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Research Article

Transcutaneous Electrical Stimulation of PC5 and PC6 Acupoints Modulates Autonomic Balance in Heart Transplant Patients: A Pilot Study

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Abstract
The increased resting heart rate (HR) in heart transplant patients is associated with enhanced metabolic demand, the potential for fatigue, and lower quality of life. In the present study, we hypothesized that transcutaneous electrical acupoint stimulation (TEAS) could modulate autonomic balance and reduce resting HR in these patients. A single-arm clinical trial was conducted with patients aged > 18 years, at ambulatorial accompaniment after heart transplantation, who were submitted to a single TEAS (40 minutes at pericardium channel acupoints PC5 and PC6). The arterial blood pressure and RR interval were recorded from 20 minutes before to 20 minutes after TEAS. The RR intervals were used to calculate HR variability (HRV) and the sympathovagal index. Linear mixed models were used for comparing variables before, during, and after TEAS. The significance level was set as $P < 0.05$. TEAS acutely improved HRV in transplant patients and enhanced the sympathovagal index during its application. Significant increases in systolic

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and diastolic blood pressure and mean arterial pressure were observed at recovery, such as a slight, but significant, decrease in HR. In conclusion, TEAS at PC5 and PC6 acutely modulates HRV and hemodynamics in transplant patients.

1. Introduction

Heart failure is the final stage of most heart diseases and the main cause of death in patients with ischemic heart disease in the USA and other Western countries [1]. When the heart cannot provide an adequate blood supply for all tissues, patients' functional capacity and quality of life worsen. As the disease advances further, morbidity and mortality increase [2, 3].

Therapeutic refractory heart failure culminates in the need for heart transplantation (HT) [4]. This treatment has immeasurable benefits. However, hearts are implanted without parasympathetic innervation, and heart rate (HR) control by the autonomic nervous system (ANS) is, thus, impaired, leading to increased resting HR and, consequently, enhanced metabolic demand, potential for fatigue, and lower quality of life [5, 6].

Thus, nonpharmacological approaches that enhance ANS control of HR may benefit heart transplant patients. One such emerging strategy is acupuncture. In animals, when applied at the Neiguan (PC6) and Jianshi (PC5) points, electroacupuncture improves left ventricular contractility, mean arterial pressure (MAP), cardiac output, and vascular blood pressure responses through sympathetic system activation [7]. Transcutaneous electrical acupoint stimulation (TEAS) at PC6 modulates autonomic balance in obese people [8], and it may reduce HR and improve HR variability (HRV) [9]. However, these effects have never been demonstrated in heart-transplanted patients.

Therefore, in the present study, we hypothesized that TEAS can acutely improve autonomic balance and reduce resting HR in heart transplant patients.

2. Materials and Methods

2.1. Study design

This pilot study was a single-arm clinical trial conducted from January to July 2017. All patients in ambulatorial accompaniment after HT at the National Institute of Cardiology were recruited for the study (convenience sampling). Those aged $<$ 18 years and with heart pacemakers, implantable cardioverter defibrillators, auditory devices, brain injury, *status epilepticus*, and tetanus were excluded from the study. Fig. 2 shows the patient recruitment process.

2.2. Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki 1975, as revised in 2013. The Ethics Committee of the National Institute of Cardiology (CAAE: 61053316.0.0000.5272) approved the study, and all patients signed an informed consent form before the beginning of the protocol. The study was registered in an International Clinical Trials Registry Platform, REBEC (identifier: RBR-5T27SB).

2.3. Measurements

Information, both the questionnaires and anthropometric and blood pressure measurements, was collected on individual assessment sheets filled out by the same researcher previously trained to perform all the procedures of the study. The following relevant baseline data were collected: age, gender, previous pathology, history of current disease, comorbidities, medications in use, and behavioral factors.

2.4. Intervention

A single TEAS session was performed by an experienced physiotherapist at an intensity of 0.8—1.9 mA and a frequency of 5—30 Hz (Neurodyn Tens Port, IBRAMED. Av. Dr. Carlos Burgos, 2800 - Jardim Italia, Amparo - SP, Brazil. CEP 13901-080; Ibramed Series 92875; ANVISA registry: 10360310012) [10]. The electrodes were placed bilaterally at the PC5 and PC6 acupuncture points, which are part of the pericardial canal (Xin Bao) located in the anterior region of the forearm near the wrist (Fig. 1). The pericardial canal is thought to regulate cardiac parameters such as HR [11].

The intervention was carried out in a quiet room with a controlled temperature (23°C). The patients remained in the supine position during the whole procedure, which consisted of three periods: control (20 minutes to allow for HR and blood pressure accommodation), TEAS (40 minutes), and recovery (20 minutes to allow for HR and blood pressure recovery). The arterial blood pressure and HR were measured every 10 minutes from the beginning of the control period until the end of the recovery period. The systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and double product were registered.

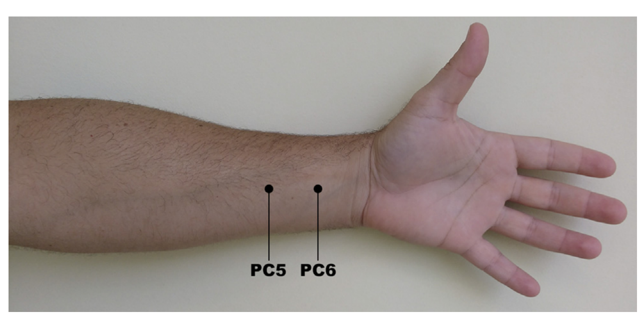

Figure 1 Location of PC5 and PC6 acupoints.

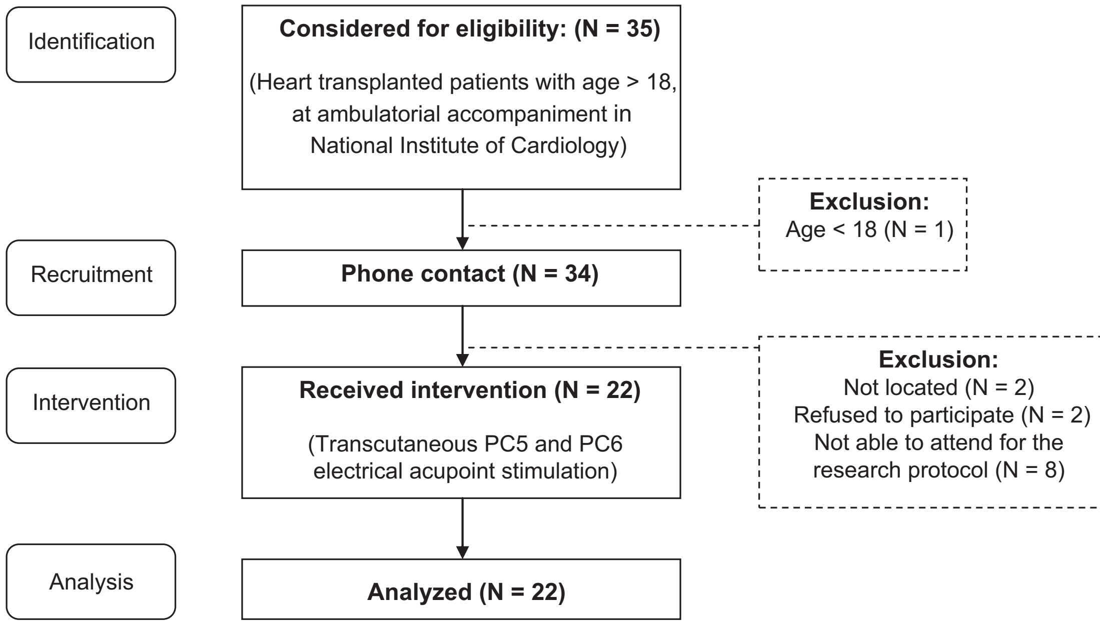

Figure 2 Recruitment flowchart.

2.5. Heart rate variability analysis

The RR interval was continuously recorded throughout the experiment using a cardiofrequencimeter (RS800 Polar, Polar Electro Oy, Oulu, Finland) and subsequently used to evaluate HRV using appropriate software (Kubios version 2.2; University of Eastern Finland, Finland). The following time-domain HRV parameters were evaluated: mean of all normal RR intervals (mean RR), standard deviation (SD) of normal RR interval (SDNN), number of consecutive normal RR interval differences greater than 50 ms (NN50), percentage of normal RR intervals that differed by more than 50 ms from the adjacent interval (pNN50), and root mean square of successive differences (RMSSD). Integration of the successive HR bands was classified in relation to the frequency domain as follows: very low frequency component (VLF; 0.003—0.04 Hz), low frequency component (LF; 0.04—0.15 Hz), and high frequency component (HF; 0.15—0.4 Hz). The ratio of LF to HF (LF/HF) was used to calculate the sympathovagal index. The normalized power of the LF and HF components was calculated in standard units (nu).

2.6. Data analysis

Descriptive analysis consisted of mean and SD for continuous variables and percentage and number of observations for categorical variables. Longitudinal effects of TEAS on primary and secondary outcomes were evaluated through linear mixed models. Residual plots of all models were examined, and the likelihood ratio test was performed to compare and select random intercept or random slope models. The significance level was set as $P < 0.05$.

3. Results

Table 1 shows the main characteristics of the volunteers, their etiologies necessitating HT, comorbidities, and current medications. Among the 22 patients who participated, five were women (22.7%) with a mean age of 52 (12.3) years; and 17 patients were men (77.3%) with a mean age of 53.8 (8.6) years. The heart failure etiologies that necessitated HT were Chagas disease, myocarditis, ischemic disease, and rheumatic valve disease, all of which occurred in four patients each (18.2%), followed by alcoholic (13.7%), idiopathic (9.1%), and peripartum (4.5%) cardiopathies. The mean time since surgery was 4.3 (2.5) years. Hypertension was the main comorbidity, presented by 11 patients (50.0%), whereas diabetes and obesity occurred in six patients (27.2%), and dyslipidemia, in five patients (22.7%). All of the patients were using immunosuppressive medications: 20 patients were using calcium channel blockers (90.9%); two were using beta blockers (9.1%); and one was using ivabradine (4.5%).

The hemodynamic variables and the time- and frequency-domain HRV parameters at baseline are presented in Table 2, while the effects of TEAS on hemodynamics are presented in Table 3. It can be observed that no change on hemodynamics during TEAS but HR has been slightly, but significantly, decreased and SBP, DBP, and MAP have been improved on recovery period.

Moreover, the volunteers related any complications or discomfort during TEAS.

The effects of TEAS on HRV are presented on Table 4. The time-domain variables mean RR, NN50, and pNN50 have been significantly improved on recovery, whereas SDNN has been significantly improved during TEAS and also on recovery period. The frequency-domain variables LF (ms^2 and nu), HF (nu), LF/HF, and total power were significantly improved during TEAS but not at recovery period.

4. Discussion

The present study found that TEAS on the PC5 and PC6 acupoints acutely improved time- and frequency-domain

Table 1 Main characteristics of the population.

Variable	Mean (SD) or number (%)
Age (years)	
Women	52.0 (12.3)
Men	53.8 (8.6)
Time since surgery (years)	4.3 (2.5)
Population	22 (100)
Sex (number)	
Women	5 (22.7)
Men	17 (77.3)
Indication of transplant (number)	
Chagas disease	4 (18.2)
Myocarditis	4 (18.2)
Ischemic	4 (18.2)
Valvular dysfunction (rheumatic)	4 (18.2)
Alcoholic	3 (3.7)
Idiopathic	2 (9.1)
Peripartum	1 (4.5)
Comorbities (number)	
Hypertension	11 (50.0)
Diabetes	6 (27.2)
Obesity	6 (27.2)
Dyslipidemia	5 (22.7)
Hypothyroidism	3 (13.7)
Kidney insufficiency	3 (13.7)
Hyperthyroidism	1 (4.5)
Class of medications in use (number)	
Immunosuppressant	22 (100)
Calcium channel blocker	20 (90.9)
Angiotensin receptor antagonist II	7 (31.8)
Hypoglycemic	5 (22.7)
ACE inhibitor/AT1 blocker	5 (22.7)
Antiplatelet	4 (18.2)
Vasodilator	4 (18.2)
Anxiolytic	3 (13.6)
Adrenergic alpha-agonist	2 (9.1)
β blocker	2 (9.1)
Diuretic	2 (9.1)
Anticoagulant	1 (4.5)
Antidepressant	1 (4.5)
Ivabradine	1 (4.5)

ACE = angiotensin-converting enzyme; AT1 = angiotensin receptor type 1; SD = standard deviation.

Table 2 Crude means (SD) of hemodynamics and HRV during protocol.

Variable	Baseline value mean (SD)
Hemodynamics	
HR (bpm)	78.8 (6.9)
SBP (mmHg)	124.6 (11.9)
DBP (mmHg)	84.0 (7.3)
MAP (mmHg)	97.5 (8.1)
DP (bpm.mmHg)	9803.0 (1104.0)
HRV	
Mean RR (ms)	769.6 (71.6)
SDNN (ms)	7.2 (3.0)
RMSSD (ms)	6.0 (3.4)
NN50 (count)	0.1 (0.3)
pNN50 (%)	0.1 (0.1)
VLF (ms^2)	32.5 (45.9)
LF (nu)	37.6 (22.4)
HF (nu)	61.4 (21.4)
LF/HF	0.9 (0.7)
Total power (ms^2)	59.1 (56.3)

DBP = diastolic blood pressure; DP = double product; HF = high frequency; HR = heart rate; HRV = heart rate variability; MAP = mean arterial pressure; mean RR = mean of all normal RR intervals; NN50 = number of consecutive normal RR interval differences greater than 50 ms; RMSSD = root mean square of successive differences; pNN50 = percentage of normal RR intervals that differed by more than 50 ms from the adjacent interval; SBP = systolic blood pressure; SD = standard deviation; SDNN = standard deviation of normal RR interval; VLF = very low frequency.
Data are expressed as mean (SD).

HRV and autonomic balance in patients who had received heart transplant. In addition, hemodynamics was improved after the end of stimulation.

Despite the paucity of literature regarding TEAS in healthy or diseased participants, similar hemodynamic findings were demonstrated using electroacupuncture (EA) at the acupoint PC6 in healthy anesthetized dogs. The treatment increased MAP, end-diastolic volume, stroke volume, cardiac output, end-systolic pressure, and end-systolic elastance, but contrary to our findings, the treatment improved HR, with return to baseline 1 hour after EA [7]. In another study, dogs submitted to hemorrhage-induced hypotension and treated using EA at PC6 recovered end-systolic pressure, end-diastolic volume, and stroke volume without changes on HR or hemorrhage-induced increases in plasma catecholamines [12]. Contradictorily, in healthy cats, EA at the PC6 acupoint caused a hypotensive effect [13, 14], suggesting that the effects of stimulation of acupuncture points could vary between species and, also, depend on health conditions.

Table 3 Effects of TEAS on hemodynamics.

	β	CI	P-value
HR (bpm)			
TEAS	−1.1	−2.7 to +0.5	0.175
Recovery	−1.1	−3.5 to −0.3	0.019
SBP (mmHg)			
TEAS	+1.0	−2.1 to +4.1	0.528
Recovery	+3.3	+0.2 to +6.4	0.039
DBP (mmHg)			
TEAS	+1.1	−1.2 to +3.3	0.343
Recovery	+2.7	+0.5 to +5.0	0.018
MAP (mmHg)			
TEAS	+1.1	−1.2 to +3.4	0.368
Recovery	+2.9	+0.6 to +5.2	0.013
DP (bpm.mmHg)			
TEAS	−56.6	−378.2 to 265.0	0.730
Recovery	−2.4	−324.0 to 319.2	0.988

CI = confidence interval; DBP = diastolic blood pressure; DP = double product; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; TEAS = transcutaneous electrical acupoint stimulation.

Table 4 Effects of TEAS on HRV.

	β	CI	P-value
Time-domain			
Mean RR (ms)			
TEAS	+12.0	−5.5 to +29.6	0.179
Recovery	+21.5	+4.0 to +39.1	0.016
SDNN (ms)			
TEAS	+1.9	+0.7 to +3.1	0.002
Recovery	+1.2	+0.1 to +2.4	0.039
RMSSD (ms)			
TEAS	+0.1	−0.9 to +1.0	0.883
Recovery	+0.3	−0.6 to +1.3	0.471
NN50 (count)			
TEAS	−24.3	−260041.7 to + 259993.1	1.000
Recovery	+2.1	+0.6 to +3.5	0.006
pNN50 (%)			
TEAS	0.0	−0.19 to +0.15	0.781
Recovery	+0.2	0.0 to + 0.4	0.039
Frequency-domain			
VLF (ms^2)			
TEAS	+35.0	−1.1 to +71.1	0.058
Recovery	+3.0	−33.1 to +39.2	0.868
LF (ms^2)			
TEAS	+9.9	+2.5 to +17.3	0.009
Recovery	+4.1	−3.3 to +11.5	0.276
HF (ms^2)			
TEAS	+2.9	−0.8 to +6.6	0.129
Recovery	+3.4	−0.3 to +7.1	0.074
LF (nu)			
TEAS	+8.5	+1.5 to +15.6	0.018
Recovery	+5.3	−1.8 to +12.3	0.141
HF (nu)			
TEAS	−7.5	−14.7 to −0.3	0.041
Recovery	−4.4	−11.6 to +2.8	0.235
LF/HF			
TEAS	+1.4	+0.7 to +2.1	0.000
Recovery	+0.8	−0.1 to +1.7	0.083
Total power (ms^2)			
TEAS	+44.8	+2.8 to +86.8	0.036
Recovery	+6.7	−35.7 to +48.3	0.769

CI = confidence interval; HF = high frequency; HRV = heart rate variability; mean RR = mean of all normal RR intervals; NN50 = number of consecutive normal RR interval differences greater than 50 ms; pNN50 = percentage of normal RR intervals that differed by more than 50 ms from the adjacent interval; RMSSD = root mean square of successive differences; SD = standard deviation; SDNN = standard deviation of normal RR interval; TEAS = transcutaneous electrical acupoint stimulation; VLF = very low frequency.
Data are expressed as mean (SD).

In humans, a study with 40 patients in the final stage of liver disease, who had undergone orthotropic liver transplantation from a deceased donor and were randomized into two groups based on how hypotension was treated during anesthesia (one group received norepinephrine as vasoconstrictor, whereas the other was treated with EA at points PC5 and PC6), demonstrated that EA reduced the severity and incidence of hypotension during anesthesia to the same extent as norepinephrine [15]. Similarly, in the present study, it has been demonstrated that after a single session of TEAS at PC5 and PC6, on heart transplant patients, there was an improvement on hemodynamics (SBP, DBP, and MAP), suggesting that the mechanism related to those alterations could be an increase in stroke volume [7] or in peripheral vascular resistance [16] because HR has been reduced.

The effects of PC5 and PC6 acupoint stimulation seem to depend on whether the participant is healthy or diseased, and acupuncture at these points appears to either enhance or suppress cardiac function, depending on whether the ANS is compromised [14]. For the normal functioning ANS, a single acupuncture stimulation at PC6, bilaterally, affects HR and HRV, specifically, increasing mean RR interval (reducing HR) and reducing HRV parameters [9]. In the case of the impaired ANS, in a randomized, controlled, crossover study, EA at the PC6 acupoint was realized on patients with orthostatic intolerance, improving hemodynamic function (increasing DBP, stroke volume, and total peripheral resistance), as well as decreasing HR and upregulating ANS (increasing HRV and sympathovagal balance) [16]. In the present study, the recruited patients differed in terms of anthropometry, etiology that necessitated HT, and, most importantly, time since surgery. In patients who receive an HT, the donated heart is implanted without innervation. Thus, the time since surgery is strongly related to the stage of reinnervation and to the recovery of ANS function [17], which can be confirmed by the effects of TEAS on PC5 and PC6 on HRV found. Our data show an important improvement in sympathovagal balance, accompanied by an increase in total HRV (suggested by SDNN and total power improvement) and in sympathetic tonus (suggested by LF improvement) during TEAS, which could justify the arterial pressure improvement observed at recovery. Interestingly, the increase in parasympathetic tonus observed during TEAS (improvement of HF) might seem contradictory but justifies the slight decrease in HR observed at recovery. Anatomically, the parasympathetic fibers innervate mainly the sinus and atrioventricular nodes, and their activation exerts negative chronotropic effect, reducing HR by inhibition of the sympathetic stimulation [18]; however, it exerts little effect on myocardial contractility [18, 19], allowing the increase of the blood pressure by mechanisms other than the HR modulation, as increasing systolic volume [7] or peripheral vascular resistance [16].

In addition, on the one hand, whether the slight acute reduction observed in HR during a single session of TEAS at PC5 and PC6 may be clinically irrelevant, or on the other hand, whether the effect of a chronic treatment with TEAS on HR is cumulative, it could be a promising novel way to nonpharmacologically treat the increased HR observed in heart transplant patients [6]. In addition, most of the published studies have used invasive acupuncture procedures, whereas we used a noninvasive TEAS. This is clinically relevant because all patients are immunosuppressed after receiving an HT. Moreover, we can affirm that TEAS is safe to use on HT patients because none of the patients experienced discomfort or symptom of exacerbation during or after TEAS, although the procedure affected hemodynamics and HRV.

The present study had some important limitations: no control group that had not received an HT was used; there was an important heterogeneity in time since surgery among the recruited participants although it had been adjusted for in the statistical analysis; and the sample size was low. However, as a pilot study, for the first time applying TEAS in a fragile and very specific disease condition, it was important for the safety verification of the intervention.

In conclusion, TEAS on PC5 and PC6 acupoints acutely improves sympathovagal balance, reduces HR, and improves blood pressure in HT patients. Further randomized controlled trials, with larger sample sizes, and chronic TEAS treatment trials are necessary to confirm these effects.

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Disclosure statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jams.2019.04.001.

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