Journal of the American Heart Association

ORIGINAL RESEARCH

Splanchnic Venous Compression Enhances the Effects of ß-Blockade in the Treatment of Postural Tachycardia Syndrome

Emily C. Smith, BSN, MPH; André Diedrich, MD, PhD; Satish R. Raj, MD, MSCI; Alfredo Gamboa, MD, MSCI; Cyndya A. Shibao, MD, MSCI; Bonnie K. Black, BSN, ANP; Amanda Peltier, MD, MS; Sachin Y. Paranjape, BS; Italo Biaggioni, MD; Luis E. Okamoto, MD

BACKGROUND: Splanchnic venous pooling induced by upright posture triggers a compensatory increase in heart rate (HR), a response that is exaggerated in patients with postural tachycardia syndrome. To assess whether abdominal compression attenuates orthostatic tachycardia and improves symptoms, 18 postural tachycardia syndrome patients (32±2 years) were randomized to receive either abdominal compression (40 mm Hg applied with an inflatable binder ≈2 minutes before standing) or propranolol (20 mg) in a placebo-controlled, crossover study.

METHODS AND RESULTS: Systolic blood pressure, HR, and symptoms were assessed while seated and standing, before and 2 hours postdrug. As expected, propranolol decreased standing HR compared with placebo (81±2 versus 98±4 beats per minute; $P<0.001$) and was associated with lower standing systolic blood pressure (93±2 versus 100±2 mm Hg for placebo; $P=0.002$). Compression had no effect on standing HR (96±4 beats per minute) but increased standing systolic blood pressure compared with placebo and propranolol (106±2 mm Hg; $P<0.01$). Neither propranolol nor compression improved symptoms compared with placebo. In 16 patients we compared the combination of abdominal compression and propranolol with propranolol alone. The combination had no additional effect on standing HR (81±2 beats per minute for both interventions) but prevented the decrease in standing systolic blood pressure produced by propranolol (98±2 versus 93±2 mm Hg for propranolol; $P=0.029$), and significantly improved total symptom burden (−6±2 versus −1±2 for propranolol; $P=0.041$).

CONCLUSIONS: Splanchnic venous compression alone did not improve HR or symptoms but prevented the blood pressure decrease produced by propranolol. The combination was more effective in improving symptoms than either alone. Splanchnic venous compression can be a useful adjuvant therapy to propranolol in postural tachycardia syndrome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00262470.

Key Words: abdominal binder ■ abdominal compression ■ postural tachycardia syndrome ■ propranolol ■ splanchnic circulation

See Editorial by Miller and Bourne

Postural tachycardia syndrome (POTS) is a chronic condition characterized by a sustained and excessive increase in heart rate (HR) in the upright position accompanied by persistent symptoms in the absence of orthostatic hypotension.[1,2] It is the most common form of orthostatic intolerance in young people, predominantly women, and can cause significant disability.[1,3,4] Multiple studies have documented low health-related quality of life in patients with POTS, comparable to those seen in heart failure patients.[5,6] It is important, therefore, to identify effective therapies that improve orthostatic tolerance and quality of life in these patients.

Correspondence to: Luis E. Okamoto, MD, 560A PRB, Vanderbilt University Medical Center, 2222 Pierce Ave, Nashville, TN 37232. E-mail: luis.e.okamoto@vumc.org

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016196

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This was a proof-of-concept study looking at the effect of abdominal compression on orthostatic tachycardia and symptoms in postural tachycardia syndrome.
- Abdominal compression, a common treatment recommendation, was not effective on its own in reducing orthostatic tachycardia or improving symptoms.
- However, when used in combination with the ß-blocker propranolol, abdominal compression prevented the decrease in blood pressure induced by the former, and improved upright symptoms.

What Are the Clinical Implications?

- Abdominal compression alone does not improve orthostatic tachycardia or symptoms in postural tachycardia syndrome, so this nonpharmacologic treatment may not be a good stand-alone recommendation.
- However, for those who are prescribed ß-blockers such as propranolol, the addition of abdominal compression may be superior in improving symptoms of postural tachycardia syndrome.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
HR	heart rate
POTS	postural tachycardia syndrome
SBP	systolic blood pressure

POTS is a heterogeneous condition associated with multiple pathophysiological mechanisms. In some patients, the orthostatic tachycardia is thought to be caused by a primary sympathetic activation, whereas in others it is thought to be secondary to chronic hypovolemia, partial sympathetic denervation in lower limbs, cardiovascular deconditioning, mast cell activation, or autoimmunity.[7–12] Regardless of the primary pathophysiologic mechanism, the upright posture induces gravitational pooling of blood in the veins of the lower body, particularly in the splanchnic vascular bed where most of the orthostatic venous pooling normally occurs,[13] resulting in decreased venous return and stroke volume, unloading of baroreceptors, and compensatory sympathetic activation that ultimately triggers the orthostatic tachycardia.

Thus, compression of venous capacitance beds in the abdomen or lower body with compression garments has been widely recommended as a nonpharmacologic approach for the treatment of POTS, alone and in combination with drug therapy, to attenuate orthostatic venous pooling,[1,4,14–17] particularly in the splanchnic capacitance bed where excessive pooling has been reported in some POTS patients.[18,19] This recommendation, however, is mostly based on studies conducted in patients with neurogenic orthostatic hypotension, microgravity-associated orthostatic intolerance (postspaceflight), and in orthostatically intolerant athletes.[15,20–27] We are aware of only 1 study showing that lower body compression (20–40 mm Hg) with an antishock garment decreased standing HR and improved orthostatic symptoms in young patients with POTS (13–19 years).[28] The efficacy of splanchnic venous compression with abdominal binders, arguably a more accepted form of compression therapy among patients,[29] is not known.

Thus, we designed this study with 2 objectives: (1) to assess whether abdominal compression attenuates tachycardia and improves orthostatic symptoms in POTS compared with placebo and propranolol; and (2) to assess whether the combination of abdominal compression and propranolol has additional beneficial effects in these patients compared with propranolol alone.

METHODS

The data that support the findings of this study will be made available by the corresponding author to any researcher upon reasonable request.

Subjects

We studied a total of 19 female patients with POTS recruited from referrals to the Vanderbilt University Autonomic Dysfunction Center with POTS between March 2012 and April 2013. Fifteen patients participated in studies for both the primary and secondary objectives, 3 participated only in studies for the primary objective, and 1 participated only in studies for the secondary objective. A diagnosis of POTS was based on ≥6-month history of orthostatic symptoms accompanied by a HR increase of ≥30 beats per minute (bpm) within 10 minutes of standing, in the absence of orthostatic hypotension (defined as a decrease in blood pressure [BP] ≥20/10 mm Hg) or alternative conditions known to cause postural tachycardia such as acute dehydration, prolonged bed rest, or medications.[1,2] All patients were ≥18 years of age, and were excluded if they were bedridden, unable to tolerate stopping their POTS medications for these studies, or had contraindications to any increase in intra-abdominal pressure (eg, severe gastroesophageal reflux). The Vanderbilt University Institutional Review board approved this study, and

written informed consent was obtained from each subject before initiating the study. The data reported are a part of "The Treatment of Orthostatic Intolerance" study (http://www.clinicaltrials.gov; unique identifier: NCT00262470), which assessed the efficacy of several interventions for the treatment of orthostatic intolerance in POTS.

Screening Procedures

Patients were admitted to the Vanderbilt Clinical Research Center and were fed a methylxanthine-free diet containing 150-mEq sodium and 70-mEq potassium per day. Medications affecting the autonomic nervous system, BP, HR, and blood volume were discontinued for ≥5 half-lives before admission. All other medications were held constant during admission. All participants had a medical history, physical examination, 12-lead ECG, laboratory assessments, and standardized autonomic function tests including a 30-minute orthostatic stress test.[30] BP and HR were obtained intermittently using an automated oscillometric sphygmomanometer (Dinamap ProCare, GE Healthcare) and continuously with a finger photoplethysmographic volume-clamp BP device (Finometer, FMS, or Nexfin, BMEYE). HR was measured by continuous ECG. During the 30-minute orthostatic stress test, blood samples were obtained for norepinephrine and epinephrine while patients were supine and upright, as described previously.[31] If the participant was unable to stand for 30 minutes, samples were obtained when the participant had to sit down. Plasma catecholamines were measured by high-performance liquid chromatography with electrochemical detection.[32]

General Protocol

Patients were studied on separate days in a randomized, crossover manner. For the primary objective, patients received either a single oral dose of placebo, propranolol 20 mg (Mylam Pharmaceuticals, Morgantown, WV), or placebo combined with abdominal compression (40 mm Hg). For the secondary objective, they received propranolol 20 mg combined with abdominal compression (40 mm Hg) and propranolol 20 mg alone. This dose of propranolol has been previously shown to effectively attenuate tachycardia and improve orthostatic symptoms in patients with POTS, while higher doses (80 mg) showed no further improvement or may even worsen symptoms.[31] The order of interventions was randomized using computer-generated random numbers. Medications were blinded to patients. We chose an abdominal compression level of 40 mm Hg based on previous studies in healthy volunteers and patients with neurogenic orthostatic hypotension, showing that this level of compression was safe, tolerable, and produced selective venous compression with no effect on total peripheral resistance or aortic blood flow, resulting in a decrease of splanchnic blood volume, a shift of blood to the thorax and improvement in upright stroke volume, cardiac output and BP compared with lower compression levels (10–20 mm Hg).[20–22,33–38]

Acute trials were done in a postvoid state and ≥2 hours after meals to avoid any acute hemodynamic effects from eating. Participants were seated comfortably in a chair for the duration of the data collection except during the prescribed periods of standing. BP and HR were recorded every 10 minutes with an automated brachial BP cuff (Dinamap ProCare, GE Healthcare). After 30 minutes of baseline measurements, patients were asked to stand for up to 10 minutes or as tolerated. BP and HR were measured at 1, 3, 5, and 10 minutes of standing (or as tolerated). The amount of time patients were able to stand was recorded by the study nurse using a timer. Immediately after sitting, the study medication was given and, on the study days with abdominal compression, an inflatable binder was placed (deflated) around the abdomen to allow participants to adjust to the presence of the binder. BP and HR were measured for the next 2 hours. At the end of this period, the binder was inflated to 40 mm Hg 1 to 2 minutes before standing, and the 10-minute assessment of orthostatic tolerance was then repeated as described above. The 2-hour time point was chosen because the peak effect of propranolol occurs at 90 minutes after a dose.[31] The time taken to inflate or deflate the bladder was <30 seconds.

Orthostatic symptoms were assessed immediately after the orthostatic tolerance tests using the Vanderbilt Orthostatic Symptoms Scale.[31,39] This scale allows patients to self-report the severity of 9 symptoms on an analog visual scale from 0 (symptom not experienced) to 10. The symptoms assessed were mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea. The sum of the scores for each of the 9 symptoms reflects the total symptoms burden. A total score of 0 would indicate no symptoms, while a score of 90 would indicate maximum severity of all symptoms. In a subset of participants, we further tested the acute effects of abdominal compression by deflating the binder at the end of the postintervention orthostatic tolerance test. Standing BP and HR were recorded for 1 more minute with the binder deflated while the subject remained upright.

Abdominal Compression With an Inflatable Binder

We applied external abdominal compression using a commercially available abdominal band or lumbar support garment made of polyester cloth with adjustable Velcro, and an inflatable cuff (commercially available

BP cuff) placed underneath. The binder was attached to patients around the abdomen with the inflatable bladder placed at the level of the umbilicus. The inflatable bladder was pressurized by a commercial inflator (Rapid Cuff Inflator E20, D.E. Hockason, Inc., Bellevue, WA) and air pump (AG101 Air Source, D.E. Hockason, Inc.) located in a cart next to the patient. The inflator was manually activated to provide a servo-controlled compression level of ≈40 mm Hg <2 minutes before the postintervention orthostatic tolerance test. The time taken to inflate or deflate the bladder was <30 seconds.

Study Objectives and Statistical Analysis

Our primary objective was to compare the effects of abdominal compression on upright HR, BP, and orthostatic symptoms with that of placebo and propranolol. The primary outcome was the maximum upright HR during the stand period at 2 hours postintervention. Secondary outcomes included total and individual orthostatic symptom scores, mean upright systolic BP (SBP), seated SBP and HR, and orthostatic changes in SBP and HR (defined as the difference between standing and seated positions) before and at 2 hours postintervention. Overall differences in the outcome measurements among treatment groups were analyzed using 2-way repeated-measures ANOVA with Greenhouse-Geisser corrected *P* value reported if variance was unequal. If a significant overall treatment difference was found, paired comparisons between treatment groups and between timepoints within groups were performed using paired *t* tests with Bonferroni correction as a post hoc test.

Our secondary objective was to compare the effects on outcome measurements between abdominal compression combined with propranolol and propranolol alone. Differences between treatment groups and between timepoints within groups were analyzed by paired *t* tests. Wilcoxon signed-rank test was used to assess changes from baseline in orthostatic symptom scores between treatment groups. Power calculation was based on previous studies and preliminary data from 5 patients. The difference in standing HR between placebo and propranolol after 2 hours of drug administration was of –17 bpm, with standard deviation of difference of 7 bpm. Assuming a minimally clinically significant effect size of 5 bpm with similar variance,[39,40] a sample size of 18 patients would have 90% power to detect a difference in mean values between treatments in the primary objective and 86% power with a sample size of 16 patients in the secondary objective, with an α level of 0.05 using paired *t* test analysis (PS Dupont, version 3.0.34). Data followed an approximately normal distribution as assessed visually with histograms and Q-Q plots. Levene's test was used to assess the variance between groups for the repeated-measures ANOVAs and paired *t* tests. Data are presented as mean±SEM unless otherwise noted. All of the tests were 2-tailed, and a *P* value of <0.05 was considered significant. Analyses were performed with Stata version 14.2.

Table 1. Patient Characteristics

Measurement	All Participants (n=19)
Age, y	32±2
Body mass index, kg/m^2	23.6±0.9
Supine	
Heart rate, bpm	69±2
Systolic blood pressure, mm Hg	103±1
Diastolic blood pressure, mm Hg	63±2
Norepinephrine, pg/mL	159±15
Standing	
Heart rate, bpm	114±5*
Systolic blood pressure, mm Hg	111±4†
Diastolic blood pressure, mm Hg	72±3*
Norepinephrine, pg/mL	759±89*
Orthostatic change (standing–seated)	
Heart rate, bpm	44±4
Systolic blood pressure, mm Hg	8±3
Diastolic blood pressure, mm Hg	9±3
Norepinephrine, pg/mL	599±79

Data are presented as mean±SEM. bpm indicates beats per min.
*P<0.001 and †P<0.05 vs supine values.

RESULTS

Patient Characteristics

We studied a total of 19 female patients with POTS (age 32±2 years, body mass index 24±1 kg/m^2): 18 patients completed the 3 treatment arms of the primary objective (placebo, propranolol, and placebo combined with abdominal compression) and 16 patients completed the 2 treatment arms of the secondary objective (propranolol and propranolol combined with abdominal compression).

Demographic data and supine and standing parameters of all participants are presented in Table 1. There were no differences in any of these parameters between patients participating in studies related to the primary or secondary objectives. On standing, patients had a similar significant increase in HR (primary objective 44±5 bpm and secondary objective 46±4 bpm; *P*=0.843 between groups), and plasma norepinephrine (primary objective 614±83 pg/mL, and secondary objective 642±83 pg/mL; *P*=0.817 between groups) consistent with POTS. Standing systolic and diastolic

BP also increased similarly in both groups (primary objective 8±4/9±3 mm Hg and secondary objective 7±3/9±3 mm Hg; *P*=0.847 for SBP and *P*=0.988 for diastolic BP between groups).

Primary Objective: Effects of Abdominal Compression Versus Placebo and Propranolol on Orthostatic Hemodynamics and Symptoms

Baseline seated and standing HRs and the orthostatic changes were similar among treatment groups (Table 2), suggesting that no significant carryover effects were present between study days. Two hours after drug administration, seated HR significantly decreased with propranolol (65±2 bpm) compared with placebo (76±3 bpm; *P*<0.001) and binder (77±3; *P*<0.001; *P*<0.001 for drug×time interaction, 2-way repeated-measures ANOVA). As expected, the binder and placebo groups had similar seated HRs given that the binder was deflated while patients were seated. Standing HR at 2 hours decreased in the 3 treatment groups compared with their respective baseline values (placebo –11±2 bpm, binder –14±3 bpm, and propranolol –25±2 bpm; *P*<0.001 versus baseline for all groups and for time effects, 2-way repeated-measures ANOVA; Table 2; Figure 1A and Figure S1A), but only propranolol had lower standing HR compared with placebo (81±2 versus 98±4 bpm, respectively; *P*<0.001 versus placebo; *P*<0.001 for drug×time interaction, 2-way repeated-measures ANOVA). Standing HR did not differ between placebo and binder groups (96±4 bpm; *P*=1.0). Similarly, the orthostatic HR increase was significantly lower in all groups compared with baseline values (placebo *P*=0.005; binder *P*=0.001; propranolol *P*<0.001; Table 2), but only propranolol had a trend toward a lower orthostatic HR increase compared with placebo (16±2 versus 22±3 bpm, respectively; *P*=0.083), whereas the binder did not (19±3 bpm; *P*=0.813).

Seated and standing SBPs and the orthostatic changes at baseline were similar in the 3 treatment groups (Table 2). Two hours postdrug, there was no statistically significant effect on seated SBP with any of the 3 interventions, but propranolol tended to have lower seated SBPs (placebo 97±2 mm Hg, abdominal binder deflated 99±2 mm Hg, and propranolol 94±2 mm Hg). On standing, abdominal compression with the binder significantly increased upright SBP compared with placebo (106±2 versus 100±2 mm Hg, respectively; *P*=0.004 versus placebo) and propranolol (93±2 mm Hg; *P*<0.001; *P*<0.001 for drug×time interaction, 2-way repeated-measures ANOVA; Table 2; Figure 1B and Figure S1B). Propranolol, on the other hand, had a significantly lower standing SBP compared with placebo (*P*=0.002). Two hours postintervention, SBP rose similarly upon standing with placebo and abdominal compression (3±2 and 7±2 mm Hg; *P*=0.261),

Table 2. Effect of Abdominal Compression, Propranolol, and Placebo on Orthostatic Hemodynamics

Measurement	Placebo	Abdominal Compression	Propranolol
Heart rate, bpm			
Baseline			
Seated	79±2	80±3	80±3
Standing	109±3	111±5	106±3
Orthostatic change	30±2	31±3	26±2
2 h postdrug			
Seated	76±3	77±3†	65±2*
Standing	98±4	96±4†	81±2*
Orthostatic change	22±3	19±3	16±2
Systolic BP, mm Hg			
Baseline			
Seated	97±2	99±2	98±2
Standing	98±2	101±2	100±2
Orthostatic change	1±2	2±2	2±2
2 h postdrug			
Seated	97±2	99±2	94±2
Standing	100±2	106±2†*	93±2*
Orthostatic change	3±2	7±2†	0±2

Data are presented as mean±SEM. The abdominal compression was applied immediately before standing at 2 hours postdrug. Orthostatic changes were determined as the difference between standing and seated positions. Overall differences between treatment groups were analyzed by 2-way repeated-measures ANOVA. BP indicates blood pressure; and bpm, beats per min.

*P<0.05 vs placebo, †P<0.05 vs propranolol, adjusted for multiple comparisons using Bonferroni correction.

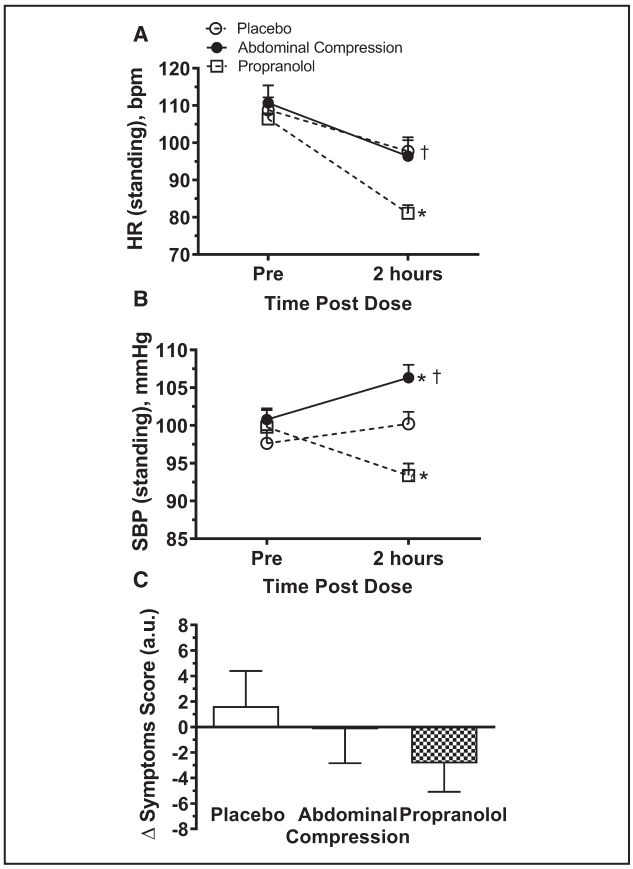


Figure 1. Effect of placebo, abdominal compression, and propranolol on upright HR, blood pressure, and orthostatic symptoms.

Standing HR (**A**), and SBP (**B**) at baseline (Pre) and 2 hours after placebo, abdominal compression 40 mm Hg (applied immediately before standing), and propranolol 20 mg (primary objective). **C**, Changes from baseline in total orthostatic symptoms score (a.u.). A negative change in score reflects a reduction in orthostatic symptom burden. Values are expressed as mean±SEM. Overall differences were analyzed by 2-way repeated-measures ANOVA. **P*<0.05 vs placebo and †*P*<0.05 vs propranolol, adjusted for multiple comparisons using Bonferroni correction. a.u. indicates arbitrary units; HR, heart rate; and SBP, systolic blood pressure.

but not with propranolol (0±2 mm Hg; *P*=0.029 versus abdominal compression; *P*=0.036 for treatment effect, 2-way repeated-measures ANOVA).

Of the 18 participants, 17 completed orthostatic symptom scores for all treatment arms; 1 patient had missing questionnaires during the abdominal compression arm. Total orthostatic symptom burden at baseline was similar among treatment groups (placebo 23±4, binder 22±3, and propranolol 27±4; *P*=0.305 by repeated-measures ANOVA). Two hours after the intervention, propranolol decreased total symptom burden (–3±2) but this effect was not statistically different from the changes from baseline in total symptom burden produced by placebo or abdominal compression (placebo 2±3 and binder 0±3; *P*=0.477 by repeated-measures ANOVA; Figure 1C and Figure S1C). The improvement in overall symptom score with propranolol was driven by a greater decrease in palpitations compared with placebo and abdominal compression, but the difference did not reach statistical significance (*P*=0.064; Figure S2).

Secondary Objective: Effects of Abdominal Compression in Combination With Propranolol Versus Propranolol Alone on Orthostatic Hemodynamics and Symptoms

Baseline seated and standing HRs and the orthostatic changes were not different between treatment groups (Table 3). As expected, propranolol alone and propranolol combined with the abdominal binder deflated produced a similar decrease from baseline in seated HR at 2 hours postdrug (*P*<0.001 versus baseline in both groups; *P*=0.783 between groups). Similarly, on standing, the binder combined with propranolol and propranolol alone decreased upright HR and the orthostatic change in HR compared with their respective baseline values (*P*<0.001 versus baseline standing HR in both groups and *P*<0.01 versus baseline orthostatic HR changes in both groups; Table 3; Figure 2A and Figure S3A), but there were no differences between

Table 3. Effect of Abdominal Compression Combined With Propranolol and Propranolol Alone on Orthostatic Hemodynamics

Measurement	Propranolol	Abdominal Compression With Propranolol
Heart rate, bpm		
Baseline		
Seated	81±3	82±3
Standing	106±4	110±4
Orthostatic change	25±2	29±3
2 h postdrug		
Seated	65±2	65±2
Standing	81±2	81±2
Orthostatic change	16±2	16±1
Systolic BP, mm Hg		
Baseline		
Seated	98±2	103±2
Standing	100±3	101±2
Orthostatic change	2±2	–3±2
2 h postdrug		
Seated	93±2	93±1
Standing	93±2	98±2*
Orthostatic change	1±2	5±2

Data are presented as mean±SEM. The abdominal compression was applied immediately before standing at 2 hours postdrug. Orthostatic changes were determined as the difference between standing and seated positions. BP indicates blood pressure; and bpm, beats per min.

**P*=0.029 vs propranolol.

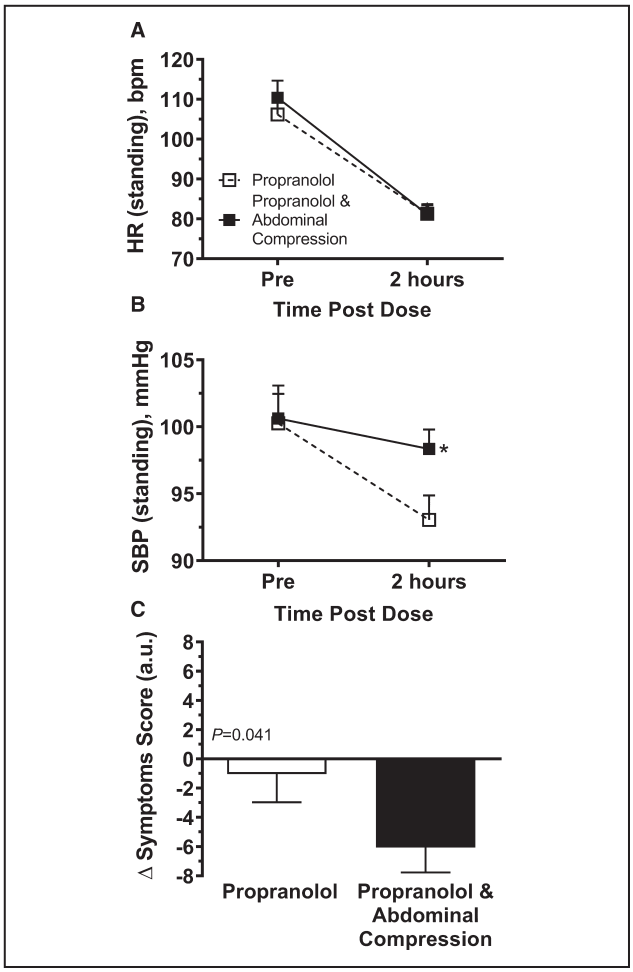


Figure 2. Effect of propranolol alone and the combination of abdominal compression and propranolol on upright HR, blood pressure, and orthostatic symptoms.
Standing HR (**A**), and SBP (**B**) at baseline (Pre) and 2 hours after propranolol 20 mg alone and after the combination of abdominal compression 40 mm Hg (applied immediately before standing) with propranolol 20 mg (secondary objective). **C**, Changes from baseline in total orthostatic symptoms score (a.u.). A negative change in score reflects a reduction in orthostatic symptom burden. Values are expressed as mean±SEM. **P*=0.029 vs propranolol. a.u. indicates arbitrary units; bpm, beats per minute; HR, heart rate; and SBP, systolic blood pressure.

treatment groups (*P*=0.946 between groups for standing HR and *P*=0.762 between groups for orthostatic HR changes), suggesting no additive effects of the abdominal compression on HR.

Baseline seated and standing SBPs and the orthostatic changes were similar in the 2 treatment groups (Table 3). Two hours after drug administration, seated SBP decreased similarly with propranolol alone and propranolol combined with the binder deflated (93±2 and 93±1 mm Hg, respectively; *P*=0.024 versus baseline for propranolol, and *P*=0.004 versus baseline for the combination and *P*=0.728 between groups). On standing, however, abdominal compression with the binder combined with propranolol significantly increased upright SBP compared with propranolol alone (98±2 versus 93±2 mm Hg, respectively; *P*=0.029 between groups; Table 3; Figure 2B and Figure S3B), and produced a significant increase from baseline in the orthostatic change in SBP at 2 hours postdrug (5±2 mm Hg; *P*=0.011 versus baseline), whereas propranolol alone did not (1±2 mm Hg; *P*=0.574).

To further assess the acute effects of the abdominal compression, we deflated the binder in a subset of patients (n=10) while they were still standing, and measured BP and HR for an additional minute (Figure S4). Standing SBP decreased significantly after releasing the abdominal compression (from 101±3 mm Hg with the binder inflated to 95±2 mm Hg with the binder deflated; *P*=0.013), to similar levels as those with propranolol alone (95±3 mm Hg; *P*=0.242), whereas HR did not change (80±3 bpm with the binder inflated and deflated; *P*=0.927).

Orthostatic symptom scores were obtained for all treatment arms in 15 participants; 1 patient had missing questionnaires during the combination arm. At baseline, total orthostatic symptom burden was similar between groups (20±4 for both groups; *P*=0.691). Two hours postdrug, the combination of abdominal compression and propranolol significantly decreased total symptom burden compared with propranolol alone (−6±2 versus −1±2, respectively; *P*=0.041; Figure 2C and Figure S3C). The individual symptoms that contributed more to the improvement in overall symptoms score with the combination were lightheadedness (*P*=0.045), blurred vision (*P*=0.055), and shortness of breath (*P*=0.014; Figure S5), whereas palpitations had a similar decrease in both groups (*P*>0.999). Interestingly, we found that standing SBP (at 3 minutes) with propranolol alone was negatively correlated with total symptom burden (*P*=0.011, *r*=−0.63), indicating that patients with lower standing SBP with propranolol were more symptomatic.

Adverse Events

All participants in both study objectives tolerated well the abdominal compression. None of them reported local pain, discomfort, or requested to lower the compression level. No other adverse events were noted.

DISCUSSION

The main findings of this study were that splanchnic venous compression alone had no effect on standing HR or orthostatic symptoms in patients with POTS, but it increased standing BP. More important, splanchnic venous compression was able to prevent the decrease in standing BP produced by propranolol and provided additional improvement in orthostatic

symptoms compared with propranolol alone. Our results also confirmed the efficacy of low-dose propranolol in reducing orthostatic tachycardia in POTS. This was associated, however, with a small but consistent decrease in seated and standing BPs, and we were not able to document a significant improvement in orthostatic symptoms with propranolol. We propose that splanchnic venous compression can be a useful adjuvant therapy to propranolol in POTS.

The splanchnic circulation is the largest blood volume reservoir of the human body; it normally stores ≈25% of the blood volume at rest,[41] and receives ≤25% of the resting cardiac output.[42] On standing, most of the venous pooling normally occurs in splanchnic veins, given the large capacity of the abdomen relative to the legs,[13] but sympathetically mediated arterial- and venoconstriction of this vascular bed prevents excessive reduction of venous return and stoke volume to maintain normotension. Thus, the autonomic regulation of splanchnic capacitance plays a major role in the maintenance of orthostatic tolerance, as is evident in patients with autonomic failure and severe orthostatic hypotension, who cannot engage these sympathetically mediated hemodynamic responses on standing. In these patients, we and others have shown that splanchnic venous compression of 40 mm Hg with abdominal binders increased upright BP and improved orthostatic symptoms by increasing stroke volume and cardiac output,[20,21] with a pressor effect similar to that of pressor agents.[43]

The role of splanchnic capacitance regulation in the pathophysiology of POTS is less clear. Previous studies have shown excessive splanchnic blood pooling during head up tilt in some, but not all, patients with POTS.[18,19] Thus, we can speculate that splanchnic venous compression would only be effective in POTS patients with abnormal contraction of splanchnic capacitance on standing. In the present study, we found that abdominal compression did not improve standing HR or orthostatic symptoms (Figure 1). We did observe a lower upright HR 2 hours after placebo or abdominal compression that can be explained by a placebo effect and/or the normal diurnal variability in orthostatic tachycardia, which we have previously shown was worse early in the morning and spontaneously improved during the day.[44,45] It could be argued that abdominal compression did not improve standing HR because our level of compression was not effective in preventing splanchnic venous pooling. We found, however, that abdominal compression significantly increased standing SBP when applied alone or in combination with propranolol. Moreover, deflation of the binder in the combination group acutely decreased standing SBP to levels similar to those seen with propranolol alone (Figure S4A), supporting the notion that the compression effectively reduced splanchnic capacitance. Taken together, these results suggest that excessive splanchnic venous pooling is not a significant contributor to the orthostatic tachycardia in this cohort of patients, but splanchnic venous compression prevents the decrease in BP induced by propranolol.

On the other hand, we confirmed our previous findings that a low dose of propranolol (20 mg) acutely reduced orthostatic tachycardia.[31] Palpitations and total symptom burden tended to improve with propranolol, but unlike our previous studies,[31] these changes did not reach statistical significance compared with placebo. The reasons for this apparent discrepancy are not clear, but it seems likely that we would need to study a larger number of patients to detect a statistically significant improvement in symptoms with propranolol alone than what we needed to show the same effect with the combination of propranolol and the binder. It is worth noting, however, that even this low dose of propranolol significantly reduced seated and standing SBP in these patients, similar to our observations in previous studies.[31] We speculate that this small but significant decrease in upright BP partially counteracted its beneficial symptomatic benefit. In support of this, several studies have shown that the dynamic and static regulation of cerebral blood flow during orthostasis is less effective in POTS patients compared with healthy controls, resulting in lower cerebral blood flow velocity despite normal BP and greater variability in cerebral blood flow velocity that is nearly perfectly synchronous with the oscillations in upright BP.[46–48] This is consistent with our finding that patients with lower standing SBP with propranolol had a higher total symptom burden. More important, the addition of abdominal compression to propranolol prevented the decrease in upright BP induced by propranolol, and significantly improved total symptom burden, even though this combination did not provide a greater improvement in orthostatic tachycardia than that afforded by propranolol alone.

There are some potential limitations to this study. First, the effects of abdominal compression were tested during an acute standing test, and long-term trials are required to assess the clinical efficacy and tolerability of the combination. Second, a sham binder was not used as a control because adequate blinding of patients wearing a sham device would require a parallel study design. We chose a crossover design rather than a sham-controlled parallel study to minimize the effects of potential interindividual variations in POTS pathophysiology. To compensate for this limitation, we further tested the acute effects of the abdominal compression in combination with propranolol by deflating the binder at the end of the orthostatic tolerance test. Our finding that abdominal

decompression acutely decreased standing BP to levels similar to those observed with propranolol alone (Figure S4A) suggested that the pressor effect was caused by a reduction in splanchnic capacitance. Third, we cannot exclude that an "arousal" effect caused by discomfort associated with abdominal compression could have contributed to its pressor effect. Sympathetic activation caused by arousal associated with the cold pressor or mental stress tests, however, results in an increase in both BP and HR in POTS.[7,49] We found that abdominal compression increased standing BP but not HR, suggesting that an arousal effect, if present, played a minor role in the pressor response to the binder. Fourth, given the lack of a sham control, it could be argued that the improvement in symptoms seen with the combination might have been because of a placebo effect. This seems unlikely given that abdominal compression combined with propranolol, but not the compression alone, improved symptoms. Finally, POTS is considered a heterogeneous disease, and it is possible that abdominal compression or propranolol, alone or in combination, may be preferentially effective in a subset of patients. Our study was too small to determine criteria that predict response to these treatments.

In summary, abdominal compression increased standing BP but did not improve orthostatic tachycardia or symptoms in POTS. The addition of abdominal compression to propranolol prevented the decrease in upright BP that we observed with even low doses of propranolol. More important, the combination was more effective in improving orthostatic symptoms than propranolol alone, suggesting that the symptomatic improvement with propranolol was blunted by its BP-lowering effects. Further research is needed to define whether there is a subset of patients more likely to benefit from either treatment alone, and to determine the long-term efficacy and tolerability of combined treatment with propranolol and abdominal compression in the management of POTS.

ARTICLE INFORMATION

Received February 7, 2020; accepted May 8, 2020.

Affiliations

From the Vanderbilt Autonomic Dysfunction Center (E.C.S., A.D., S.R.R., A.G., C.A.S., B.K.B., A.P., S.Y.P., I.B., L.E.O.), Vanderbilt Heart and Vascular Institute (A.P.), Division of Clinical Pharmacology (E.C.S., A.D., S.R.R., A.G., C.A.S., B.K.B., S.Y.P., I.B., L.E.O.), and Departments of Medicine (E.C.S., A.D., S.R.R., A.G., C.A.S., B.K.B., S.Y.P., I.B., L.E.O.), Pharmacology (I.B.), Neurology (A.P.), and Biomedical Engineering (A.D.), Vanderbilt University School of Medicine, Nashville, TN; Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Canada (S.R.R.).

Acknowledgments

We acknowledge the patients who volunteered for these studies and the Clinical Research Center nurses who made this study possible.

Sources of Funding

This work was supported by National Institutes of Health (NIH) grants R01 HL144568, PO1 HL56693, U54 NS065736, R01 HL122847, and UL1 TR000445 (National Center for Advancing Translational Sciences). Additional support was provided by American Heart Association grant 14CRP20380211 (Okamoto) and NIH RO1 HL142583 (Diedrich). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the NIH.

Disclosures

Okamoto, Diedrich, and Biaggioni have a US patent for the use of an automated inflatable abdominal binder as a medical device for the treatment of orthostatic hypotension. The remaining authors have no disclosures to report.

Supplementary Materials

Figures S1–S5

REFERENCES

1. Sheldon RS, Grubb BP, Olshansky B, Shen W-K, Calkins H, Brignole M, Raj SR, Krahn AD, Morillo CA, Stewart JM, et al. 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;12:e41–e63.
2. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci*. 2011;161:46–48.
3. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci*. 1999;317:75–77.
4. Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome—diagnosis, physiology, and prognosis. *Auton Neurosci*. 2018;215:3–11.
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.
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.
7. Jacob G, Costa F, Shannon JR, Robertson RM, Wathen M, Stein M, Biaggioni I, Ertl A, Black B, Robertson D. The neuropathic postural tachycardia syndrome. *N Engl J Med*. 2000;343:1008–1014.
8. Raj SR, Biaggioni I, Yamhure PC, Black BK, Paranjape SY, Byrne DW, Robertson D. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation*. 2005;111:1574–1582.
9. Low PA, Sandroni P, Joyner M, Shen W-K. Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol*. 2009;20:352–358.
10. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, Lennon VA, Shen W-K, Low PA. Postural orthostatic tachycardia syndrome: the Mayo Clinic experience. *Mayo Clin Proc*. 2007;82:308–313.
11. Shibao C, Arzubiaga C, Roberts LJ, Raj S, Black B, Harris P, Biaggioni I. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension*. 2005;45:385–390.
12. Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, Zillner C, Benbrook A, Reim S, Collier D, et al. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc*. 2014;3:e000755. DOI: 10.1161/JAHA.113.000755.
13. Diedrich A, Biaggioni I. Segmental orthostatic fluid shifts. *Clin Auton Res*. 2004;14:146–147.
14. Bryarly M, Phillips LT, Fu Q, Vernino S, Levine BD. Postural orthostatic tachycardia syndrome: JACC focus seminar. *J Am Coll Cardiol*. 2019;73:1207–1228.
15. Fu Q, Levine BD. Exercise and non-pharmacological treatment of POTS. *Auton Neurosci*. 2018;215:20–27.
16. Cutsforth-Gregory JK, Sandroni P. Clinical neurophysiology of postural tachycardia syndrome. *Handb Clin Neurol*. 2019;161:429–445.
17. Lei LY, Chew DS, Sheldon RS, Raj SR. Evaluating and managing postural tachycardia syndrome. *Cleve Clin J Med*. 2019;86:333–344.

18. Stewart JM, Medow MS, Glover JL, Montgomery LD. Persistent splanchnic hyperemia during upright tilt in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2006;290:H665–H673.
19. Tani H, Singer W, McPhee BR, Opfer-Gehrking TL, Haruma K, Kajiyama G, Low PA. Splanchnic-mesenteric capacitance bed in the postural tachycardia syndrome (POTS). *Auton Neurosci*. 2000;86:107–113.
20. Smit AAJ, Wieling W, Fujimura J, Denq JC, Opfer-Gehrking TL, Akarriou M, Karemaker JM, Low PA. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. *Clin Auton Res*. 2004;14:167–175.
21. Denq JC, Opfer-Gehrking TL, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelioration of orthostatic hypotension. *Clin Auton Res*. 1997;7:321–326.
22. Figueroa JJ, Singer W, Sandroni P, Sletten DM, Gehrking TL, Gehrking JA, Low P, Basford JR. Effects of patient-controlled abdominal compression on standing systolic blood pressure in adults with orthostatic hypotension. *Arch Phys Med Rehabil*. 2015;96:505–510.
23. Platts SH, Tuxhorn JA, Ribeiro LC, Stenger MB, Lee SMC, Meck JV. Compression garments as countermeasures to orthostatic intolerance. *Aviat Space Environ Med*. 2009;80:437–442.
24. Stenger MB, Brown AK, Lee SMC, Locke JP, Platts SH. Gradient compression garments as a countermeasure to post-spaceflight orthostatic intolerance. *Aviat Space Environ Med*. 2010;81:883–887.
25. Stenger MB, Lee SMC, Westby CM, Ribeiro LC, Phillips TR, Martin DS, Platts SH. Abdomen-high elastic gradient compression garments during post-spaceflight stand tests. *Aviat Space Environ Med*. 2013;84:459–466.
26. Stenger MB, Lee SMC, Ribeiro LC, Phillips TR, Ploutz-Snyder RJ, Willig MC, Westby CM, Platts SH. Gradient compression garments protect against orthostatic intolerance during recovery from bed rest. *Eur J Appl Physiol*. 2014;114:597–608.
27. Privett SE, George KP, Whyte GP, Cable NT. The effectiveness of compression garments and lower limb exercise on post-exercise blood pressure regulation in orthostatically intolerant athletes. *Clin J Sport Med*. 2010;20:362–367.
28. Heyer GL. Abdominal and lower-extremity compression decreases symptoms of postural tachycardia syndrome in youth during tilt table testing. *J Pediatr*. 2014;165:395–397.
29. Robinson LJ, Pearce RM, Frith J. Acceptability of non-drug therapies in older people with orthostatic hypotension: a qualitative study. *BMC Geriatr*. 2018;18:69.
30. Okamoto LE, Raj SR, Gamboa A, Shibao CA, Arnold AC, Garland EM, Black BK, Farley G, Diedrich A, Biaggioni I. Sympathetic activation is associated with increased IL-6, but not CRP in the absence of obesity: lessons from postural tachycardia syndrome and obesity. *Am J Physiol Heart Circ Physiol*. 2015;309:H2098–H2107.
31. Raj SR, Black BK, Biaggioni I, Paranjape SY, Ramirez M, Dupont WD, Robertson D. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation*. 2009;120:725–734.
32. Goldstein DS, Eisenhofer G, Stull R, Folio CJ, Keiser HR, Kopin IJ. Plasma dihydroxyphenylglycol and the intraneuronal disposition of norepinephrine in humans. *J Clin Invest*. 1988;81:213–220.
33. Sieker HO, Burnum JF, Hickam JB, Penrod KE. Treatment of postural hypotension with a counter-pressure garment. *J Am Med Assoc*. 1956;161:132–135.
34. Stanford W. Use of an air force antigravity suit in a case of severe postural hypotension. *Ann Intern Med*. 1961;55:843–845.
35. Elizondo LL, Doerr DF, Sims MA, Hoffler GW, Convertino VA. Application of USAF G-suit technology for clinical orthostatic hypotension: a case study. *Aviat Space Environ Med*. 1996;67:344–350.
36. Tanaka H, Yamaguchi H, Tamai H. Treatment of orthostatic intolerance with inflatable abdominal band. *Lancet*. 1997;349:175.
37. Wangensteen SL, Ludewig RM, Eddy DM. The effect of external counterpressure on the intact circulation. *Surg Gynecol Obstet*. 1968;127:253–258.
38. Hauswald M, Greene ER. Aortic blood flow during sequential MAST inflation. *Ann Emerg Med*. 1986;15:1297–1299.
39. Green EA, Black BK, Biaggioni I, Paranjape SY, Bagai K, Shibao C, Okoye MC, Dupont WD, Robertson D, Raj SR. Melatonin reduces tachycardia in postural tachycardia syndrome: a randomized, crossover trial. *Cardiovasc Ther*. 2014;32:105–112.
40. 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.
41. Rowell LB, Detry JM, Blackmon JR, Wyss C. Importance of the splanchnic vascular bed in human blood pressure regulation. *J Appl Physiol*. 1972;32:213–220.
42. Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology*. 2008;108:735–748.
43. Okamoto LE, Diedrich A, Baudenbacher FJ, Harder R, Whitfield JS, Iqbal F, Gamboa A, Shibao CA, Black BK, Raj SR, et al. Efficacy of servo-controlled splanchnic venous compression in the treatment of orthostatic hypotension: a randomized comparison with midodrine. *Hypertension*. 2016;68:418–426.
44. 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*. 2012;122:25–31.
45. Nwazue VC, Arnold AC, Raj V, Black BK, Biaggioni I, Paranjape SY, Orozco C, Dupont WD, Robertson D, Raj SR. Understanding the placebo effect in clinical trials for postural tachycardia syndrome. *Clin Exp Pharmacol Physiol*. 2014;41:325–330.
46. Ocon AJ, Medow MS, Taneja I, Clarke D, Stewart JM. Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2009;297:H664–H673.
47. Jacob G, Atkinson D, Jordan J, Shannon JR, Furlan R, Black BK, Robertson D. Effects of standing on cerebrovascular resistance in patients with idiopathic orthostatic intolerance. *Am J Med*. 1999;106:59–64.
48. Stewart JM, Del Pozzi AT, Pandey A, Messer ZR, Terilli C, Medow MS. Oscillatory cerebral blood flow is associated with impaired neurocognition and functional hyperemia in postural tachycardia syndrome during graded tilt. *Hypertension*. 2015;65:636–643.
49. Masuki S, Eisenach JH, Johnson CP, Dietz NM, Benrud-Larson LM, Schrage WG, Curry TB, Sandroni P, Low PA, Joyner MJ. Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. *J Appl Physiol*. 2007;102:896–903.

SUPPLEMENTAL MATERIAL

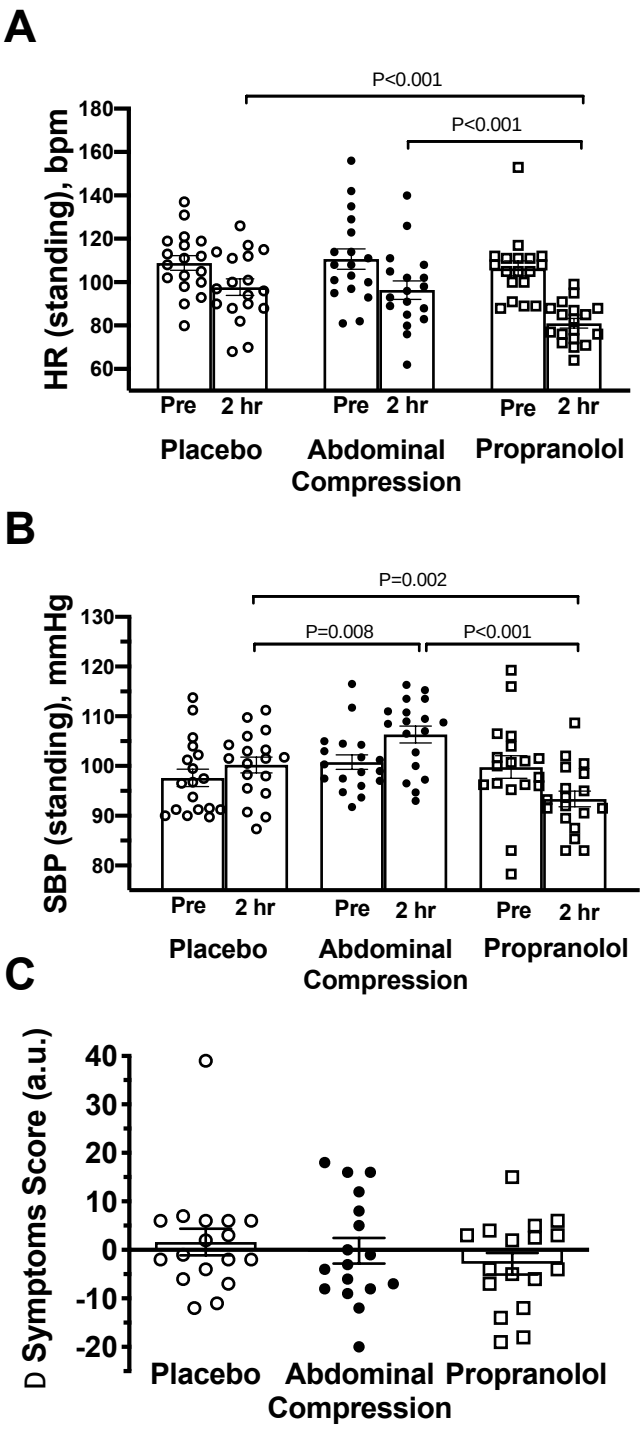
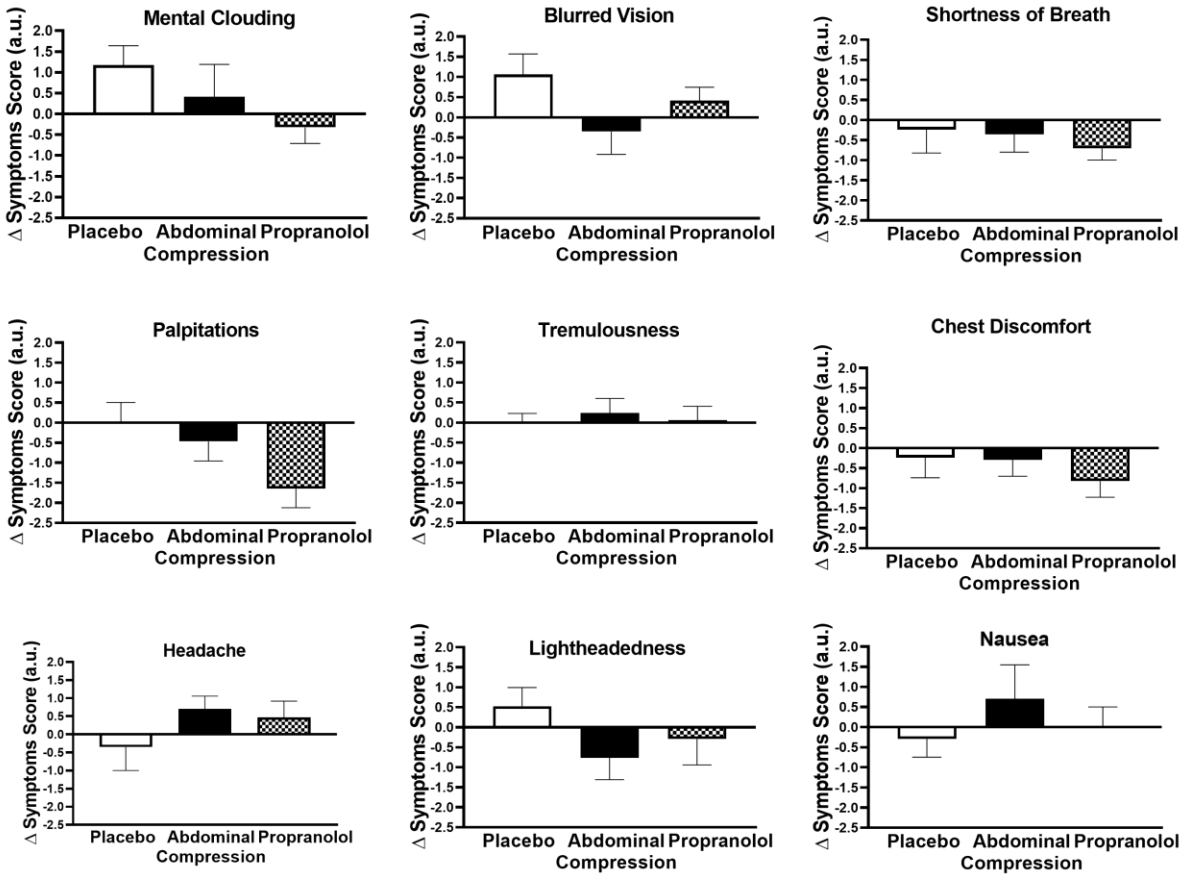


Figure S1. ndividual data on standing heart rate (HR; Panel A), and systolic blood pressure (SBP; Panel B) at baseline (Pre) and 2 hours (2 hr) after placebo, abdominal compression 40mm Hg (applied immediately before standing) and propranolol 20 mg (primary objective). Panel C shows changes from baseline in total orthostatic symptoms score (arbitrary units, a.u.). A negative change in score reflects a reduction in orthostatic symptom burden. Values are expressed as mean±SEM. Overall differences were analyzed by 2-way repeated-measures ANOVA. *P* values were adjusted for multiple comparisons using Bonferroni correction.

Figure S2. Changes from baseline in individual symptoms (arbitrary units, a.u.) after placebo (clear bars), abdominal compression 40mm Hg (applied immediately before standing; black bars) and propranolol 20 mg (bars with black dots) in the primary objective.



A negative number represents an improvement in symptoms. Values are expressed as mean±SEM.

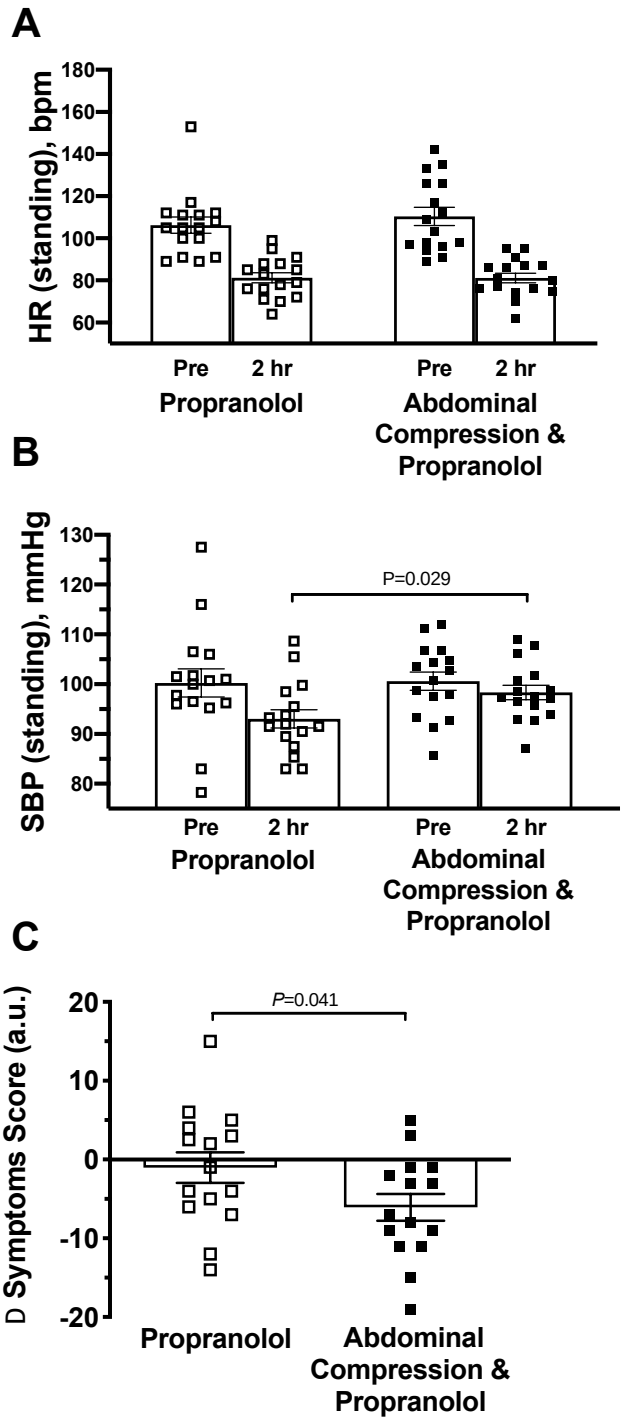
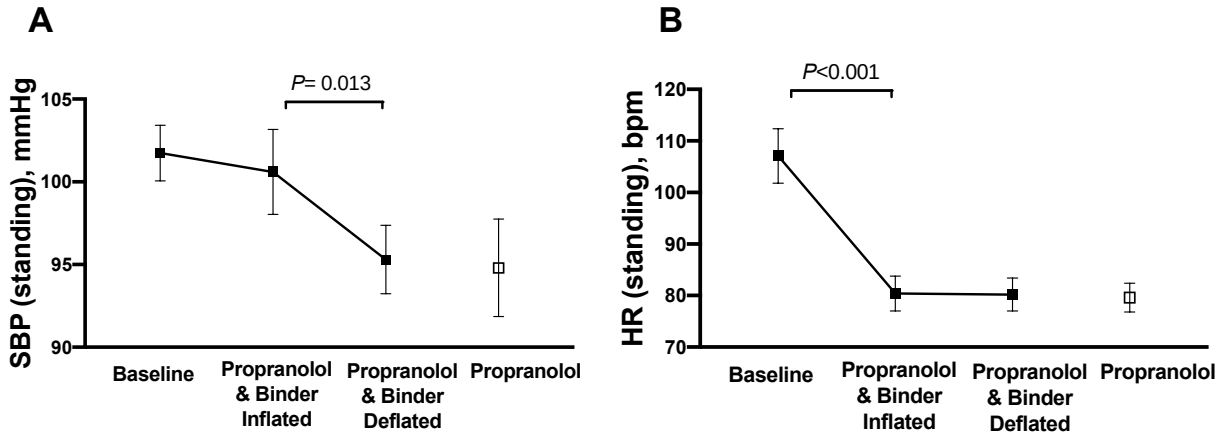


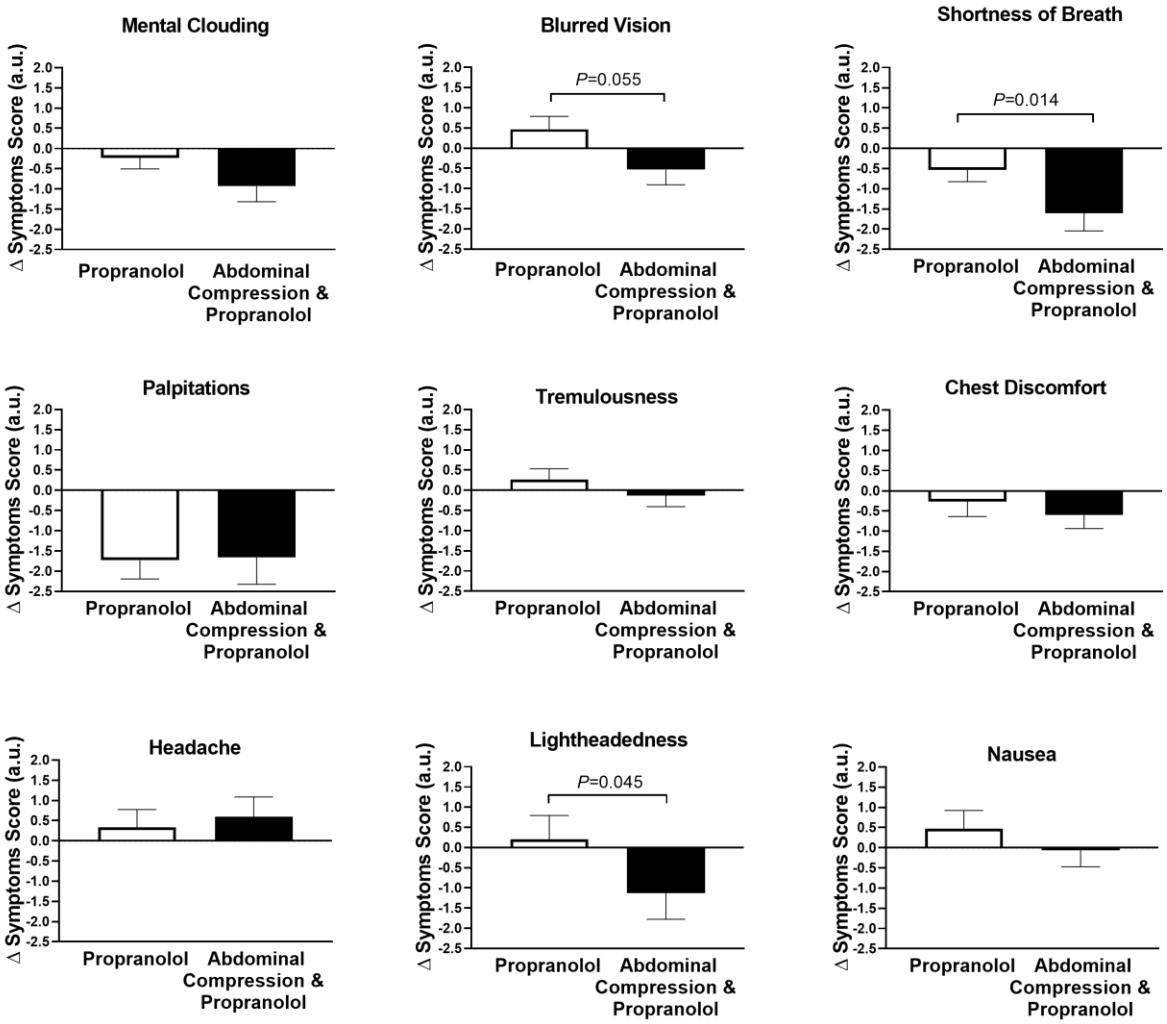
Figure S3. Individual data on standing heart rate (HR; Panel A), and systolic blood pressure (SBP; Panel B) at baseline (Pre) and 2 hours (2 hr) after propranolol 20 mg alone and after the combination of abdominal compression 40mm Hg (applied immediately before standing) with propranolol 20 mg (secondary objective). Panel C shows changes from baseline in total orthostatic symptoms score (arbitrary units, a.u.). A negative change in score reflects a reduction in orthostatic symptom burden. Values are expressed as mean±SEM.

Figure S4. Standing systolic blood pressure (SBP; Panel A) and heart rate (HR; Panel B) at baseline, 2 hours after the combination of abdominal compression 40mm Hg (applied immediately before standing) with propranolol 20 mg ("binder inflated"), and at 1minute after deflation of the binder ("binder deflated") in 10 participants of the secondary objective.



The open square represents the standing SBP and HR 2 hours after receiving propranolol alone. Standing SBP decreased significantly 1 min after releasing the abdominal compression whereas HR did not change.

Figure S5. Changes from baseline in individual symptoms (arbitrary units, a.u.) after propranolol 20 mg alone (clear bars) and after the combination of abdominal compression 40mm Hg (applied immediately before standing) with propranolol 20 mg (black bars) in the secondary objective.



A negative number represents an improvement in symptoms. Values are expressed as mean±SEM. *P* values were generated by using Wilcoxon rank-sum tests.