interferential electrical stimulation* (IES, a middle frequency current) may present some advantages over TENS, such as a higher maximum total current and better penetration into deep tissues[6] through kilohertz-carrier-frequency pulsed or sinusoidal currents to overcome the impedance of the skin. Because these currents are not uncomfortable for subjects, two currents can be delivered out of phase; these currents interfere with each other within tissues where the currents cross[7]. The resultant amplitude-modulated interference wave can be achieved by rhythmically increasing and decreasing amplitude, a technique called *amplitude modulation frequency* (AMF). It is necessary to avoid motor end inhibition (Wedensky inhibition)[8] with beat frequencies ranging from 1 to 250 Hz, which have been reported to induce analgesia in humans[9].

Interestingly, the application of TENS and IES has recently been studied with special focus on non-analgesic effects that might be related to effects on blood flow and vasodilatory mechanisms[10-13]. In this regard, it has been suggested that the application of low- and middle-frequency current to the stellate ganglions may induce local vasodilation[10,13,14]. Recently, we have shown that TENS applied 30 minutes prior to exercise to the stellate ganglion region (cervical region between C7-T4) attenuated blood-flow redistribution to the upper limbs. This

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phenomenon is known as the muscle metaboreflex and results in increased peripheral vasodilatory capacity and reduced blood pressure at the end of exercise in both young and older healthy subjects[13].

In contrast, two studies failed to observe these effects[10]; however, Olson et al.[15] reported a significant increase in blood flow with IES but found no differences in effect between placebo and TENS. Although another study found increased arterial blood flow and skin perfusion during and after IES[14] the underlying mechanisms are still unclear. A study evaluating the influence of a range of IES settings (10-20 Hz, 10-100 Hz, 80-100 Hz, placebo and control) on cutaneous blood flow (local effect)[11] found no evidence of increased blood flow, although there was a short-lived increase in the 10-20 Hz group after 12 minutes.

These currents could have a favorable impact on the sympathetic nervous system by mitigating the effects on the pressor reflex[16]. Neuromodulation may vary depending on the duration, intensity, and area of application[16]. Previous studies have demonstrated that time of electrical stimulation seem to promote different responses, changes in local circulation[10,17-19], increase in myocardial oxygen, and reduction in oxygen demand[20]; however, it is still unclear whether interferential current stimulation can improve blood flow during muscle metaboreflex induction. Indergand and Morgan[10] applied IES for only 10 min[10], but in our study, the opposite results were obtained when IES was applied for 30 min, suggesting that improvement of blood-flow control might be time-dependent. Finally, a recent study of TENS found a blunted muscle metaboreflex accompanied by low-frequency component reduction, indicating that low-frequency current favorably influences the sympathetic nervous system[13].

Therefore, the aim of this study was to analyze the effects of IES applied to the ganglion region on the attenuation of the reflex response of the autonomic nervous system (ANS) to the triggering of the muscle metaboreflex in healthy individuals. Based on the principle of activation with an interferential current, which does not allow for an accommodation of fibers, we hypothesized that static exercise with metaboreflex activation would be more effective than TENS.

Method

Subjects

The study sample consisted of 11 healthy young individuals (5 women and 6 men). All subjects were non-smokers, non-obese and free of any signs or symptoms of disease, as assessed by medical history, physical examination and electrocardiogram at rest and during exercise. The exclusion criteria were pregnancy, breastfeeding, alcohol or drug abuse and use of any medication with potential effects on the circulation. The subjects were instructed not to consume foods or beverages containing caffeine and not to exercise 48 hours before the protocol. All procedures were approved by the Institutional Review Board of the Hospital de Clinicas de Porto Alegre (HCPA), RS, Brazil. Subjects were informed about the study protocol and gave their informed written consent before participation (CEP-HCPA 110374).

Experimental protocol

The study was a randomized crossover investigation that involved three visits to the laboratory. During the first visit, subjects completed a health questionnaire and performed a maximal cardiopulmonary exercise test, as previously described[21]. At least 72 hours after the initial assessment, subjects came to our laboratory on two different days, and muscle metaboreflex activity was measured with and without the previous use of IES (Figure 1 – Flow diagram of study).

Interferential electrical stimulation

Interferential electrical stimulation or placebo intervention was randomized and acutely applied before the muscle metaboreflex protocol. The individuals were treated acutely with IES using the Endophasys nms.0501® (KLD Biosistemas, Amparo, SP, Brazil) for 30 min, providing a continuous flow of symmetrical rectangular interferential current biphasic pulses using bipolar electrodes with two channels and a slope of 1/5/1. The fixed current was adjusted to 4000 Hz, with the current AMF at 100 Hz and an AMF variation of 25 Hz (25% of AMF). The sensory level was intended to elicit strong sensations of paresthesia that at the same time were not painful or unpleasant, with no contractions of the shoulder or other muscles. The intensity was increased from zero until the perceived sensation reached the maximal sensory threshold without pain, discomfort or involuntary contraction. Adhesive electrodes (MultiStick®, Axelgaard Manufacturing CO, Ltd, Fallbrook, CA, USA) were placed on each side, approximately 3 cm to the right and left of midline vertebral process, at C7 (Channel 1) and T4 (Channel 2; Figure 2). The same instructions and electrode positions were provided to the placebo, although the equipment did not provide any stimulating current[22].

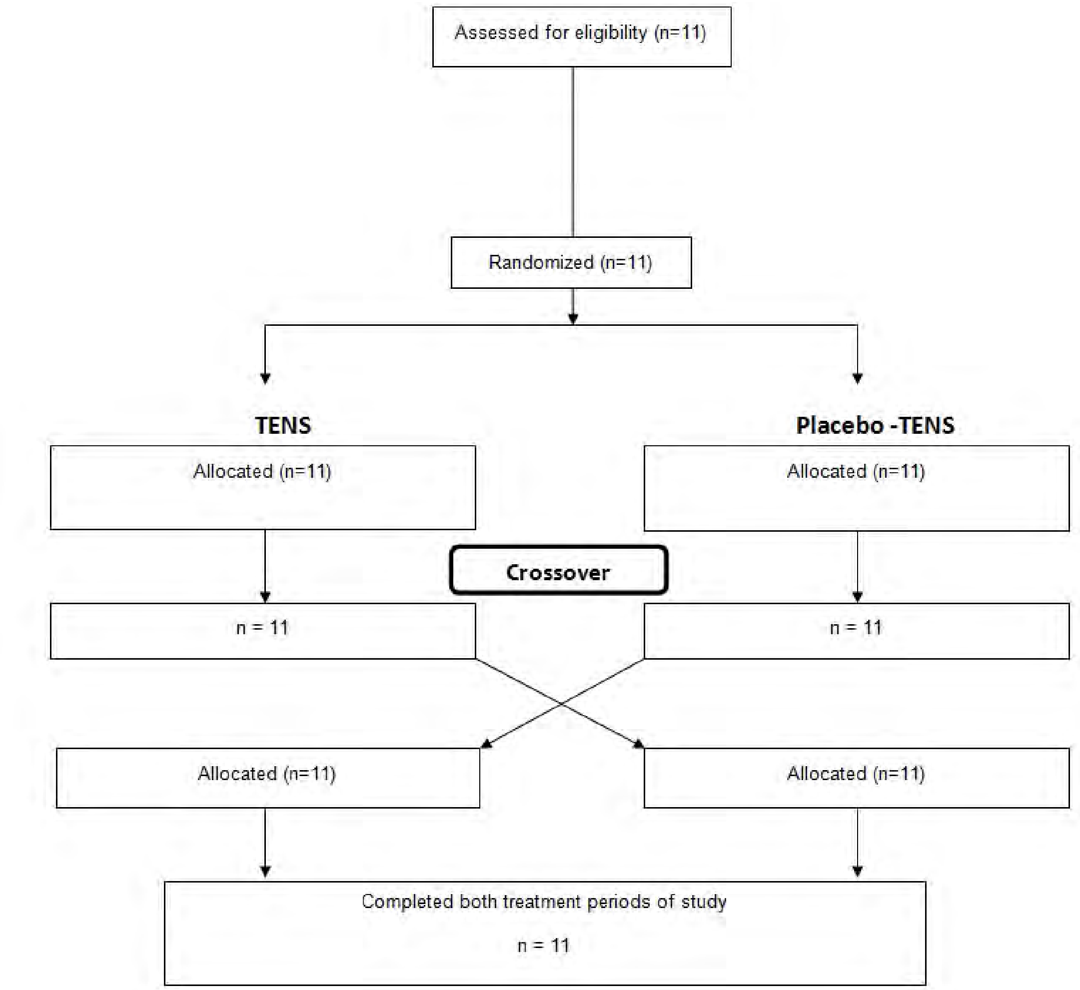

Figure 1. CONSORT flow diagram of study.

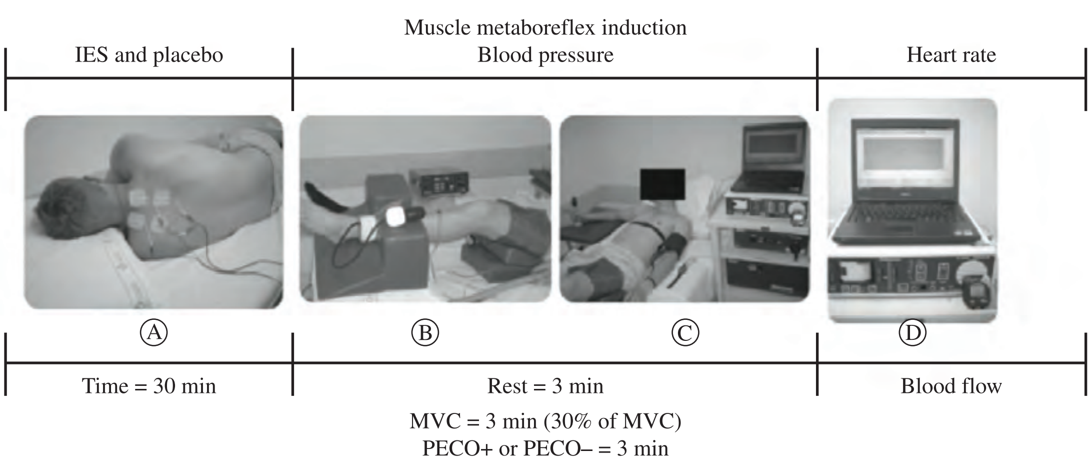

Figure 2. Study protocol. A) electrode placement for interferential electrical stimulation (IES); B) blood pressure-occluding cuff was positioned on the exercising arm; C) handgrip exercise on the dominant forearm and systemic blood pressure (BP) on the non-exercised (non-dominant) arm were recorded continuously; D) heart rate was calculated from monitored R-R interval of the electrocardiogram, and calf vascular resistance was measured by venous occlusion strain gauge plethysmography. MVC = maximal voluntary contraction; PECO+ = post-exercise circulatory occlusion; PECO- = post-exercise without circulatory occlusion.

Muscle metaboreflex activity

The muscle metaboreflex was evaluated as described elsewhere[23]. As shown in Figure 2, baseline blood pressure was recorded for 3 minutes (resting baseline). Briefly, maximal voluntary contraction (MVC) of the dominant arm was initially determined with a handgrip dynamometer (Jamar® Hydraulic Hand Dynamometer, Sammons Preston CO, Bolingbrook, Illinois, USA). A static handgrip exercise was performed at 30% of MVC for 3 min and immediately followed by vascular occlusion (PECO+) or non-occlusion (PECO-) of the exercising arm to promote selective induction of the metaboreflex. During the last 15 s of exercise, a pneumatic cuff on the upper arm was inflated to suprasystolic pressure for 3 min (PECO+). Heart rate (HR) was measured by a heart rate monitor (POLAR model RS800, Kempele, Finland), and mean blood pressure (MBP) was measured in the non-dominant arm using a calibrated oscillometric automatic device (Dinamap 1846SX/P, Critikon, Tampa, Florida, USA). Calf blood flow (CBF) was measured by venous occlusion plethysmography (Hokanson, TL-400, Bellevue, USA). Calf vascular resistance (CVR) was calculated as MBP/CBF[21]. Determination of muscle metaboreflex was performed by changes in mean blood pressure and plotted against protocol time for both PECO+ and PECO- treatments. The area under each curve was estimated, and the calculated difference in the area between PECO+ and PECO- was regarded as MM. The changes in calf vascular resistance were measured continuously by plethysmography during the handgrip test, and differences in the area under the curve between the PECO+ and PECO- treatments were used to represent muscle metaboreflex activity-induced changes in vascular resistance in the non-exercised limb. All flow recordings were manually traced by an operator who was blinded to the intervention and time. Reproducibility of CBF measurements in our laboratory has been observed to be good, with coefficients of variation of 5.7% and 5.9% for intra- and inter-day measurements, respectively[23].

Data analysis

Values are shown as the means ± SE. Hemodynamic responses to exercise and to PECO+/PECO- treatments were compared by two-way ANOVA for repeated measures and Tukey–Kramer's for post hoc comparisons. P-values <0.05 were considered significant. Data were analyzed using SigmaPlot® version 11 software (Systat Software, Inc., San Jose, CA, USA).

Results

Table 1 shows the characteristics of the participants. No adverse events occurred during the protocols. Figure 3 shows the responses of MBP, HR (left panels) and CBF, CVR (right panels) at baseline, during the handgrip exercise, and during recovery with the PECO+ or PECO- treatments, with and without previous application of IES. MBP was significantly reduced during baseline, at peak exercise and during recovery with the previous use of IES in comparison to the control. The HR response at peak exercise was greater in the control / PECO- treatment, with no difference observed during recovery. The HR response at peak exercise was increased in the control protocol (PECO-), indicating that IES attenuated the chronotropic response in the PECO- exercise protocol. Previous application of IES also resulted in increased CBF and decreased CVR, with IES throughout the PECO+protocols. During the PECO+ protocol, subjects experienced smaller increases in MBP both with and without occlusion after application of IES. Compared to the control group, the use of IES lowered MBP values in both PECO+ and PECO- protocols at baseline, exercise and recovery. Additionally, CBF was increased after IES, with the CVR response reduced in comparison to the control (Figure 3).

Table 1. Subject characteristics and resting hemodynamics.

	Individuals (n=11)
Age, yr	23±1
Height, cm	172±2
Weight, kg	65±3
BMI, kg/m^2	23±1
CPET	
VO_2 peak, mL.min^{-1}	3678±550
Hemodynamics	
SBP, mmHg	125±8
DBP, mmHg	91±7
MBP, mmHg	86±8
CBF, ml.min^{-1}.100 g^{-1}	2.5±0.5
CVR, units	40±10
Handgrip Force, N	44±6

Data expressed in mean±SE. BMI = body mass index; CPET = Cardiopulmonary Exercise Test; VO_2 peak = Oxygen Uptake; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MBP = Mean Blood Pressure; CBF = Calf Blood Flow; CVR = Calf Vascular Resistance.

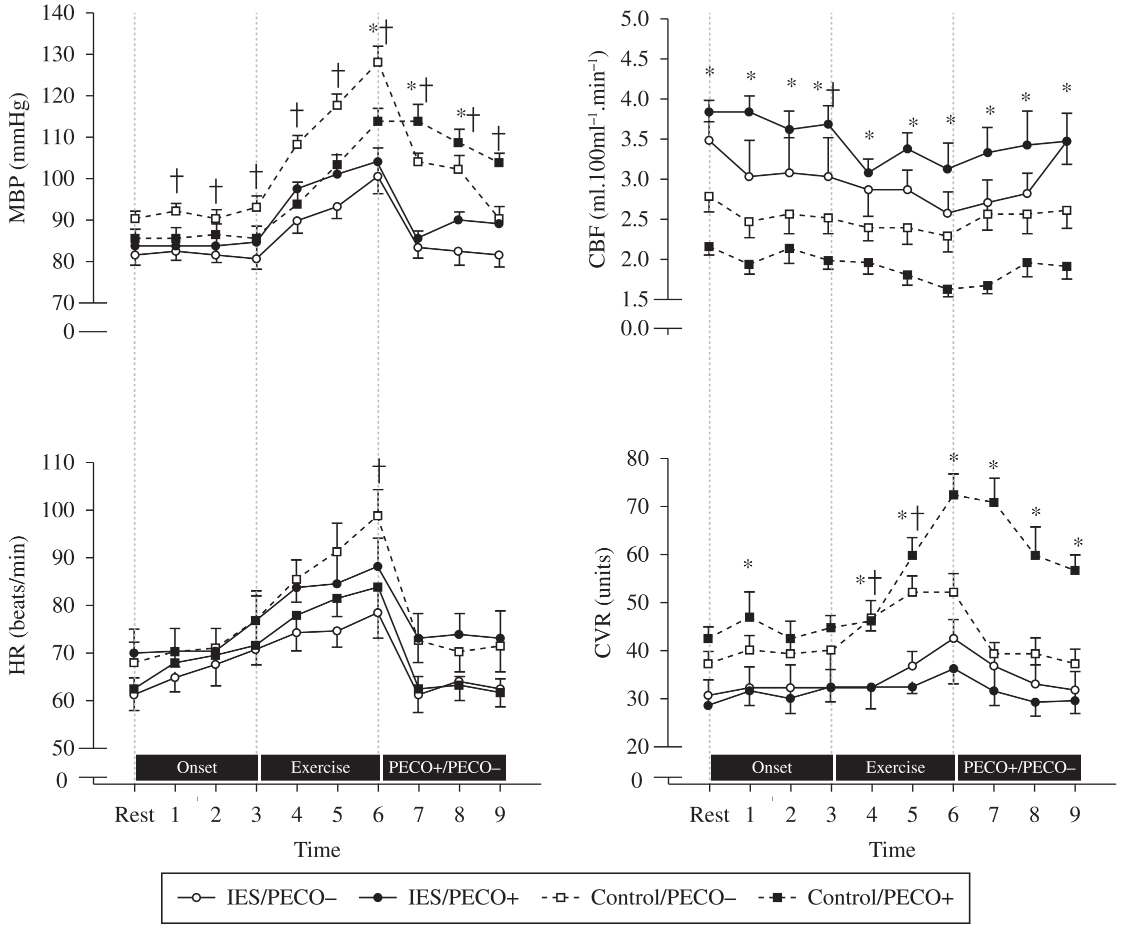

Figure 3. Mean blood pressure (MBP), heart rate (HR), calf blood flow (CBF), and calf vascular resistance (CVR) in absolute values during the static handgrip exercise, post-exercise circulatory occlusion (PECO+) or placebo (PECO-) periods in healthy young (left panels) and older (right panels) subjects. *Two-way repeated-measures ANOVA (P<0.05): IES *vs.* Placebo: PECO+ (IES) *vs.* PECO+ (placebo); † two-way repeated-measures ANOVA (P<0.05): IES *vs.* Placebo: PECO- (IES) *vs.* PECO- (placebo).

As shown in Figure 4, the difference in the areas under the CVR curve during the occlusion protocol (PECO+/PECO-), which estimates metaboreflex activity, was reduced with the prior use of IES, indicating that application of IES reduced metaboreflex activity in healthy subjects.

Discussion

The main findings of this study are that the application of IES to the stellate ganglion region **1)** significantly lowers MBP (vasoconstrictor tone), as was observed even during blood pressure increases during the handgrip exercise, and **2)** significantly reduces muscle metaboreflex activity, suggesting that IES may attenuate sympathetic nervous system activity. In agreement with our hypotheses, transcutaneous electrical stimulation

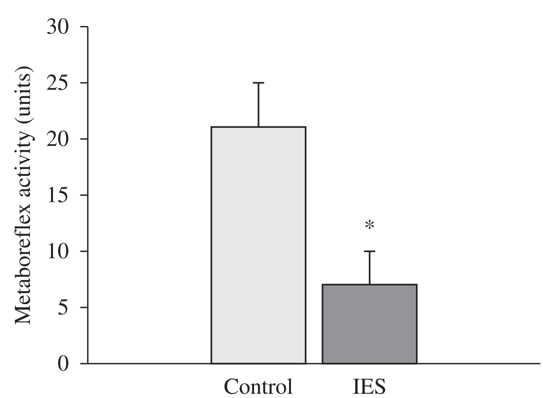

Figure 4. Estimated muscle metaboreflex control of calf vascular resistance (obtained by subtracting the area under the curve during circulatory occlusion from the area under the curve from the control period) in young and older individuals during interferential electrical stimulation (IES) or under placebo treatment (PLA). *significantly (P<0.01) different from placebo.

with IES improved peripheral muscle blood flow through attenuation of muscle metaboreflex and vasoconstrictor tone during exercise, indicating a putative vasodilatory effect induced by interferential electrical stimulation.

In this study, under control conditions, we observed a progressive increase in HR and MBP throughout the handgrip exercise. Under the PECO+ treatment, HR returned to resting values, while MBP remained high. The increase in HR after the handgrip exercise is attributed to the loss of central command and muscle mechanoreceptor input and parasympathetic reactivation following effort, with the latter overriding the sympathetic activity caused by the maintenance of muscle metaboreflex under the PECO+treatment[24]. The maintenance of high MBP levels at the end of the exercise phase and during the PECO+ treatment may be explained by an increase in CVR and baroreflex control due to an increase in sympathetic activity caused by the maintenance of the muscle metaboreflex[1,21,24-26].

Our findings demonstrated an attenuation of MBP and HR during the PECO+ treatment, resulting in lower values at the end of the exercise when IES was applied. Several studies have shown a reduction in MBP with application of a similar current (transcutaneous electrical neuromuscular stimulation of low frequency, TENS)[27,28].

Importantly, IES reduced metaboreflex activity, thereby attenuating the behavior of CBF and CVR. The effect of IES on CBF has not been fully elucidated, and previously reported results showed only the analysis of CBF with IES administered directly to the site studied[10]. The main mechanism proposed by these authors for the improvement in CBF in healthy individuals is the blocking of sympathetic arteriolar fibers, leading to an increase in peripheral circulation at the site of application due to a reduction in sympathetic tonus in the muscle layer of these vessels[10]. Some studies have employed a similar methodology to examine the role of the site place of IES application. In a thermogram-based analysis of local temperature, Nussbaum et al.[12] found no significant alteration in peripheral vasodilatation with the use of IES at the cervical sympathetic chain and dorsal-lumbar region, regardless of the application site and intensity of the current[12]. In a previous study; however, Ganne[29] demonstrated substantial vasodilatation in the upper limbs with the administration of IES to the brachial plexus region. Finally, other studies demonstrated improved blood flow with ganglionar application of IES in subjects with Raynaud's Syndrome[30] and Endarteritis Obliterans[31].

To our knowledge, this is the first study to report the effects of IES application on muscle metaboreflex, peripheral vascular responses and blood pressure. Reduced CVR was observed throughout the exercise period and under the PECO+ treatment. This result expands on the findings of Indergand and Morgan[10], who found no changes in resting vascular resistance in the forearm of healthy individuals with the administration of an interferential current to the ganglion. Therefore, this study provides novel findings regarding the positive effects of IES on responses during exercise and metaboreflex stimulation.

Limitations

In this small study, we showed that 30 min of IES applied to the stellate ganglion has a consistent effect on muscle metaboreflex; however, this study was designed to evaluate only the efficacy of IES on blood flow redistribution to the upper limbs. Our findings are limited to healthy subjects, but other study evaluated blood flow responses during 10 min of IES in healthy subjects[10]. Studies testing different levels of frequency and application times have found no differences in the results[12,14]. Our study used a 30-minute application time and 100 Hz AMF frequency. As the metaboreflex is mediated by the sympathetic nervous system[1,32], part of the beneficial effects of transcutaneous electrical stimulation could be mediated by a reduction in sympathetic vasoconstrictor activity to peripheral muscle; however, sympathetic nerve activity were not directly assessed in this study. Mechanistic studies should be conducted to test whether sympathetic nervous system activity would be related to IES effects on the vasculature. Additionally, our control intervention consisted of using IES turned off, as described elsewhere[13]. Thus, no stimulation and no neuromodulation was provided.

Clinical implications

Further studies are needed to assess the effects of this current on the variables analyzed in the present study, testing other levels of intensity and application times. Therefore, our results cannot be directly generalized to other populations (e.g., older subjects, heart patients), although no effect of middle-frequency transcutaneous electrical stimulation to the ganglion during acute exercise has been demonstrated. These findings suggest that IES can influence the autonomic activity in a manner similar to TENS[13], which may help to explain the improvement in vasodilatory capacity. Future investigations of both acute and chronic applications of IES in patient populations with increased neurohumoral activity are necessary. Moreover, our findings suggest that IES is a feasible tool to improve peripheral blood flow and reduce vasoconstrictor tone, especially under conditions of increased pressoric responses.

Conclusion

The results of the present study demonstrate that ganglion mid-frequency neuromuscular electrical stimulation with an interferential current attenuates the peripheral responses caused by muscle metaboreflex activity, maintaining peripheral blood flow and peripheral vascular resistance within the normal range. These findings contribute to a better understanding of this therapy.

Acknowledgments

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