Published in final edited form as:

Clin Exp Pharmacol Physiol. 2014 May ; 41(5): 325–330. doi:10.1111/1440-1681.12221.

Understanding the Placebo Effect in Clinical Trials for Postural Tachycardia Syndrome

Victor C Nwazue, MD^{*}, Amy C Arnold, PhD^{*}, Vidya Raj, MB ChB[#], Bonnie K Black, RN CNP^{*}, Italo Biaggioni, MD^{*,§}, Sachin Y Paranjape, BS^{*}, Carlos Orozco, BS^{*}, William D. Dupont, PhD[§], and David Robertson, MD^{*,§,¶}

^{*}Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA

[#]Department of Psychiatry, Vanderbilt University, Nashville, Tennessee, USA

[§]Department of Pharmacology, Vanderbilt University, Nashville, Tennessee, USA

[§]Department of Biostatistics Vanderbilt University, Nashville, Tennessee, USA

[¶]Department of Neurology, Vanderbilt University, Nashville, Tennessee, USA

Abstract

Postural tachycardia syndrome (POTS) is characterized by excessive increases in heart rate (HR) upon standing. Previous studies have shown that standing HR decreases over time in POTS patients given placebo. We hypothesized that this reduction is due to cardiovascular physiological alteration, as opposed to psychological benefit from perceived therapy. To prospectively test this hypothesis, we examined the effects of an open-label "No Treatment" intervention (NoRx) compared to a patient-blinded placebo on standing HR in POTS patients. Twenty-one POTS patients participated in a randomized, crossover trial with oral placebo versus NoRx administered at 9 AM. Seated blood pressure (BP) and HR were measured at baseline and every hour for 4 hours (h). Similarly, BP and HR were measured while patients stood for 10 minutes at these time points. Standing HR significantly decreased over time with both NoRx (baseline: 112 ± 13 bpm, 4h: 103 ± 16 bpm) and placebo (baseline: 112 ± 14 bpm, 4h: 102 ± 16 bpm; $P_{\text{time}} < 0.001$), but this effect was not different between interventions ($P_{\text{drug}} = 0.771$). POTS patients have exaggerated

Corresponding Author & Address for Reprints: Satish R Raj MD MSCI FACC, AA3228 Medical Center North, Vanderbilt University, 1161 21st Avenue South, Nashville, TN, 37232-2195, USA, Phone: 615-343-6499, Fax: 615-343-8649, satish.raj@vanderbilt.edu.

CONFLICTS OF INTEREST:

None

AUTHOR CONTRIBUTIONS:

Nwazue – Analysis & interpretation of data; drafting article

Arnold - interpretation of data; drafting article, critical revisions to draft

V Raj – study conception, interpretation of data; drafting article, critical revisions to draft

Black - study conception; collection of data; critical revisions to draft

Biaggioni – study conception; interpretation of data; critical revisions to draft

Paranjape – collection & analysis of data; critical revisions to draft

Orozco – collection of data; interpretation of data; critical revisions to draft

Dupont – analysis & interpretation of data; critical revisions to draft

Robertson - study conception; interpretation of data; critical revisions to draft

S Raj – study conception & design; collection, analysis & interpretation of data; drafting article

orthostatic tachycardia in the morning that decreases over time with either placebo or NoRx interventions, suggesting this phenomenon is due to cardiovascular physiologic variation. These data highlight the need for a placebo arm in hemodynamic clinical trials in POTS, and may have important implications for diagnosis of these patients.

Keywords

placebo; postural tachycardia syndrome; diurnal variability

INTRODUCTION

Postural tachycardia syndrome (POTS) is characterized by a sustained increase in heart rate (HR) ≥ 30 bpm within 10 minutes of standing that occurs in the absence of orthostatic hypotension, and accompanied by symptoms such as palpitations, chest pain syndrome, dyspnea, mental clouding and difficulties with concentration.^{1,2} POTS is likely the most common disorder of young individuals seen at autonomic specialty centers and predominantly affects premenopausal females.^{3,4} POTS can be debilitating and most patients experience significant fatigue and poor health-related quality of life.^{5,6}

Previous acute trials in POTS patients have reported significant decreases in standing HR over time with blinded placebo tablets.⁷⁻⁹ The explanation for this finding, however, is unclear. One potential explanation is that this HR reduction is due to a psychological placebo effect with the patient responding physiologically to a perceived active therapy. Indeed, the placebo effect has been shown to have important implications in studies of cardiovascular diseases, particularly in the area of neurocardiology (e.g. studies of pacing in vasovagal syncope).¹⁰⁻¹² Patients with POTS are may be particularly susceptible to the expected benefits of pharmacological therapy, although there is lack of evidence underlying this belief.

An alternative explanation for the time-related HR reduction in POTS with placebo is a background cardiovascular variability unrelated to the therapy. Blood pressure (BP) and HR are known to exhibit significant diurnal variability over a 24-hour period, with an increase in these measures in the early morning that is associated with sympathetic activation.¹³⁻¹⁵ Furthermore, numerous cardiovascular events such as myocardial ischemia, stroke, and arrhythmia exhibit some degree of circadian variability, with a peak in event rates in the early morning.¹⁶⁻¹⁸

To determine which of these possibilities may best explain the decrease in standing HR with placebo over time, we performed a prospective, randomized, crossover trial comparing an open-label no treatment intervention with a blinded placebo in POTS patients. We hypothesized that the reduction in HR in these patients is due to cardiovascular physiological alteration, rather than psychological benefit from perceived therapy.

RESULTS

Patient Characteristics

This study included 21 patients with POTS (17 female; 34 ± 11 years of age), with the clinical characteristics shown in Table 1. During the posture study, which is used to clinically characterize these patients, standing elicited a significant increase in HR (supine: 74 ± 14 bpm, standing: 124 ± 16 bpm; $p < 0.001$) with no difference in SBP (supine: 109 ± 10 mmHg, standing: 110 ± 17 mmHg; $p = 0.679$) and a modest increase in DBP (supine: 70 ± 10 mmHg, standing: 75 ± 12 mmHg; $P = 0.006$).

Standing Heart Rate over Time

The standing HR at 2 hours post intervention, the primary outcome, was not significantly different between PL and NoRx (107 ± 15 vs. 101 ± 17 bpm, respectively; $P = 0.166$; Figure 1A, Table 2). Similarly, there was no difference in standing HR at 4 hours between interventions (PL: 102 ± 16 bpm vs. NoRx: 103 ± 16 ; $P = 0.724$). On both study days, standing HR was highest in the morning at baseline (PL: 112 ± 14 bpm vs. NoRx: 112 ± 13 bpm, $P = 0.377$), and showed a steady and significant decline over the 4-hour study period (ANOVA $P_{\text{time}} = 0.001$), with no difference between interventions (ANOVA $P_{\text{int}} = 0.214$; Table 2, Figure 1A).

Seated Heart Rate over Time

At baseline, seated HR was not different between interventions (PL: 82 ± 13 bpm vs. NoRx: 86 ± 16 bpm; $P = 0.609$; Table 2, Figure 1B). Seated HR decreased over time following PL and NoRx (ANOVA $P_{\text{time}} = 0.008$), with no significant difference between the interventions (ANOVA $P_{\text{int}} = 0.801$).

Delta Heart Rate over Time

The delta HR, which is an objective reflection of orthostatic tachycardia, decreased over time following both PL and NoRx (ANOVA $P_{\text{time}} = 0.029$; Table 2), with no difference between interventions ($P_{\text{int}} = 0.793$). Furthermore, the magnitude of delta HR was not different between PL and NoRx at baseline (PL: 29 ± 12 bpm vs. NoRx: 26 ± 12 bpm; $P = 0.123$) or at 4 hours post intervention (PL: 24 ± 12 bpm vs. NoRx: 21 ± 11 bpm; $P = 0.884$; Table 2).

Seated and Standing Blood Pressure

As shown in Table 2, baseline SBP (PL: 102 ± 11 mmHg vs. NoRx: 104 ± 13 mmHg; $P = 0.805$) and DBP (PL: 67 ± 7 mmHg vs. NoRx: 69 ± 11 mmHg; $P = 0.663$) were not different between interventions. When measured over time, there was not a significant decline in either standing SBP (ANOVA $P_{\text{time}} = 0.739$) or DBP (ANOVA $P_{\text{time}} = 0.712$) between interventions.

METHODS

Study Participants

This study included 21 POTS patients referred to the Vanderbilt University Autonomic Dysfunction Center for evaluation between November 2003 and September 2006. Patients were diagnosed with POTS if they met the following criteria: (1) HR increase ≥ 30 bpm within 10 min of standing; (2) absence of orthostatic hypotension (a fall in BP $\geq 20/10$ mmHg); and (3) chronic symptoms of orthostatic intolerance (≥ 6 months), in the.^{1,2,19} The diagnosis of POTS was made on a separate morning from either study day and in a fasted state, by measurement of supine and standing BP and HR (Table 1). All patients were at least 18 years of age, and had absence of other disorders known to cause orthostatic intolerance such as prolonged bed rest. The Vanderbilt University Institutional Review Board approved this study, and written informed consent was obtained from each patient before study participation. These data are a part of the “Treatment of Orthostatic Intolerance” study, which is registered with clinicaltrials.gov (NCT00262470).

Study Conditions

All studies were performed in the Elliot V. Newman Clinical Research Center at Vanderbilt University. POTS patients consumed a low monoamine, methylxanthine-free diet containing 150 mEq/day of sodium and 60–80 mEq/day of potassium for at least three days prior to testing. Medications affecting the autonomic nervous system or hemodynamic function were discontinued for at least five half-lives prior to admission, with fludrocortisone discontinued for at least five days prior to the study.

Medication Trials

POTS patients participated in a randomized, single-blind, crossover study (nurse was unblinded; patient and principal investigator were blinded) with oral placebo (PL; patient not aware of inactive therapy) or No Treatment (NoRx; patient aware of no active therapy) administered on two separate study days. Thirteen of the 21 patients were randomized to receive NoRx followed by PL, while the remaining patients received these interventions in the opposite order. The placebo was a commercially available lactose tablet (“Cebocaps”; Forest Pharmaceuticals, New York, NY). Patients were studied two hours after a light breakfast, to avoid acute hemodynamic effects from food ingestion, and in a post void state. PL or NoRx was instituted at approximately 9 am. Patients were seated in a chair during data collection except during prescribed periods of standing, consistent with our previous medication trials in these patients. BP and HR were measured using an oscillometric brachial cuff (Dinamap Vital Signs Monitor, Critikon Company, Tampa, FL) and data were digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation, Redmond, WA). At baseline, and hourly for 4 hours post-intervention, patients stood for 10 minutes (or as long as tolerated) while standing HR and BP were recorded. The delta HR was calculated as the difference between seated HR and maximal standing HR.

Statistical analysis

In the primary analysis, standing HR at 2 hours after study drug administration was compared between PL and NoRx using a paired t-test. This time point was chosen as prior studies have demonstrated a significant reduction in standing HR at 2 hours after PL administration.^{8,20} In the secondary analysis, we compared standing HR at 4 hours, seated HR at 2 hours, delta HR (standing minus seated) at 2 hours, and the parallel systolic BP (SBP) and diastolic BP (DBP) changes at 2 hours after study drug administration using paired t-tests. Changes in HR, SBP and DBP over time between treatment groups were compared using two-way repeated measures ANOVA. The Greenhouse-Geisser probability value for the interaction between study drug (PL vs. NoRx) and time was reported. Changes in standing HR over time were analyzed using one-way repeated measures ANOVA. Values are reported as mean $\pm$ SD unless otherwise noted. Probability values <0.05 were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed with SPSS for Windows (version 20.0, IBM Corporation; Armonk, NY). Prism for Windows (version 5.02, GraphPad Software Inc; La Jolla, CA) was used for graphical presentation.

DISCUSSION

The primary finding of this study is that standing HR decreases from morning to early afternoon without intervention in POTS patients, and this effect is not further augmented by a placebo effect attributable to the receipt of a pill. These findings suggest that cardiovascular physiological variability, as opposed to psychological mechanisms from perceived therapeutic benefit, contributes to the time-dependent decrease in orthostatic tachycardia following placebo administration in acute medication trials in these patients.^{7-9,20}

Orthostatic HR Reduction and Placebo Effect in POTS Patients

Previous studies have shown that standing HR decreases over time in POTS patients randomized to PL and active drugs, although the active drug effect was significantly greater.^{8,9,20} It is possible that this phenomenon is due to either a placebo effect or cardiovascular variability in these patients. The placebo effect has been identified across numerous areas of medicine²¹⁻²³ and the therapeutic benefits of this inactive treatment can confound interpretation of clinical studies. Indeed, it has been suggested that about 35% of patients respond to placebo in clinical trials.^{24,25} Several mechanisms are thought to contribute to this effect including: (a) psychological responses to therapeutic contexts including patient expectations, motivation, classical conditioning, learning, and emotions that target prospective symptom changes^{22,23}; (b) neurophysiologic effects such as release of endogenous neurotransmitters or neuromodulators; and (c) a vasodilation response controlled by the effect of nitric oxide signaling on catecholamine synthesis.²⁶

The inclusion of a no treatment arm in the present study allowed for control of the natural history of POTS as well as regression to the mean, thus revealing the true contribution of a placebo effect. Interestingly, the reduction in orthostatic tachycardia over 4 hours was of equal magnitude with PL and NoRx, whether or not patients were expecting active

treatment. Thus, while a placebo effect cannot be entirely excluded, is likely to play a limited role in the time-dependent variability in orthostatic tachycardia in POTS.

Diurnal Variability of HR in POTS

Given the finding of a lack of a true placebo effect in POTS patients, the most probable explanation for this phenomenon is changes related to physiologic cardiovascular variability. Furlan et al. have reported a circadian pattern of HR and BP that peaks in the morning around 10am and gradually declines throughout the day and night.¹³ This cardiovascular variability may be due to circadian changes in autonomic neural activity that persists even in the absence of physical activity.^{13,18,27} For example, sympathetic nerve activity increases during the day and declines at night, with the opposite pattern observed for parasympathetic activity.^{13,27} Catecholamines and plasma cortisol levels are also higher during the day than at night.²⁸ This surge in sympathetic activity in the morning may be associated with an increased incidence of adverse cardiovascular events.^{16,17}

We have previously shown a circadian variability in HR and BP in a mouse model of POTS.²⁹ In addition, patients with POTS exhibit significant diurnal variability in HR, with orthostatic tachycardia being greater in the morning (8 am) compared to the evening (8 pm).³⁰ Since a similar pattern was observed in healthy subjects, it was suggested that POTS patients have exaggeration of this normal physiological response. Interestingly, in this previous study we assessed changes in HR from the supine to seated position, which is more clinically relevant for diagnosis, and still observed diurnal changes. We observed a similar significant decline in standing HR over time following placebo in the present study. While the 4-hour time period of this study was relatively short, it reflects the window of observation commonly used in acute medication trials in these patients, and thus has important implications for interpretation of these studies. Extrapolation of our findings to a full 24-hour diurnal variability is not possible, but future studies will better characterize the long-term profile in these patients.

Potential Mechanisms Involved in HR Reduction in POTS

The precise mechanisms underlying reductions in HR in POTS patients were not examined in this study. One possibility is that changes in hormones involved in cardiovascular regulation (i.e. catecholamines, angiotensin peptides and cortisol) track with the HR changes in these patients. It is unlikely that this effect is due to failure of vasoconstriction or reductions in stroke volume, since there was no difference in standing BP over time in this study. . In our previous study examining diurnal variability in POTS patients, morning assessments were conducted in a fasting state, raising the possibility that the difference in standing HR between morning and evening was due to hydration status. In the present study, however, patients were observed in a post-absorptive state and still showed an initial higher HR that decreased over time without further hydration. Finally, it is possible that POTS patients “trained” themselves to standing during the study because they stood up for 10 minutes earlier in the study or were sitting for longer periods as the study progressed. While this cannot be excluded, it seems unlikely as all patients were allowed to use the restroom and to walk around in the morning prior to each study day.

Clinical Implications for Diagnosis of POTS

The finding of time-related variability in orthostatic tachycardia has important implications for the conduct of physiologic research trials in these patients, as they are often started in the morning with repeated assessments over the course of the day. The knowledge of this hemodynamic decline may inform data interpretation and conclusions that arise from such studies. In the present study, we assessed HR changes from the sitting to standing position, which may be a clinically more relevant measure that reflects the standard body position during the day when not standing. This study design, however, did not allow us to determine how many patients met consensus criteria for POTS following interventions. Regardless, our previous studies showed similar diurnal variation when assessing supine to standing HR changes in these patients and provided evidence that more patients met POTS criteria in the morning compared to the evening. These collective findings suggest that time of day may affect the accurate diagnosis of POTS. It is unclear whether it would be better to diagnose patients in the morning (where more patients may meet criteria) versus the afternoon (where some patients may not meet criteria). However, these findings certainly illustrate the need to standardize the time of assessment.

Study Limitations

The major limitation of this study is the relatively small sample size of POTS patients enrolled at a tertiary care center for autonomic disorders. While a larger study may be required for greater generalizability, our sample size is similar to other clinical studies in these patients. The HR and BP measurements in our study may have been subject to other sources of variance including adaptation to BP cuff-related discomfort, or changes in the release of catecholamines and other hormones over the time course of the study. Our study did randomize the order of PL and NoRx days, helping to avoid a day-to-day training effect. Furthermore, most patients are physiologically acclimatized to repeated standing on a daily basis, which should reduce the magnitude of a genuine “training effect” in our acute study. Finally, we did not assess symptoms in the present study and thus it is unclear whether diurnal changes in tachycardia are associated with changes in orthostatic symptoms in POTS. Anecdotally, however, many patients report that somatic symptoms such as palpitations and lightheadedness are worse in the morning, when exaggerated orthostatic tachycardia is observed.

Conclusions

Orthostatic tachycardia decreases over time, from morning to early afternoon, in patients with POTS. These HR changes appear to be due to physiological cardiovascular variability and not due to a psychological effect from expected beneficial therapy as there was no additive reduction in HR with placebo compared to no drug. These findings highlight the need for a placebo arm in hemodynamic clinical trials, and may have broad implications for the study of cardiovascular diseases including POTS. Furthermore, this study illustrates the importance of standardizing diagnostic assessments for POTS, as there is clinically meaningful variability of orthostatic vital signs based on the time of assessment in these patients.

Acknowledgments

We would like to thank our patients who participated in this study and to recognize the highly professional care provided by the staff of the Elliot V. Newman Clinical Research Center.

RESEARCH FUNDING:

Supported by NIH grants R01 HL102387, U54 NS065736, P01 HL56693, UL1 TR000445.

Reference List

1. Raj SR. Postural tachycardia syndrome (POTS). *Circulation*. 2013; 127:2336–2342. [PubMed: 23753844]
2. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology*. 1993; 43:132–137. [PubMed: 8423877]
3. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am J Med Sci*. 1999; 317:88–101. [PubMed: 10037112]
4. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, Lennon VA, Shen WK, Low PA. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc*. 2007; 82:308–313. [PubMed: 17352367]
5. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc*. 2002; 77:531–537. [PubMed: 12059122]
6. Bagai K, Song Y, Ling JF, Malow B, Black BK, Biaggioni I, Robertson D, Raj SR. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med*. 2011; 7:204–210. [PubMed: 21509337]
7. Green EA, Raj V, Shibao CA, Biaggioni I, Black BK, Dupont WD, Robertson D, Raj SR. Effects of norepinephrine reuptake inhibition on postural tachycardia syndrome. *J Am Heart Assoc*. 2013; 2:e000395. [PubMed: 24002370]
8. Coffin ST, Black BK, Biaggioni I, Paranjape SY, Orozco C, Black PW, Dupont WD, Robertson D, Raj SR. Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome. *Heart Rhythm*. 2012; 9:1484–1490. [PubMed: 22561596]
9. Ross AJ, Ocon AJ, Medow MS, Stewart JM. A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural tachycardia syndrome. *Clin Sci (Lond)*. 2014; 126:289–296. [PubMed: 23978222]
10. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA*. 2003; 289:2224–2229. [PubMed: 12734133]
11. Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J Am Coll Cardiol*. 2007; 49:415–421. [PubMed: 17258086]
12. Linde C, Gadler F, Kappenberger L, Ryden L. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. PIC Study Group. *Pacing In Cardiomyopathy*. *Am J Cardiol*. 1999; 83:903–907. [PubMed: 10190407]
13. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombardi F, Pagani M, Malliani A. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation*. 1990; 81:537–547. [PubMed: 2297860]
14. Hossmann V, Fitzgerald GA, Dollery CT. Circadian rhythm of baroreflex reactivity and adrenergic vascular response. *Cardiovasc Res*. 1980; 14:125–129. [PubMed: 7397713]
15. Rubenstein JC, Freher M, Kadish A, Goldberger JJ. Diurnal heart rate patterns in inappropriate sinus tachycardia. *Pacing Clin Electrophysiol*. 2010; 33:911–919. [PubMed: 20353418]
16. Muller JE. Circadian variation and triggering of acute coronary events. *Am Heart J*. 1999; 137:S1–S8. [PubMed: 10097240]

17. Willich SN, Linderer T, Wegscheider K, Schroder R. Circadian variation in the incidence of myocardial infarction. New perceptions about the mechanisms of acute coronary disease. *Dtsch Med Wochenschr.* 1989; 114:613–617. [PubMed: 2651060]
18. Guo YF, Stein PK. Circadian rhythm in the cardiovascular system: chronocardiology. *Am Heart J.* 2003; 145:779–786. [PubMed: 12766733]
19. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol.* 2009; 20:352–358. [PubMed: 19207771]
20. Raj SR, Black BK, Biaggioni I, Harris PA, Robertson D. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation.* 2005; 111:2734–2740. [PubMed: 15911704]
21. Boyle K, Batzer FR. Is a placebo-controlled surgical trial an oxymoron? *J Minim Invasive Gynecol.* 2007; 14:278–283. [PubMed: 17478356]
22. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet.* 2010; 375:686–695. [PubMed: 20171404]
23. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol.* 2008; 59:565–590. [PubMed: 17550344]
24. Beecher HK. The powerful placebo. *J Am Med Assoc.* 1955; 159:1602–1606. [PubMed: 13271123]
25. Turner AS, Watson OF, Brocklehurst JE. Prazosin in hypertension. Part II. Effects of the initial dose. *N Z Med J.* 1977; 86:286–289. [PubMed: 343006]
26. Stefano GB, Fricchione GL, Slingsby BT, Benson H. The placebo effect and relaxation response: neural processes and their coupling to constitutive nitric oxide. *Brain Res Brain Res Rev.* 2001; 35:1–19. [PubMed: 11245883]
27. Wickramasekera I. A conditioned response model of the placebo effect predictions from the model. *Biofeedback Self Regul.* 1980; 5:5–18. [PubMed: 7370359]
28. Turton MB, Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. *Clin Chim Acta.* 1974; 55:389–397. [PubMed: 4412449]
29. Keller NR, Diedrich A, Appalsamy M, Tuntrakool S, Lonce S, Finney C, Caron MG, Robertson D. Norepinephrine transporter-deficient mice exhibit excessive tachycardia and elevated blood pressure with wakefulness and activity. *Circulation.* 2004; 110:1191–1196. [PubMed: 15337696]
30. Brewster JA, Garland EM, Biaggioni I, Black BK, Ling JF, Shibao CA, Robertson D, Raj SR. Diurnal variability in orthostatic tachycardia: implications for the postural tachycardia syndrome. *Clin Sci (Lond).* 2012; 122:25–31. [PubMed: 21751966]

Figure 1. Seated and standing changes in heart rate before and after No Drug vs. placebo

Heart rate (HR) data are presented immediately before (pre), and hourly for 4 hours (4H) following study drug administration for the No Drug day (solid circles) and the placebo day (open squares). Peak HR after standing (Fig 1A), and seated HR immediately before standing (Fig 1B) are shown. The error bars represent the standard error of the mean. The ANOVA P values are presented for the overall change in HR over time (P_{time}) and for the interaction between drugs (P_{int}). bpm, beats per minute.

Table 1

Clinical Characteristics of POTS Patients

Total Subjects (n)	21
Woman, (n)	17 (81%)
Age (years)	34 ± 11
Supine	
Heart Rate (beats/min)	74 ± 14
Systolic Blood Pressure (mmHg)	109 ± 10
Diastolic Blood Pressure (mmHg)	70 ± 10
Standing	
Heart Rate (beats/min)	124 ± 16 **
Systolic Blood Pressure (mmHg)	110 ± 17
Diastolic Blood Pressure (mmHg)	75 ± 12 *
Change from Supine to Standing	
Heart Rate (beats/min)	50 ± 11
Systolic Blood Pressure (mmHg)	1 ± 13
Diastolic Blood Pressure (mmHg)	6 ± 9

Data are presented as mean ± standard deviation. Reported P values are for paired t-test comparing supine and upright parameters.

**
P < 0.001;

*
P < 0.05

Table 2

Hemodynamic changes following placebo and no drug in POTS patients.

	Baseline	2 Hours	4 Hours	RM ANOVA (<i>P_{int}</i>)
Seated HR (beats/min)				
Placebo	82 ± 13	80 ± 15	78 ± 14	
No drug	86 ± 16	82 ± 16	82 ± 16	0.801
<i>P_{drug}</i>	0.609	0.730	0.783	
Standing HR (beats/min)				
Placebo	112 ± 14	107 ± 15	102 ± 16	
No drug	112 ± 13	101 ± 17	103 ± 16	0.214
<i>P_{drug}</i>	0.377	0.166	0.724	
Delta HR (beats/min)				
Placebo	29 ± 12	25 ± 16	24 ± 12	
No drug	26 ± 12	19 ± 16	21 ± 11	0.793
<i>P_{drug}</i>	0.123	0.260	0.884	
Seated SBP (mmHg)				
Placebo	102 ± 11	107 ± 14	104 ± 13	
No Drug	104 ± 13	103 ± 11	105 ± 16	0.164
<i>P_{drug}</i>	0.805	0.045	0.760	
Standing SBP (mmHg)				
Placebo	106 ± 14	110 ± 15	106 ± 20	
No drug	111 ± 12	111 ± 12	117 ± 15	0.147
<i>P_{drug}</i>	0.420	0.723	0.006	
Seated DBP (mmHg)				
Placebo	67 ± 7	72 ± 8	73 ± 7	0.830
No drug	69 ± 11	71 ± 9	72 ± 11	
<i>P_{drug}</i>	0.663	0.163	0.939	
Standing DBP (mmHg)				
Placebo	76 ± 8	78 ± 7	75 ± 11	0.212
No drug	77 ± 8	77 ± 10	78 ± 9	
<i>P_{drug}</i>	0.565	0.410	0.278	

Repeated- measures analysis of variance (RM ANOVA) was used to determine the p value for the overall change between No drug and Placebo. P values are reported for the interaction of study-drug effect over time (*P_{int}*). Comparisons between drugs (*P_{drug}*) were made with the paired t-test. Deltas were calculated as standing – seated values.

Data are presented as mean ± standard deviation. *P* < 0.05 was considered significant.

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.