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RESEARCH ARTICLE

Effects of Transcutaneous Electrical Nerve Stimulation in Autonomic Nervous System of Hypertensive Patients: A Randomized Controlled Trial

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Abstract: ***Background*:** Patients with hypertension have altered autonomic nervous system function, which are increased sympathetic activity. Transcutaneous Electrical Nerve Stimulation (TENS) is a useful modality for pain control and has also been shown to be effective in the reduction of sympathetic activity in healthy subjects and individuals with cardiovascular diseases.

***Objective*:** The aim of this study was to verify the effects of transcutaneous electrical nerve stimulation by the evaluation of heart rate variability (HRV) in patients with essential hypertension.

***Method*:** Twenty-eight patients received an application of low-frequency TENS(4 Hz) n=8, high-frequency TENS (100 Hz) n=10 or placebo TENS n=10 in paravertebral ganglionar region during thirty minutes.

***Results*:** After 4 Hz TENS, there was a decrease in the low-frequency (LFn.u.) component (57.71±9.46 vs 45.58±13.51, p<0.026) and an increase in the high-frequency (HFn.u.) component (33.03±13.83 vs 45.83±20.19, p <0.05) of HRV. After 100 Hz TENS and placebo, there were no changes in the LF and HF components. No significant differences were found in systolic blood pressure with low-frequency TENS (129.37± 15.48 vs 126.69 ± 15.21, p<0.490). There was an increase, although not significant, with high-frequency TENS (131.00 ± 15.97 vs 138.75 ± 25.79, p<0.121) and placebo (133.80 ± 29.85 vs 134.80 ± 29.72, p< 0.800). No differences were found in the diastolic blood pressure with low-frequency TENS and placebo, but there was a significant increase in high-frequency TENS (81.00 ± 11.78 vs 85.65 ± 13.68, p< 0.018).

***Conclusion*:** Low-frequency TENS decreases sympathetic nervous system activity and increases parasympathetic nervous system activity and high-frequency TENS increases diastolic blood pressure, when applied on the paravertebral ganglionar region in the hypertensive patients.

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1. INTRODUCTION

The autonomic nervous system performs an important role in blood pressure regulation and Heart Rate Variability (HRV). Patients with hypertension have altered autonomic nervous system function, such as increased sympathetic activity and decreased parasympathetic tone [1]. Arterial hypertension seems to be characterized by altered autonomic regulation, as indicated by reduced heart rate variability, sympathetic hyperactivity and blunted Baroreflex Sensitivity (BRS) [2].

Transcutaneous Electrical Nerve Stimulation (TENS) has been a useful modality for pain control [3] since the gate control theory was introduced by Melzack & Wall [4]. TENS has also shown to be effective in the reduction of sympathetic activity in healthy subjects and individuals with cardiovascular diseases. In healthy subjects, sympathetic activity decreases [5] after low-frequency TENS. In addition, patients with hypertension show a reduction of Blood Pressure (BP) through blood pressure measurement after low-frequency TENS [6, 7] and, in heart failure patients, TENS decreases sympathetic activity [8]. However, the positive effects of TENS have not been uniformly reported: some researchers found that TENS was not effective to lower arterial pressure in patients with hypertension [9].

The results of these studies differ with the application site of stimulation, which may be involved in the effectiveness of

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the sympathetic system stimulation. There is no consensus in the literature in which parameters can contribute to reduce the sympathetic nervous system activity. Therefore, the aim of this study is to assess the acute effects of the application of TENS at high, low frequencies and placebo to cardiovascular sympathetic and parasympathetic nervous system modulation in patients with hypertension.

2. METHODS

2.1. Study Design/Selection Criteria

A prospective, randomized, controlled and double-blinded trial was conducted in patients with a diagnosis of essential hypertension, recruited from the Hypertension Clinic of Instituto de Cardiologia do Rio Grande do Sul. Data collection was performed at the Laboratório de Investigação Clínica, Serviço de Medicina Experimental, Instituto de Cardiologia/Fundação Universitária de Cardiologia, Porto Alegre, RS, Brazil.

Inclusion criteria for the study were: previous hypertension diagnosis, *i.e*. systolic blood pressure (SBP) > 140 mm Hg and/or Diastolic Blood Pressure (DBP) > 90 mm Hg, patients of both sexes, aged between eighteen and eighty years old, and clinical stability. Patients that presented any comorbidity such as diabetes, congestive heart failure, myocardial infarction, cardiac pacemaker, obesity, changes in the electrocardiogram, smoking, treatment with beta blockers, or change in drug therapy for at least 2 months preceding the study were excluded.

Eligible subjects were randomly assigned in blocks, by electronic randomization (www.randomization.com), to the group of low frequency (4 Hz / 200μs), high frequency (100 Hz / 200μs) or placebo. Subjects and main investigators were unaware of any subject's group allocation. Investigators were informed of group allocation by telephone or e-mail.

The protocol was approved by the Ethics Committee of Federal University of Health Sciences of Porto Alegre, according to the ethical guidelines of the 1975 Declaration of Helsinki. All subjects signed an informed consent form. The methodological design was based on the determinations of the CONSORT Statement, 2010 [10]. The identification of this study on the ClinicalTrials.gov website is NCT02292199.

2.2. Intervention

Initially, patients rested for 30 minutes and, during this period, filled out the evaluation form, which contained identification data and questions about the patient's clinical status, such as weight and height. Before and after the intervention, an Electrocardiogram (ECG) was taken and blood pressure was measured.

Adhesive electrodes measuring 9x5 cm were used, being placed on the bilateral paravertebral region in the paravertebral ganglionar region (from T1 to L2). Before the application of TENS (IBRAMED®), the skin site for the current application was cleaned with alcohol to avoid any barrier conduction of the electrical current. *TENS* was applied for thirty minutes, being the frequency defined according to randomization. The current was delivered at sensory-level intensity, adjusted every 5 minutes by the sensory threshold as tolerated by each subject, but with no motor contraction or pain reported.

The sessions took place at the same time of the day throughout the protocol. The participants were comfortably accommodated in an acclimatized room (23ºC) in supine position, with head elevation of 30º and knees resting on a wedge. All participants were forbidden to perform exhaustive exercises and ingest caffeine at least twelve hours before the intervention, and they were instructed to have a meal before the assessment.

2.3. Outcomes

2.3.1. Heart Rate Variability

The analysis of autonomic control was performed by means of a sensor placed on the patient's middle finger and connected to a *Finapres* device (Ohmeda 2300, Colorado, USA), which recorded blood pressure beat to beat. Then, the signal conversion was performed using PowerLab (LabChart). The analysis was carried out using the Kubios 2.0 software (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland).

For the analysis of heart rate variability (HRV), RR intervals were obtained from the continuous ECG signal recorded by the *Finapres* device. The time series of RR intervals were analyzed in time and frequency, and variability parameters and autonomic balance were obtained. In the time domain, we calculated the mean values of RR intervals, standard deviation, and the square root of the sum of the square of successive differences (rMSSD). The signal was acquired immediately before and after the interventions, for a 10-minute period. The outcome variable consisted of the analysis of the HRV performed by an individual blinded to the subject's group assignment. The time series obtained from the tachogram, related to each selected segment, were quantitatively evaluated considering heart rate (HR) values, total and normalized powers (n.u) of low-frequency (LF – 0.04 to 0.15 Hz) and high-frequency (HF – 0.15 to 0.40 Hz) components of HRV, and the sympatho-vagal index (LF/HF). Normalized units (n.u.) were obtained by dividing the power of a given component by the total power (from which VLF has been subtracted), and multiplying it by 100 [11].

2.3.2. Arterial Blood Pressure

Blood Pressure (BP) was measured as proposed by the VI Brazilian Guidelines on Hypertension [12], with an automatic calibrated device, model HEM-705CP (Omron Healthcare Inc., Illinois, USA), and the cuff adjusted for arm circumference. The subject was seated and three measurements were obtained. Then the respective mean value was calculated, which was used in the data analysis.

2.3.3. Sample

The sample size was calculated based on the study by Ferreira [13], which showed that a variation of 21.9% LF variable nu and with a power of 90% and 5% error in the calculated value was 60 patients. In this study, we present preliminary data that was determined based on the following

Table 1. Baseline characteristics of patients.

-	Placebo (n=10)	TENS Low Frequency (n=8)	TENS High Frequency (n=10)
Gender (M/F)	1/9	5/3	3/7
Age (years)	59.8 ±10.7	58.1 ±8.4	59.4 ±10.0
Body mass index (kg/m2)	27 ±4.4	27.7 ±4.2	26.8 ±4.9
Cholesterol (mg/dL)	220.2 ±23.3	195.5 ±27.0	200.6 ±54.1
Triglycerides (mg/dL)	119.1 ±52.9	154.3 ±61.8	151.5 ±98.7
Glucose (mg/dL)	96.9 ±8.2	103.8 ±11.9	97.6 ±9.4
HDL (mg/dL)	65.3 ±21.1	47.9 ±9.0	53.7 ±15.4
LDL (mg/dL)	129.4 ±18.0	116.6 ±24.4	116.5 ±40.1
Creatinine (mg/dL)	0.8 ±0.2	0.9 ±0.2	0.9 ±0.2
Potassium (mEq/L)	4.3 ±0.4	4.5 ±0.5	4.4 ±0.8
Drugs (%)			
Diuretics	60 %	75%	50 %
ACE inhibitors	60%	12.5%	40%
Calcium channel blockers	10%	25%	20%
Angiotensin II receptor blocker	40%	25%	50%

Values reported as meanSD e per cent (%). HDL: *high density lipoprotein*; LDL: *low density lipoprotein*; ACE inhibitors: Angiotensin-converting enzyme (ACE) inhibitors.

aspects: similar size to the one used in studies with heart rate variability analysis [5, 13], and that most experiments conducted with humans involving TENS and heart rate variability have used samples with 18 to 22 participants [14, 15]. Therefore, a total of 28 subjects were initially determined.

2.3.4. Statistical Analyses

The normality of the variables was verified by the Shapiro-Wilk test. Changes were made to variables that did not meet this assumption, such as natural logarithm, square root and reverse. For normally distributed variables, analyses of variance (ANOVA) were performed at baseline and post intervention, and Kruskal-Wallis tests were used for variables that did not meet the assumption. The comparison between moments was carried out using Student's *t* test or Wilcoxon as the distribution of variables. A *P*- value of <0.05 was considered statistically significant for all tests. All analyses were performed with the SPSS 22.0 software (SPSS, Chicago, IL, USA).

3. RESULTS

3.1. Baseline Characteristics

From July 2013 to October 2014, 168 patients with essential hypertension were screened for the study. Out of those, 140 patients did not meet the inclusion criteria or met one or more of the exclusion criteria; therefore, 28 patients were randomized. No significant difference was found in the baseline values. Clinical characteristics of subjects were comparable among the three groups (Table **1**).

3.2. Heart Rate Variability

There was a decrease in LF (%) after low-frequency TENS (4 Hz) (LF: 57.71±9.46 vs 45.58±13.51, p<0.026) but not after high-frequency TENS (100 Hz) (LF: 50.57±9.46 vs 49.98±13.54, p<0.887) or placebo (LF: 45.22±10.82 vs 42.10±14.52, p<0.485). In addition, there was an increase in HF n.u. in the low-frequency TENS group (33.03±13.83 vs 45.83±20.19, p <0.05) but not in the high-frequency TENS (39.60±13.30 vs 43.11±15.88, p<0.556) or the placebo group (48.18±12.15 vs 52.23±17.42, p<0.465). Moreover, sympathovagal balance, expressed by the LF/HF index, was lower after low-frequency TENS, indicating an increase in parasympathetic modulation in relation to sympathetic modulation (2.52±1.37 vs 1.76±1.65, p<0.05) while it did not change with high-frequency TENS (1.77±0.83 vs 1.79±1.61, p<0.623) or placebo (1.21±0.60 vs 1.08±0.59, p<0.391). Results of the spectral analysis are shown in Table **2**.

3.3. Arterial Blood Pressure

No significant differences were found in systolic blood pressure with low-frequency TENS (129.37± 15.48 vs 126.69 ± 15.21, p<0.490). There was an increase, although not significant, with high-frequency TENS (131.00 ± 15.97 vs 138.75 ± 25.79, p<0.121) and placebo (133.80 ± 29.85 vs 134.80 ± 29.72, p< 0.800).

No differences were found in the diastolic blood pressure with low-frequency TENS (84.69 ± 12.03 vs 84.31 ± 10.51, p<0.824) and placebo (80.35 ± 19.56 vs 81.00 ± 17.07, p< 0.715), but there was a significant increase in high-frequency

Table 2. Results of spectral analysis and arterial blood pressure.

-	-	TENS Low frequency (n=8)	TENS High frequency (n=10)	Placebo (n=10)	*P*
HR(bpm)	BEFORE	63.96 ±8.80	63.41± 9.94	66.15± 11.18	*0.818*[a]
	AFTER	61.59± 8.43	61.33± 8.43	63.77± 10.50	*0.815*[a]
	P	*0.045*[b]	*0.044*[b]	*0.020*[b]	
LF (%)	BEFORE	57.71± 9.46	50.57± 9.46	45.22± 10.82	*0.046*[a]
	AFTER	45.58± 13.51	49.98± 13.54	51.66± 12.21	*0.457*[a]
	P	*0.026*[b]	*0.887*[b]	*0.485*[b]	
LF (n.u.)	BEFORE	66.89± 3.78	60.25± 13.30	51.66± 12.21	*0.063*[a]
	AFTER	54.05± 20.27	56.75± 15.99	47.64± 17.50	*0.513*[a]
	P	*0.052*[b]	*0.557*[b]	*0.469*[b]	
HF (%)	BEFORE	29.30± 13.80	34.07± 13.33	42.18± 10.79	*0.108*[a]
	AFTER	41.13± 20.58	38.35± 14.95	47.27± 17.72	*0.524*[a]
	P	*0.064*[b]	*0.486*[b]	*0.353*[b]	
HF (n.u)	BEFORE	33.03± 13.83	39.60± 13.30	48.18± 12.15	*0.065*[a]
	AFTER	45.83± 20.19	43.11± 15.88	52.23± 17.42	*0.509*[a]
	P	*0.051*[b]	*0.556*[b]	*0.465*[b]	
LF/HF	BEFORE	2.52± 1.37	1.77 ± 0.83	1.2± 0.60	*0.050*[a]
	AFTER	1.76± 1.65	1.79± 1.61	1.08± 0.59	*0.437*[a]
	P	*0.052*[b]	*0.623*[b]	*0.391*[b]	
SBP(mmHg)	BEFORE	129.37 ± 15.48	131.00 ± 15.97	133.80± 29.85	*0.909*[a]
	AFTER	126.69 ± 15.21	138.75± 25.79	134.80 ± 29.72	*0.595*[a]
	P	*0.490*[b]	*0.121*[b]	*0.800*[b]	
DBP(mmHg)	BEFORE	84.69± 12.03	81.00± 11.78	80.35± 19.56	*0.815*[a]
	AFTER	84.3± 10.51	85.65± 13.68	81.00± 17.07	*0.758*[a]
	P	*0.824*[b]	*0.018*[b]	*0.715*[b]	

Values reported as mean SD. Heart Rate=HR; LF=Low Frequency component; HF=High Frequency component; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; statistical difference ($p<0.05$) related to before condition. [a]= ANOVA; [b]= Student's *t* test.

TENS (81.00 ± 11.78 vs 85.65 ± 13.68, $p< 0.018$). Arterial blood pressure results are shown in Table **2**.

4. DISCUSSION

This is the first study to investigate the acute effects of the application of different frequencies of TENS on the paravertebral ganglionar region on the cardiac sympathetic and parasympathetic nervous system in hypertensive patients. In this study, we demonstrated that low-frequency TENS improved the cardiovascular autonomic control, which is related to cardiovascular risk factors, by reducing sympathetic modulation (LF component) and increasing parasympathetic modulation (HF component) in patients with essential hypertension.

This study's TENS stimulation site is different from other studies that have shown the effect of TENS on the autonomic nervous system. Another study of our group indicated that low-frequency TENS applied to the paravertebral ganglionar region decreases the sympathetic nervous system activity, and that high-frequency TENS increases the sympathetic and decreases the parasympathetic modulation in healthy subjects [5]. We believed that the paravertebral ganglionar region would improve the autonomic nervous system balance by the anatomical organization of the sympathetic and parasympathetic systems.

The gate control theory of pain is used to explain the effects of high-frequency TENS, and the release of endogenous opioids is used to explain the effects of low-frequency TENS analgesia [16]. However, the release of endogenous opioids could be activated by high or low frequencies. Especially, low-frequency TENS (<10 Hz) activates μ-opioid receptors, and high-frequency TENS (>50 Hz) activates δ-

opioid receptors, respectively, in the spinal cord and rostral ventral medulla [17, 18]. Endogenous opioids mediate the relationships between blood pressure levels, risk for hypertension, and pain sensitivity [7]. In its turn, low-frequency TENS altering endogenous opioid release may have some potential influence on reducing the risk of the development of sustained high blood pressure [6].We consider that low-frequency TENS is able to modulate the autonomic nervous system by the release of endogenous opioids. Thus, the physiologic mechanisms that TENS can promote for the cardiovascular system remain to be elucidated with further studies.

Some studies have shown a reduction in blood pressure and consequently in the sympathetic nervous system activity through peripheral blood flow measurement [19, 20] or manual blood pressure measurement [6, 7]. TENS high frequency (80HZ/150 μs) reduced systolic blood pressure and central blood pressure in younger subjects after an acute application for 45 minutes on the cervical-thoracic ganglion region [21]. In our study, we believe that low-frequency TENS does not show a significant reduction in blood pressure because the sample size was determined based on the heart rate variability, which is our primary outcome.

TENS high frequency (80HZ/150 μs) has shown, through heart rate variability, that it might modulate sympatho-vagal balance when applied to the stellate ganglion during the handgrip exercise in young and older subjects. An improvement in the sympatho-vagal balance was demonstrated by a reduction in the LF/HF ratio. Moreover, the increase of local blood flow attenuates metaboreflex activation, reducing blood pressure and vasoconstrictor responses during exercise [15]. These results are compatible with the findings of another previous study [22].

In addition to these findings, TENS applied to the stellate ganglion can also improve tolerance during a cardiopulmonary exercise test by the increase of blood flow in peripheral muscles, probably due to the reduction of sympathetic nervous system activity and the increase of oxygen into peripheral muscles [23]. Currently, a further study has shown that the application of low frequency TENS in the ganglion region is more effective to increase vasodilation in lower limbs when compared to the application of TENS in acupunture points or with the control group, in healthy subjects, proving the change in sympathetic activity [24]. These changes in the vascular tone caused by TENS might stem from the interaction of the endothelial cell layer and physical or chemical stimuli that share a functional antagonism with the sympathetic nervous system in maintaining blood vessel tone, by the release of substances that affect the vascular tonus [25].

The process of regulatory blood pressure depends on the interaction of several regulatory mechanisms such as the autonomic system, hormonal mechanisms, autoregulatory mechanisms and intrinsic physical regulatory mechanisms [26]. The blood pressure is a function of vascular resistance and cardiac output. Cardiac output is dependent of end-diastolic volume, myocardial contractility and heart rate, and the venous pressure is related to blood volume and venous smooth muscle tone. Changes elicited by vascular resistance fluctuations investigate the balance between central autonomic and baroreflex cardiac control [27]. Changes in blood pressure are due to the alterations in peripheral resistance and reflexive mechanical influences of cardiac and aortic walls and central autonomic commands [27, 28]. This interaction balances the response of the cardiovascular system, showing distinct responses of autonomic nervous system interactions, determined according to the methodology of the studies.

The limitation of the study is that we did not perform direct measurements of the sympathetic nervous system by muscle sympathetic nerve assessment or by plasma catecholamine evaluation, what could be used to elucidate the effects of TENS on sympathetic outflow and the limited number of subjects. This study has clinical implications on the importance to elucidate the effects of TENS in patients with sympathetic hyperactivity, especially in the rehabilitation clinic for safety and recognition of factors that may increase sympathetic activity and also in the future as possible non-pharmacological treatment.

CONCLUSION

Our preliminary results suggest that low-frequency TENS decreases sympathetic nervous system activity and increases parasympathetic nervous system activity when applied on the paravertebral ganglionar region in hypertensive patients, however, the blood pressure did not change. When high-frequency TENS is applied, there were no changes on the autonomic nervous system but there was a significant increase in the diastolic blood pressure. The results of the current study highlight the importance of continuing research in this area.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was approved by the Ethics Committee of Federal University of Health Sciences of Porto Alegre. The methodological design was based on the determinations of the CONSORT Statement, 2010. The identification of this study on the ClinicalTrials.gov website is NCT02292199.

HUMAN AND ANIMAL RIGHTS

No animal were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki <https://www.wma.net/policiespost/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

All subjects signed an informed consent form.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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