

# The Effect of Transcutaneous Electrical Nerve Stimulation in Peripheral and Central Hemodynamic Parameters on Resistant Hypertension: A Case Report

Luiz Tadeu Giollo-Junior<sup>1,2</sup>, Luciana Neves Cosenso-Martin<sup>2</sup>, Valquiria da Silva Lopes<sup>2</sup>, Manoel Paz Landim<sup>2</sup>, Leticia Aparecida Barufi Fernandes<sup>2</sup>, Kleber Aparecido de Oliveira<sup>2</sup>, Amanda Oliva Spaziani<sup>2</sup>, Aleandra Polegati Santos<sup>2</sup>, Marco Antonio Silva<sup>2</sup>, Juan Carlos Yugar-Toledo<sup>2</sup>, Jose Fernando Vilela-Martin<sup>2</sup>

<sup>1</sup>General Hospital at Brazilian Army, Curitiba, Parana, Brazil; <sup>2</sup>Hypertension Clinic - Internal Medicine Department, State Medical School in Sao Jose do Rio Preto (FAMERP), Sao Jose do Rio Preto, São Paulo, Brazil

Correspondence: Jose Fernando Vilela-Martin, Hypertension Clinic - Internal Medicine Department, State Medical School in Sao Jose do Rio Preto (FAMERP), Ave Brig. Faria Lima 5416, São Jose do Rio Preto, 15090-000, São Paulo, Brazil, Email vilelamartin@uol.com.br

**Abstract:** Resistant hypertension (RH) is characterized by being difficult to control, even with the use of various antihypertensive drugs and is associated with target organ lesions and other comorbidities. Thus, new treatment alternatives such as transcutaneous electrical nerve stimulation (TENS) can offer benefits to resistant hypertensive patients by reducing blood pressure (BP) in a non-invasive way and without the need for the association of more antihypertensive drugs. In this case, a patient with RH was submitted to three weekly applications of TENS on the stellate ganglion lasting 40 min each for 1 month. Peripheral and central hemodynamic assessments were performed by 24-h ambulatory BP monitoring (ABPM) before and after TENS applications. After completion of the TENS applications, significant reductions in office systolic (SBP) and diastolic BP (DBP) were observed. There was also a decrease in peripheral SBP and DBP in the 24-h ABPM and sleep and SBP during wakefulness. Additionally, central parameters including central SBP and pulse wave velocity presented a significant reduction in the 24-h ABPM, during the wakefulness and sleep. TENS is able to attenuate the sympathetic hyperactivity present in RH cases and decrease the peripheral and central hemodynamic parameters of a resistant hypertensive patient.

**Keywords:** resistant hypertension, blood pressure, central hemodynamic, arterial stiffness, non-pharmacological therapy

## Introduction

Resistant hypertension (RH) is characterized by an increase in blood pressure (BP) above the recommended targets, even with the use of three antihypertensive drugs of different classes, including a renin–angiotensin system blocker (angiotensin converting enzyme inhibitor or angiotensin receptor blocker), a long-acting calcium channel blocker, and a long-acting thiazide diuretic.<sup>1</sup> All of these drugs must have synergistic actions, be used in maximum recommended and tolerated doses, with proven adherence. Resistant hypertension is associated with extrinsic and intrinsic factors, such as advanced age, female gender, black race, increased salt intake, physical inactivity, obesity, left ventricular hypertrophy, diabetes mellitus, chronic nephropathy, metabolic syndrome, and autonomic changes, including sympathetic hyperactivity.<sup>1</sup> Hypertensive individuals with RH have a worse prognosis than those with controlled hypertension because they present an elevated risk of target-organ damage, cardiovascular morbidity, and mortality. The Brazilian Society of Cardiology has already published two positions on RH, approaching specific recommendations for diagnosis, evaluation, and nonpharmacological and pharmacological treatments of this clinical situation.<sup>2,3</sup>

In recent years, options for treatment of RH are being evaluated, such as carotid baroreflex stimulation and the denervation of renal sympathetic ganglia, without presenting definitive results.<sup>4,5</sup> Basically, these therapeutic methods reduce BP by inhibiting sympathetic activity. Recently, the study SPYRAL HTN-OFF MED (SPYRAL Pivotal) showed that catheter-based renal denervation was superior to a sham procedure and safe for lowering BP without use of antihypertensive medications.<sup>6</sup> Additionally, RADIANCE-HTN TRIO demonstrated that endovascular ultrasound renal denervation, compared with a sham procedure, reduced BP in individuals with RH using a standardized triple combination antihypertensive therapy.<sup>7</sup> However, these treatments are based on invasive techniques and present high financial costs.

On the other hand, transcutaneous electrical nerve stimulation (TENS) is a low-cost, noninvasive intervention that has been shown to reduce BP in experimental and human studies, including healthy and hypertensive individuals.<sup>8–12</sup> Briefly, TENS is a non-pharmacological method that modulates the nervous system activity. TENS has also been used for treating or preventing ventricular tachycardia storm, postoperative cognitive dysfunction, migraine, fibromyalgia, pain relief and control, spasticity in spinal cord injury, and even for inducing analgesia.<sup>13–18</sup> This case report describes the effects of TENS on peripheral and central hemodynamic parameters of a resistant hypertensive individual.

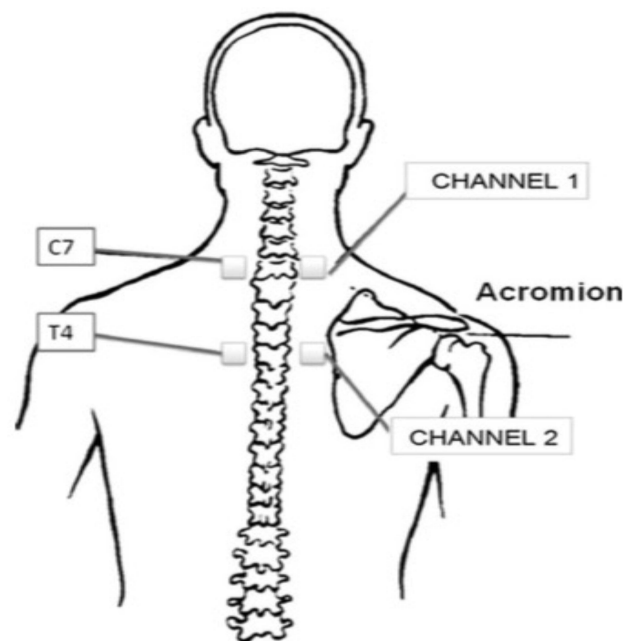
## Case Presentation

The patient was a 53-year-old white woman with a 20-year history of hypertension and diabetes mellitus, with difficult-to-control BP. She was taking valsartan (320 mg/d), amlodipine (10 mg/d), chlorthalidone (25 mg/d), and spironolactone (100 mg/d), besides metformin (2000 mg/d), gliclazide (120 mg/d), dapagliflozin (10 mg/d), and 10U NPH insulin at bedtime. However, she did not adhere to diet to control diabetes. The patient was taking all the medications correctly, according to pill counts method used for assessing lack of adherence. Her physical examination revealed BP: 152×100 mm Hg (mean of three measures), heart rate: 78 bpm, weight: 80 Kg, body mass index (BMI): 32.1 kg/m<sup>2</sup>, and waist circumference: 91 cm. She had no abnormalities of the heart, lungs, or abdomen. According to complementary exams, the patient had unsatisfactory diabetes control with fasting glycemia of 308 mg/dL and glycosylated hemoglobin (HbA1c) of 9.8%; her creatinine level was 1.2 mg/dL with an estimated glomerular filtration rate of 52 mL/min/1.73 m<sup>2</sup> (CKD-EPI). Her 24-h urinary sodium was 158 mEq/L. Other biochemical parameters (potassium, sodium, lipids, and microalbuminuria) were normal. The patient received all the orientations for lifestyle changes. In a 3- to 6-month period, she lost weight (approximately 6 kg – weight: 74 Kg and BMI: 29.5 kg/m<sup>2</sup>) and her HbA1c was reduced to 8.0%. Nevertheless, there was no improvement in office BP levels, which continued elevated (154×100 mm Hg). Patient was submitted to 24-h ambulatory blood pressure monitoring (24-h ABPM), which confirmed elevated BP levels (mean: 146.6×98.3 mm Hg), using the same antihypertensive drugs related above. All the investigations for secondary hypertension came out negative (renal artery stenosis, obstructive sleep apnea, primary hyperaldosteronism, and pheochromocytoma). Thus, we discussed the therapeutic options for the management of hypertension with the patient, and after her approbation, we started the evaluation with TENS.

The application of TENS was performed in the cervical-thoracic ganglion region, located between the vertebral processes C7 and T4, three times a week for 40 min for a total period of 4 weeks. An electrostimulator (Endomed 684, Enraf Nonius, Rotterdam, Netherlands) was used, containing two output channels, with a stimulus frequency of 80 Hz and pulse width of 150µs, with intensity adjusted in milliamps (mA), according to the sensitivity of the patient. This electrical stimulus has a high-frequency current that causes mild local paresthesia, without causing painful or unpleasant stimuli. The intensity was high, starting from zero, until the perceived sensation reached the maximum of the sensory limit, without pain, discomfort, or involuntary muscle contractions. Self-adhesive electrodes (dimensions 5×5 cm) were used for the stimulation coupled longitudinally over the patient's skin, maintaining proper hygiene with the use of 70% alcohol to reduce bioimpedance, marking the previous demarcation of the site using a dermatographic pencil. The electrodes were always placed parallel to the spinal processes in C7 (channel 1) and T4 (channel 2) (Figure 1).<sup>10–12</sup>

Peripheral and central hemodynamic parameters [central systolic BP and pulse wave velocity (PWV)] were obtained through 24-h ABPM, with the Mobil-O-Graph® equipment (version 12, 2000, UK) according to the manufacturer's instructions, before and immediately after the end of applications from the electric stimulation.

Important changes in hemodynamic parameters were seen after 4 weeks from TENS application (Table 1), with significant reductions of the office systolic BP (SBP) and diastolic BP (DBP). There was also a significant decrease in



**Figure 1** Diagram showing the location for application of the transcutaneous electrical nerve stimulation.

peripheral SBP and DBP in the 24-h ABPM and sleep, and SBP during wakefulness. Additionally, central parameters including central SBP, and PWV presented a significant reduction during 24 h, wakefulness, and sleep in the ABPM. There were no alterations in metabolic and biochemical parameters (data not shown). One month after finishing the application of TENS, the office BP remained within the values considered normal ( $136 \times 84$  mm Hg).

**Table 1** Peripheral and Central Hemodynamic Parameters Observed in Ambulatory Blood Pressure Monitoring Before, and Immediately After Four Weeks from TENS Application

Variables		Before TENS	Four Weeks After TENS	P-value
24 h Monitoring (n=63)	SBP (mm Hg)	146.6	126.8	<0.0001
	DBP (mm Hg)	98.3	92.7	0.0444
	Central SBP (mm Hg)	135.1	119.5	0.0034
	PWV (m/s)	8.2	7.5	<0.0001
	HR (bpm)	77	83	0.0309
Wakefulness (n=43)	SBP (mm Hg)	143.7	130.0	0.0107
	DBP (mm Hg)	95.5	93.9	0.6578
	Central SBP (mm Hg)	134.9	122.2	0.0170
	PWV (m/s)	8.1	7.6	0.0135
	HR (bpm)	75	81	0.0742

(Continued)

**Table 1** (Continued).

Variables		Before TENS	Four Weeks After TENS	P-value
Sleep (n=20)	SBP (mm Hg)	149.7	124.4	<0.0001
	DBP (mm Hg)	101.1	91.8	0.0214
	Central SBP (mm Hg)	135.4	117.3	0.0493
	PWV (m/s)	8.31	7.4	0.0003
	HR (bpm)	80	84	0.2326

**Note:** P-value significant < 0.05.

**Abbreviations:** TENS, transcutaneous electrical nerve stimulation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PWV, pulse wave velocity.

## Discussion

In this case report, we discuss the presentation of a middle-aged female subject with a history of uncontrolled hypertension in the long term, which was investigated for RH with all the diagnostic steps for excluding confounding factors, including pseudo-resistant hypertension.

It is common to find individuals with increased BP in an outpatient care specialized in hypertension, even when using three or more antihypertensive drugs, a fact that complies with the initial definition of RH and is compatible with the history of the patient, who was taking four antihypertensive drugs. Thus, for true RH diagnosis, we investigated causes of pseudoresistance. Causes of pseudo-RH are attributed to six principal etiologies—errors in BP measurement, white-coat effect, drugs prescription failure, use of medicines that elevate BP, poor adhesion to lifestyle alterations, and medical treatment. Moreover, causes of secondary hypertension were also excluded.<sup>19</sup> Therefore, we decided to offer patients a new therapeutic option, which may reduce sympathetic modulation, increase vagal modulation, and decrease blood pressure in RH individuals.

In this report, there was a significant reduction in peripheral and central hemodynamic values immediately after four-week period from the application of TENS, an effect that remained by 1 month after the procedure, as evidenced with the office BP values. This therapeutic option represents a new method for the management of hypertension, it is an easy application, low cost, and it has low risk of adverse events. The hypotensive effect observed by the application of TENS can be explained by the inhibition of sympathetic activity, which is exacerbated in individuals with RH.<sup>20</sup> Bang et al demonstrated significant reductions in systolic BP by directly stimulating the median nerve at different frequency ranges (3, 10, 30, and 300 Hz). The hypotensive effect was due to a reduction in sympathetic tone, at both low and high frequencies of stimulation.<sup>9</sup> Sympathetic stimulation also acts adversely on metabolism, leading to greater insulin resistance and dyslipidemia.<sup>20</sup> Spiridonov et al evaluated the effect of applying TENS on fructose-induced metabolic syndrome (MetS) parameters (12.5% of fructose solution as the only drinking source for 10 weeks) in male Wistar rats.<sup>8</sup> The development of hypertension in this experimental model along with impaired glucose tolerance and increased serum concentration of triglycerides (TG) and lipid peroxidation products (LPO) caused a decrease in the content of serum blood calcitonin gene-related peptide (CGRP). Low-frequency TENS performed in 8 weeks after the beginning of fructose treatment reduced systolic BP and serum concentration of TG and LPO products and improved glucose tolerance. After TENS, CGRP content returned to normal values and the content of nitric oxide (NO) metabolites increased. It seems that CGRP and NO are involved in mechanisms mediating the therapeutic effect of low-frequency TENS on hypertension in this model.<sup>8</sup>

Insulin resistance and compensatory hyperinsulinemia observed in MetS may lead to activation of the sympathetic nervous system (SNS), oxidative stress, enhanced production of vasoconstrictors, inhibition of endothelial NO synthase (eNOS),<sup>21</sup> and additional reduction of CGRP content in afferent neurons and nerve fibers innervating blood vessels.<sup>22</sup> CGRP, a neurotransmitter of primary sensory neurons, produces a vasorelaxation effect mediated by NO and cyclic

adenosine monophosphate (cAMP).<sup>23</sup> Thus, a possible mechanism for the hypotensive effect and improvement of insulin resistance in MetS after low-frequency stimulation can be related to a decrease in activity of the SNS,<sup>12</sup> activation of afferent nerves,<sup>24</sup> and stimulation of the expression of the sensory nerve transmitter CGRP.<sup>25</sup> Briefly, TENS modules the autonomic function, reducing SNS activity and increasing parasympathetic nervous system activity. Consequently, it may induce widespread cutaneous and muscular vasodilatation, as demonstrated in spontaneously hypertensive rats (SHR)<sup>24</sup> and in patients with hypertension<sup>12,26</sup> due to sympatho-inhibition. This response has been shown to be associated with a lowering of the systemic vascular resistance and blood pressure. Moreover, in patients with diabetes mellitus, there is carbohydrate and lipid metabolism normalization and improved insulin resistance in fructose-induced MetS.<sup>27</sup> Since our patient also had MetS, these explanations could be related to the present case.

In this case, the stellate ganglion was used for TENS application, which is predominantly characterized by its sympathetic activity. Formed by the fusion of pre-ganglionic fibers from the lower cervical and upper thoracic ganglia,<sup>28</sup> it influences cardiac electrical activity and the neuromodulation of peripheral blood vessels, causing the release of endogenous vasodilators.<sup>29</sup> Previously, our group demonstrated the acute application of TENS attenuated arterial stiffness in healthy younger adults as well as hemodynamic measures in the middle-aged group.<sup>10</sup> Recently, a Brazilian group demonstrated that the acute transcranial direct current stimulation (tDCS), a noninvasive procedure, decreased central and peripheral hemodynamic parameters and improved autonomic modulation in individuals with RH.<sup>30</sup> Apparently, both methods (TENS and tDCS) present the same pathophysiological basis for reducing the central and peripheral BP, possibly mediated by autonomic modulation.

This case report has both strengths and limitations. Its strengths include the contribution of a low-cost, noninvasive, and clinically relevant intervention for treatment of RH, which could have implications in clinical practice. Nevertheless, some limitations should be considered. First, the major limitation is that the central hemodynamic parameters were obtained noninvasively by applying transfer function analysis to an oscillometric reconstructed waveform (Mobil-O-Graph) rather than via a direct measurement. Indeed, there are some questions about the principle of one-site central BP and PWV, measurements by oscillometry.<sup>31,32</sup> However, oscillometry is a method that can be easily and conveniently employed for 24-h monitoring of central hemodynamics, a fact that allows to obtain repeated measurements in daily life conditions with hardly any discomfort to the patient. Additionally, the device used in this case has been properly validated versus alternative algorithms for computing arterial stiffness indexes and central hemodynamics, according to commonly accepted and standardized protocols. Several studies have documented a good agreement between the oscillometric cuff-based estimates of central BP and PWV measured by invasive methods and the established radial tonometry methods.<sup>33,34</sup> Second, we do not know if the continuation of the application of TENS for a longer time will be able to improve the metabolic alterations. Finally, two important questions have not been answered in this case report: whether the hypotensive effect will persist after discontinuing TENS and if there will be a need for continued use of the procedure. In part, the first question has been answered since the office blood pressure remained controlled 1 month after discontinuing TENS.

Thus, even with evidence showing that TENS can influence sympathetic activity, positively interfere with metabolism, and reduce peripheral and central hemodynamic parameters, large-scale studies are needed, at different BP levels and with different dosages of electrical current to better elucidate its pathways, action, and its effects on the organism. Due to the high incidence of cardiovascular morbidity and mortality caused by RH, we have proposed a study with a more effective, highly specific, and non-invasive therapeutic approach that is reproducible and less costly from a financial point of view.<sup>35</sup>

## Conclusion

In conclusion, to the best of our knowledge, this is the first report that suggests an effect of the TENS in the central and peripheral hemodynamic parameters of one resistant hypertensive patient. Anyway, given that one case report is not a proof of the effect of TENS in these parameters, a study that evaluates the effectiveness of TENS as an antihypertensive therapy in RH patients has been proposed in a higher number of individuals. We believe that other forms of non-pharmacological treatment and autonomic modulation, such as TENS application, should be experimented in cases of RH.

## Abbreviations

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CGRP, calcitonin gene-related peptide; cAMP, cyclic adenosine monophosphate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eNOS, endothelial NO synthase; HbA1c, glycosylated hemoglobin; HDLc, high-density lipoprotein cholesterol; HR, Heart Rate; LDLc, low-density lipoprotein cholesterol; LPO, lipid peroxidation products; MetS, metabolic syndrome; NO, nitric oxide; PWV, pulse wave velocity; RH, Resistant hypertension; SBP, systolic blood pressure; TC, total cholesterol; TENS, transcutaneous electrical nerve stimulation; tDCS, transcranial direct current stimulation; TG, triglycerides.

## Consent Statement

A statement confirming consent to publish the case has been obtained from patient. This statement is available if requested to corresponding author. An institutional approval was not required.

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## Disclosure

The authors declare that they have no competing interests.

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