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Title page

HOME ORTHOSTATIC TRAINING IN VASOVAGAL SYNCOPE MODIFIES AUTONOMIC TONE- RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED PILOT STUDY

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STRUCTURED ABSTRACT

Aims

To detect possible autonomic changes due to home orthostatic training (HOT) and to assess the feasibility of a larger, placebo-controlled study of HOT in vasovagal syncope (VVS).

Method

22 consecutive patients, aged 18 to 85, diagnosed with VVS following a positive head-up tilt-table test were randomized to 40 minutes' HOT (n=12) or 10 minutes' sham training (n=10) daily for six months. Baroreflex sensitivity (BRS) and heart rate variability (HRV) were measured at weeks 0, 1, 4 and 24. Symptom response was assessed by event diaries.

Results

Home orthostatic training resulted in increases in up and down slope BRS at week 4 ($e^{\log \text{difference}}$=1.59;95%confidence interval(CI)=0.84,3.03 and 1.79;95%CI=1.00,3.22) and week 24 ($e^{\log \text{difference}}$=1.75;95%CI=1.01,3.06 and 1.53;95%CI=0.66,2.68) compared to placebo. Relative improvements in low and high frequency HRV were also observed in the HOT group compared to placebo at week 4 ($e^{\log \text{difference}}$ =3.22;95%CI=1.06,9.86 and 3.19;95%CI=1.03,10.59) and week 24 ($e^{\log \text{difference}}$ 2.11;95%CI=0.72,6.17 and 2.13;95%CI=0.52,8.79). Fifty percent of HOT subjects and 20% of control subjects were syncope-free at 6 months.

Conclusions

This was the first placebo-controlled study in orthostatic training which has demonstrated that such a study is indeed feasible. An enhancement in overall autonomic tone is observed with HOT in tandem with a non-significant trend in symptom improvement. A larger, adequately powered, randomized, controlled trial of tilt-training is now needed.

Keywords

CONDENSED ABSTRACT

Serial measurements of baroreflex sensitivity (BRS) and heart rate variability (HRV) were conducted in 22 patients with vasovagal syncope (VVS) randomized to daily home orthostatic training or placebo over six months. Home orthostatic training was associated with increased overall HRV and BRS in tandem with non-significant improvements in symptoms.

INTRODUCTION

Vasovagal syncope (VVS) is the commonest cause of transient loss of consciousness, accounting for 40% of syncopal episodes presenting to the emergency department [1]. It was previously assumed to be rare in older adults but has been diagnosed with increasing frequency since the head-up tilt-table (HUT) test was described in 1986 [2, 3]. While VVS in most patients either occurs infrequently or responds well to conservative measures, many patients continue to have persistent symptoms. The treatment options for the latter group of individuals are currently limited, with the recent randomized, controlled trials involving beta-adrenergic receptor blockers [4] and permanent cardiac pacemakers [5, 6] being negative.

Tilt-training or orthostatic training has been advocated as a possible effective treatment for VVS. There have been a handful of small, uncontrolled studies demonstrating promising results, though there were large variations in methodologies between the studies which included both formal tilt-table training and informal home orthostatic training [7-12]. The randomized, controlled studies published so far did not show any beneficial effects for tilt-training probably due to poor compliance [13-16]. In addition, control subjects in these studies were randomized to conventional treatment, not placebo. The haemodynamic effects and mechanisms of action of tilt-training have never been studied in the context of a randomized, controlled trial. Despite this lack of good quality evidence, tilt-training is recommended by consensus guidelines as a treatment for VVS [3, 17, 18].

Our aim was to conduct the first randomized, placebo (sham)-controlled study of home orthostatic training (HOT) in vasovagal syncope. The objectives of this study were firstly, to determine the changes in autonomic function in response to orthostatic training; and secondly, to explore the feasibility of conducting such a study in order to inform a future large scale, multi-centre study.

METHODS

Subjects

Consecutive patients aged 18 years and over diagnosed with VVS following a positive HUT test were invited to participate in the study if they had a symptom burden of 2 episodes of syncope; or 1 episode of syncope with 3 episodes of presyncope; or 5 episodes of presyncope within the previous six months. A positive HUT test was defined as a reduction of blood pressure and/or heart rate during HUT with reproduction of original symptoms [18]. The exclusion criteria were: (i) inability to provide informed consent; (ii) inability to stand for 40 minutes according to clinical judgment; (iii) inability to temporarily discontinue cardioactive medications for autonomic function testing; and (iv) pregnancy.

Interventions

Written informed consent was obtained from all participants, and they continued to receive routine clinical care which included lifestyle modification advice. Restricted randomization using computer generated random numbers was performed by an independent investigator. The treatment allocations were concealed in opaque, sealed envelopes. The physical treatments were demonstrated to the participants during their first visit. Participants were then asked to continue their training once daily at home for six months. Participants and clinicians providing routine clinical care were blinded to the randomization.

HOT Therapy

Participants within this arm were asked to stand with their upper backs against a wall and their heels approximately 15 centimeters (cm) from the wall with a cushioned "drop zone". They were

asked to maintain this position without movement for up to 40 minutes or until they experienced prodromal symptoms, presyncope or syncope.

Sham Training

Participants were asked to stand against a wall as described above, but to do so for only 10 minutes. They were also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, in order to enhance believability, counter venous pooling and prevent any possible orthostatic training effect.

Measurements

Haemodynamic and Autonomic Parameters

During each of these visits, autonomic function was assessed with heart rate variability (HRV) and baroreflex sensitivity (BRS) at enrolment and at one week, four weeks and six months after enrolment. All haemodynamic measurements were conducted in the morning. Participants were asked to refrain from caffeinated beverages on the day of the test. Following a 10-minute period of supine rest for stabilization, continuous ECG and non-invasive beat-to-beat blood pressure measurements were obtained using a vascular unloading device (Taskforce™, CNSystems, Austria).

Heart rate variability

Continuous ECG was recorded during 10-minutes' supine rest with spontaneous breathing. Ectopics and artefacts were removed by automated software, and manually if necessary. Low frequency: 0.04-0.15Hz (LF) and high frequency: 0.15-0.4Hz (HF) power spectral densities for at least 250 beats of artefact free segments were calculated using the autoregressive method for HRV [19].

Baroreflex Sensitivity

Baroreflex sensitivity (BRS) was determined during 10 minutes of supine rest by the sequence method. The slope of regression was determined for increases in systolic blood pressure (SBP) accompanied by lengthening of the R-R interval (RRI) (up sequences) and decreases in SBP associated with shortening of the RRI (down sequences) for three or more consecutive R-waves [20]. The blood pressure sequences were paired with the RRI at which the changes occurred (lag 0).

Symptom and training diaries

All participants were asked to complete a daily event diary throughout the six months' training period. They were asked to record whether training had been performed; the length of time trained each day, the presence of symptoms during training, as well as the presence of actual daily symptoms. To encourage compliance with diary and training exercises, all participants were contacted by telephone on a weekly basis. Information from the diaries was analyzed by an independent data interpreter blinded to the treatment group.

Data Analysis

All continuous variables were reported as mean with standard deviation for normally distributed data and median with interquartile range for non-normally distributed data. All categorical data were reported as number of subjects with percentages in parentheses. For the haemodynamic variables measured during clinic visits, comparisons were made between groups for the changes in LF-HRV, HF-HRV, up BRS and down BRS from baseline to week 4 and baseline to week 24, using the independent t-test. Low frequency heart rate variability, HF-HRV, up slope BRS and down slope BRS were first natural logarithmically transformed to form normal distributions before calculating the differences of the logged variables between week 4 and baseline as well as week 24 and baseline. The exponential values for mean differences of the logarithmic values ($e^{log\ difference}$),

with 95% confidence intervals, were subsequently presented. The anti-log of mean differences therefore represent the ratio of the differences between logarithmic values of each variable for HOT and placebo (change ratio), thus a value of 1 indicates no difference between HOT and placebo. Syncope-free survival between the two groups was compared with the χ^2 test. A two-tailed p-value of <0.05 was considered statistically significant and no adjustments were made for multiple testing. All data analysis was performed using SPSS^{TM} 15.0 for Windows.

Our study was intended to be a pilot study, and hence did not have adequate power to detect a significant change in the primary outcome measure of syncope recurrence. The number of subjects who remained syncope-free throughout the follow-up period and the median number of days with syncope were reported. Blinding of the study was assessed by asking participants whether they were able to guess which arm of the study they thought they were allocated to at the end of six months' training.

This study was granted a favorable ethical opinion by the Local Research Ethics Committee.

RESULTS

Recruitment

Two hundred and thirty-one HUT tests were performed at our specialist syncope facility from September 2006 to July 2007, of which 95 were positive. Fifty-four (57%) met the study criteria, and were invited to participate in the study (Figure 1).

Twenty-two (41%) subjects, aged 18 to 85 years, agreed to participate in the study. Twelve participants were randomized to HOT therapy, and the remaining 10 participants were randomized

to placebo. Two subjects, one in each arm, withdrew from the study, and one subject in each arm was lost to subsequent follow-up. One subject in the placebo arm discovered she was at the early stages of pregnancy at six months and therefore did not have haemodynamic measurements at the end of the study. Clinical and haemodynamic characteristics of the participants in our study are summarized in Table 1.

Autonomic Cardiovascular Reflexes

Baroreflex Sensitivity

Both up slope and down slope BRS increased with HOT training compared to sham training (Figure 2). The improvements from baseline observed with HOT compared to placebo for up slope BRS was non-statistically significant at week 4 ($e^{\text{log difference}}$ =1.59, 95%CI=0.84 to 0.84 to 3.03) but statistically significant at week 24 ($e^{\text{log difference}}$ =1.75, 95% CI=1.01 to 3.06). Down slope BRS also showed larger improvements over baseline for HOT compared to placebo at week 4 ($e^{\text{log difference}}$ =1.79, 95%CI=1.00 to 3.22) and week 24 ($e^{\text{log difference}}$ =1.53, 95% CI=0.88 to 2.68) (Table 2).

Heart Rate Variability

The changes in LF-HRV and HF-HRV in response to HOT and sham training are depicted graphically in Figure 3. Both LF-HRV and HF-HRV improved with HOT but not sham training. The $e^{\text{log difference}}$ between HOT and placebo for the change ratio in LF-HRV from baseline was 3.22 (95% confidence interval (CI) =1.06 to 9.86) for week 4 and 2.11 (95%CI=0.72 to 6.17) for week 24. The $e^{\text{log difference}}$ for the change ratio in HF-HRV was 3.19 (95%CI=1.03 to 10.59) for week 4 and 2.13 (95%CI=0.52, 8.79) (Table 2).

Symptom and Training Diaries

Symptom diaries were returned by 10 subjects in the HOT group and 7 subjects in the sham training group. The median number of minutes per session trained was 10 (8 to 10) for the control group and 25 (18 to 35) for the HOT group. Five (50%) of subjects in the placebo arm and 6 (50%) of subjects in the intervention arm, reported having trained for more than 50% of the time. Four (40%) participants in the control arm and four (30%) of subjects in the intervention arm reported symptoms of presyncope or syncope during training, but no injuries were sustained.

Five out of seven (71%) subjects reported syncope recurrence in the placebo arm, compared to 4/10 (40%) subjects in the intervention arm. Two of the ten subjects (20%) in the control arm, and 6/12 (50 %) in the intervention arm were known to be syncope free at the end of 6 months, but this observed difference was not statistically significant (p=0.201). The median number of days with syncope reported by subjects throughout the trial period was 1 (0 to 2) for the sham training group and 0 (0 to 4) for the HOT group.

Blinding

Only 3/10 (30%) subjects who completed the study in the HOT group and 2/8 (25%) subjects in the sham training group correctly identified the treatment group they were randomized to.

DISCUSSION

Our study was the first placebo-controlled pilot study involving orthostatic training in vasovagal syncope, and the first to involve serial assessments of autonomic cardiovascular reflexes in response to orthostatic training. Improvements were observed in BRS using the sequence method in

response to HOT when compared to placebo throughout the study. Similar improvements were also observed for the frequency domain heart rate variability parameters of LF-HRV and HF-HRV. Our results, therefore, indicate that HOT increases overall autonomic tone with significant increases in parasympathetic and sympathetic activity, as well as BRS within 4 weeks of daily orthostatic training.

Traditionally, clinical assessment of autonomic function involves the assessment of blood pressure and heart rate changes in response to a series of physical maneuvers including active standing [21]. The battery of tests mentioned above has relatively poor reproducibility, and is only sensitive to gross changes in autonomic function. Newer, more sensitive measures of autonomic function based on spontaneous variations in heart rate and blood pressures are now widely used as research tools [19, 22]. Regular physiological changes in heart rate occur at rest in normal, healthy individuals. When the heart rate is plotted against time, these changes follow regular patterns appearing as oscillations, and can be separated into oscillations of varying frequencies. Changes in heart rate during normal breathing appear as oscillations within the HF range and therefore represent parasympathetic function. Oscillations in the LF range are considered a marker of sympathetic function, but there are controversies about the relative contribution of the parasympathetic system. The steepness of the slope of increase (up slope) or decrease (down slope) in SBP corresponding to increases or decreases of 3 or more consecutive heart beats at rest is a measure of baroreflex response (the sequence method) [22]. Heart rate variability and BRS are highly sensitive measures, with increments occurring in an exponential rather than linear fashion.

Few previous studies have addressed the likely mechanisms of action underlying the possible beneficial effects of tilt-training or orthostatic training. Verheyden et al [12] recently published the results of an uncontrolled study which demonstrated an improvement in vasoconstrictor reserve with initial in-hospital tilt-training followed by six weeks of home

orthostatic training, using digital estimations of cardiac stroke volume. The authors also found a significant increase in LF-HRV at the reference point of syncope during HUT [12]. Piccirillo et al [23] reported an increase in LF-HRV and BRS associated with tilt-training, but only in late rather than early responders in their study which mainly addressed the predictors of responders versus non-responders. This increase in LF-HRV was not confirmed by Gajek et al [24] who found increases in HF-HRV at rest and during HUT following a period of tilt-training, but no changes in LF-HRV. The results of our study suggest that, when compared to a placebo control group, improvements occur in LF-HRV, HF-HRV and BRS following orthostatic training. In addition to providing insights into the mechanism of action of tilt-training, serial measurements of HRV and BRS will also serve well as a highly sensitive secondary outcome measure for future trials. Heart rate variability and BRS could also be useful tests to clinicians and patients as markers of treatment response, which will both encourage adherence and guide treatment decisions.

The pathogenesis of VVS at present remains unconfirmed, with conflicting findings emerging from the published literature. The susceptibility to tilt-induced syncope appears to be associated with inadequate sympathetic activation [25], resulting in a reduction in sympathetically-mediated peripheral vascular resistance [26]. Several studies have demonstrated a reduction in BRS at rest or an exaggerated drop in BRS during HUT in individuals with VVS [26]. Reports on HRV have been conflicting, but appear to consistently suggest a lower of increase in LF-HRV during HUT in vasovagal syncope patients with a positive response to HUT [27]. Jardine et al [28] also reported a greater reduction in HF-HRV immediately after assuming the upright position, in HUT positive subjects [28]. Our findings therefore suggest that this depressed BRS and HRV response could be corrected using the safe and simple non-pharmacological intervention of orthostatic training. These physiological changes also raise the possibility of an intriguing inverse relationship with space physiology. Astronauts acquire an increased susceptibility to syncope on return to earth. The effects of zero gravity appear to result in reduced BRS and absolute values of HRV on landing day [29].

Several uncontrolled studies have advocated in-hospital tilt-training and home orthostatic training as effective treatments for refractory VVS [7-11]. More recently, a handful of small, single-centre, randomized-controlled trials have reported lack of efficacy for tilt-training due to poor compliance [13-16]. The subjects in the control arm of the above studies were, however, randomized to conventional treatment, not placebo. With the serial publication of four negative randomized, controlled trials in the last few years, should we now conclude that tilt-training is ineffective? The outcome measures reported by previous studies included time to positivity during subsequent HUT tests and syncope recurrence. Head-up tilt tests have low reproducibility and are of limited value as a test of clinical efficacy for therapeutic interventions [30]. Furthermore, spontaneous syncope is a relatively infrequent symptom in sufferers of VVS. Many patients also experience spontaneous resolution of symptoms with minimal or no medical intervention. Therefore, large studies with prolonged follow-up periods are required in order to detect significant reductions in syncope recurrence.

While conservative measures suffice for the majority of patients with VVS, a small number of patients continue to have refractory or malignant VVS for which treatment options are woefully inadequate. A handful of pharmacological treatments have been tested, but few have been subjected to the rigors of large randomized, placebo-controlled trials [17]. The only multi-centre placebo-controlled study involving metoprolol, a beta-adrenoreceptor antagonist, has been negative [4]. Two multi-centre placebo controlled studies of permanent cardiac pacing in subjects with VVS have also been negative [4-6]. There is therefore an urgent need for new evidence-based treatment options for sufferers of recurrent VVS. Home orthostatic training provides an easily performed, non-invasive and side-effect free alternative to drug and pacing treatment with an inadequate evidence base.

Our feasibility study has first demonstrated that a placebo-controlled study of home orthostatic training is indeed feasible and second that HOT has a sound physiological basis, significantly improving autonomic tone. Our study included subjects from a broad age range, and is therefore unique in its inclusion of elderly subjects, who have so far rarely been considered in studies involving tilt-training or any other form of treatment for VVS [3]. Subjects in the intervention arm of our study were 2.5 times more likely to be syncope free than subjects in the placebo arm, but this difference in actual numbers was not statistically significant, as our study was not powered to detect significant differences in symptom outcomes. The selection of study participants in a future study will be vital, as subjects with lower symptom burdens and higher likelihood of spontaneous recovery are neither likely to benefit from nor comply with such an arduous treatment [13].

CONCLUSION

Our study was the first ever randomized, placebo controlled trial for HOT in VVS. Orthostatic training increases the overall autonomic tone in subjects with VVS when compared to placebo. This pilot study has also demonstrated that, with minor modifications, a large scale randomized, placebo-controlled study of this nature is both feasible and desirable. The significant improvements in autonomic parameters and positive trends in symptom improvements indicate that a future, adequately powered multi-centre, randomized placebo-controlled trial is now indicated as a matter of urgency.

ACKNOWLEDGEMENTS

REFERENCES

1.   Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, et al. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. . *Eur Heart J* 2006; **27**(1):76-82.

2.   Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986; **1**(8494):1352-1355.

3.   Tan MP, Parry SW. Vasovagal syncope in the older patient. *J Am Coll Cardiol* 2008; **51**(6):599-606.

4.   Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, et al. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation* 2006; **113**(9):1164-1170.

5.   Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, et al. 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**(17):2224-2229.

6.   Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). *Eur Heart J* 2004; **25**(19):1741-1748.

7.   Abe H, Kondo S, Kohshi K, Nakashima Y. Usefulness of orthostatic self-training for the prevention of neurocardiogenic syncope. *Pacing Clin Electrophysiol* 2002; **25**(10):1454-1458.

8.   Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: A controlled study. *Circulation* 1999; **100**(17):1798-1801.

9.   Kinay O, Yazici M, Nazli C, Acar G, Gedikli O, Altinbas A, et al. Tilt training for recurrent neurocardiogenic syncope: effectiveness, patient compliance, and scheduling the frequency of training sessions. *Jpn Heart J* 2004; **45**(5):833-843.

10.   Lafuente EA, Martinez LC, Moguel JO, David RN, Garcia JD, Tejeda AO, et al. Response to treatment during medium-term follow-up in a series of patients with neurocardiogenic syncope. *Arch Med Res* 2004; **35**(5):416-420.

11.   Reybrouck T, Heidbuchel H, Van De Werf F, Ector H. Long-term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. *Pacing Clin Electrophysiol* 2002; **25**(10):1441-1446.

12.   Verheyden B, Ector H, Aubert AE, Reybrouck T. Tilt training increases the vasoconstrictor reserve in patients with neurally mediated syncope evoked by head-up tilt testing. *Eur Heart J* 2008; **29**(12):1523-1530.

13.   Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. *Europace* 2004; **6**(3):199-204.

14.   On YK, Park J, Huh J, Kim JS. Is Home Orthostatic Self-Training Effective in Preventing Neuraly Mediated Syncope? *Pacing Clin Electrophysiol* 2007; **30**:638-643.

15.   Duygu H, Zoghi M, Turk U, Akyuz S, Ozerkan F, Akilli A, et al. The Role of Tilt Training in Preventing Recurrent Syncope in Patients with Vasovagal Syncope: A Prospective and Randomized Study. *Pacing Clin Electrophysiol* 2008; **31**:592-596.

16.   Gurevitz O, Barsheshet A, Bar-Lev D, Zimlichman E, Rosenfeld GF, Benderly M, et al. Tilt training: does it have a role in preventing vasovagal syncope? *Pacing Clin Electrophysiol* 2007; **30**(12):1499-1505.

17.   Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, et al. Guidelines on management (diagnosis and treatment) of syncope--update 2004. *Europace* 2004; **6**(6):467-537.

18.   Parry SW, Reeve P, Lawson J, Shaw FE, Davison J, Norton M, et al. The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders. *Heart* 2009; **95**(5):416-420.

19.   Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; **93**(5):1043-1065.

20.   Steptoe A, Vogele C. Cardiac baroreflex function during postural change assessed using non-invasive spontaneous sequence analysis in young men. *Cardiovasc Res* 1990; **24**(8):627-632.

21.   Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *British Medical Journal Clinical Research Ed* 1982; **285**(6346):916-918.

22.   Parati G, Di Rienzo M, Bertinieri G, Pomidossi G, Casadei R, Groppelli A, et al. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. *Hypertension* 1988; **12**(2):214-222.

23.   Piccirillo G, Magri D, Di Carlo S, Matera S, Magnanti M, De Laurentis T, et al. Power spectral analysis of heart rate variability as a predictive test in choosing the most effective length for tilt-training. *Int J Cardiol* 2006; **111**(1):59-66.

24.   Gajek J, Zysko D, Halawa B, Mazurek W. Influence of tilt training on activation of the autonomic nervous system in patients with vasovagal syncope. *Acta Cardiol* 2006; **61**(2):123-128.

25.   Bechir M, Binggeli C, Corti R, Chenevard R, Spieker L, Ruschitzka F, et al. Dysfunctional baroreflex regulation of sympathetic nerve activity in patients with vasovagal syncope. *Circulation* 2003; **107**(12):1620-1625.

26.   Thomson HL, Wright K, Frenneaux M. Baroreflex sensitivity in patients with vasovagal syncope. *Circulation* 1997; **95**(2):395-400.

27.   Piccirillo G, Naso C, Moise A, Lionetti M, Nocco M, Di Carlo S, et al. Heart rate and blood pressure variability in subjects with vasovagal syncope. *Clin Sci* 2004; **107**(1):55-61.

28.   Jardine DL, Ikram H, Frampton CM, Frethey R, Bennett SI, Crozier IG. Autonomic control of vasovagal syncope. *Am J Physiol* 1998; **274**(6 Pt 2):H2110-2115.

29.   Blaber AP, Bondar RL, Kassam MS. Heart rate variability and short duration spaceflight: relationship to post-flight orthostatic intolerance. *BMC Physiology* 2004; **4**:6.

30.   Moya A, Permanyer-Miralda G, Sagrista-Sauleda J, Carne X, Rius T, Mont L, et al. Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. *J Am Coll Cardiol* 1995; **25**(1):65-69.

FIGURE LEGENDS

Figure 1. Study Design and Recruitment of Participants.

HUT=head-up tilt-test; HOT=home orthostatic training

Figure 2. Changes in Baroreflex Slope Over Baseline

Mean change in log(Up Slope) and log(Down Slope) baroreflex slope over visits for HOT and placebo groups. Error bars represent standard errors about the mean. The individual values of up slope BRS and down slope BRS were first log-transformed before deriving the difference between each value at week 1, week 4 and week 24 from baseline.

BRS=baroreflex slope.

Figure 3. Changes in Heart Rate Variability Over Baseline.

Mean change in log(LF) and log(HF) heart rate variability over visits for HOT and placebo groups. Error bars represent standard errors about the mean. The individual values of LF-HRV and HR-HRV were first log-transformed before deriving the difference between each value at week 1, week 4 and week 24 from baseline.

LF=low frequency; HF= high frequency.

FIGURES

Figure 1
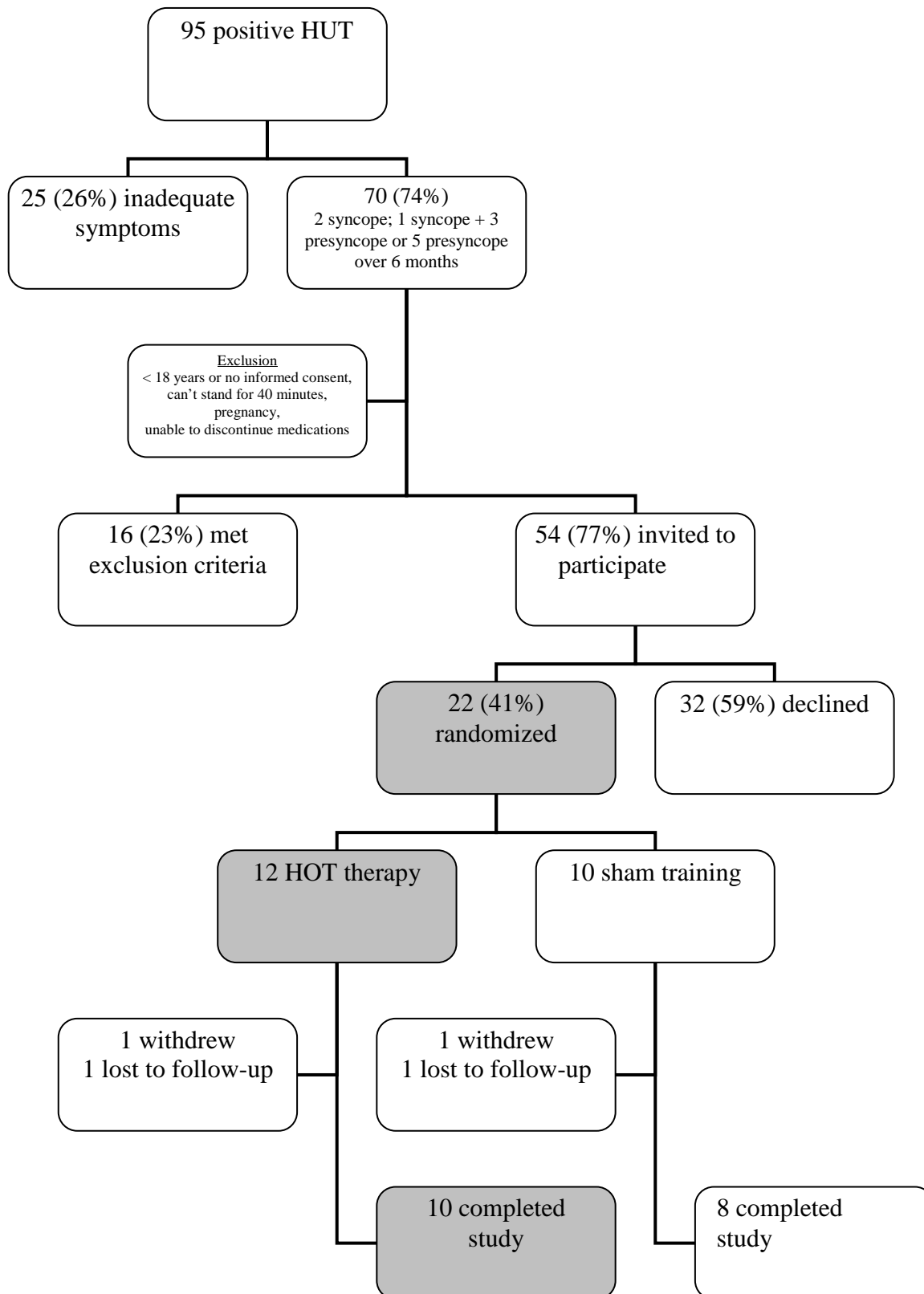
TABLES

Table 1 Characteristics of Participants.

Characteristics	Participants (n=22)
Female [n (%)]	17 (77%)
Age, yrs [mean (SD)]	45 (20)
Any occlusive vascular disease [n (%)]	1 (5%)
Hypertension [n (%)]	5 (23%)
Smoker [n (%)]	4 (18%)
Alcohol [n (%)]	5 (23%)
Vasoactive drugs* [n (%)]	4 (18%)
Syncopal episodes in last 6 months [Median (quartile)]	1 (0, 3)
Presyncopal episodes in last 6 months [Median (quartile)]	10 (1, 113)
Baseline systolic blood pressure, mmHg [mean (SD)]	130 (21)
Baseline diastolic blood pressure , mmHg [mean (SD)]	82(13)
Baseline heart rate, bpm [mean (SD)]	74 (11)

HUT=head-up tilt-table; SD=standard deviation.

*includes antihypertensive and antianginal medications **Table 2.** Changes in Autonomic Variables from Baseline Observed at Week 4 and Week 24.

		Week 4/ Baseline			Week 24/ Baseline		
		Mean ratio (SD)	$e^{log\ difference}$ (95%CI)	p-value	Mean ratio (SD)	$e^{log\ difference}$ (95%CI)	p-value
Up Slope BRS*	HOT	1.34 (1.90)	1.59 (0.84, 3.03)	0.148	1.49 (1.86)	1.75 (1.01, 3.06)	*0.047*
	placebo	0.84 (2.05)			0.85 (1.42)		
Down Slope BRS*	HOT	1.48 (1.82)	1.79 (1.00, 3.22)	0.052	1.42 (1.84)	1.53 (0.88, 2.68)	0.148
	placebo	0.82 (1.93)			0.93 (1.46)		
LF-HRV*	HOT	1.70 (2.66)	3.22 (1.06, 9.86)	*0.04*	1.28 (2.44)	2.11 (0.72, 6.17)	0.159
	placebo	0.51 (4.01)			0.61 (3.25)		
HF-HRV*	HOT	2.01 (1.97)	3.19 (1.03, 10.59	*0.045*	1.57 (4.36)	2.13 (0.52, 8.79)	0.275
	placebo	0.61 (5.37)			0.74 (3.14)		

*comparisons were made using log-transformed values. Antilog of mean and mean differences between log-transformed values is presented. The mean values with standard deviation therefore

represent the unitless ratio between week 4 over baseline and week 24 over baseline. The exponential value of the mean differences presented represents the ratios between the two groups. A lower confidence limit of >1, therefore, indicates significant difference.

LF= low frequency; HF=high frequency; PSD=power spectral density; BRS=baroreflex sensitivity; HOT=home orthostatic training; $e^{\text{log difference}}$= antilog of mean differences