Home orthostatic training in vasovagal syncope modifies autonomic tone: results of a randomized, placebo-controlled pilot study

Maw Pin Tan1, Julia L. Newton1,2, Tom J. Chadwick3, Janine C. Gray2, Samiran Nath4, and Steve W. Parry1,2*

1Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK; 2Falls and Syncope Service, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK; 3Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK; and 4Department of Cardiology, North Tyneside General Hospital, North Shields, UK

Received 16 May 2009; accepted after revision 21 October 2009; online publish-ahead-of-print 17 November 2009

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).

Methods and results
Twenty-two consecutive patients, aged 18–85, diagnosed with VVS following a positive head-up tilt-table test were randomized to 40 min of HOT (n = 12) or 10 min of sham training (n = 10) daily for 6 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. Home orthostatic training resulted in increases in up and down slope BRS at week 4 (elog difference = 1.59, 95% CI = 0.84–3.03 and 1.79, 95% CI = 1.00–3.22) and week 24 (elog difference = 1.75, 95% CI = 1.01–3.06 and 1.53, 95% CI = 0.66–2.68) compared with placebo. Relative improvements in low- and high-frequency HRV were also observed in the HOT group compared with placebo at week 4 (elog difference = 3.22, 95% CI = 1.06–9.86 and 3.19, 95% CI = 1.03–10.59) and week 24 (elog difference = 2.11, 95% CI = 0.72–6.17 and 2.13, 95% CI = 0.52–8.79). Fifty percentage of HOT subjects and 20% of control subjects were syncope-free at 6 months.

Conclusion
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
Vasovagal syncope • Autonomic nervous system • Tilt training • Heart rate variability • Baroreflex sensitivity

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 Although 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 blockers4 and permanent cardiac pacemakers5–6 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 (HOT).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.\textsuperscript{3,17,18}

Our aim was to conduct the first randomized placebo (sham)-controlled study of HOT in VVS. The objectives of this study were: first, to determine the changes in autonomic function in response to orthostatic training; and second, to explore the feasibility of conducting such a study in order to inform a future large-scale multicentre 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 two episodes of syncope; or one episode of syncope with three episodes of presyncope; or five episodes of presyncope within the previous 6 months. A positive HUT test was defined as a reduction in blood pressure and/or heart rate during HUT with reproduction of original symptoms.\textsuperscript{18} The exclusion criteria were: (i) inability to provide informed consent; (ii) 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 6 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 ~15 cm from the wall with a cushioned ‘drop zone’. They were asked to maintain this position without movement for up to 40 min 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 min. 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 1 week, 4 weeks, and 6 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 min 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\textsuperscript{TM}, CNSystems, Austria).

**Heart rate variability**

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

**Baroreflex sensitivity**

Baroreflex sensitivity was determined during 10 min 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.\textsuperscript{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 6 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 analysed by an independent data interpreter blinded to the treatment group.

**Data analysis**

All continuous variables were reported as mean with SD 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 HRV, HF-HRV, up slope BRS, and down slope BRS were first natural logarithmically transformed to form normal distributions before calculating the differences in 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\textsuperscript{log difference}), with 95% confidence intervals, were subsequently presented. The antilog of mean differences therefore represents 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 x\textsuperscript{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\textsuperscript{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 6 months training.

This study was granted a favourable 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 18–85 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 6 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 compared with sham training (Figure 2). The improvements from baseline observed with HOT compared with placebo for up slope BRS were non-statistically significant at week 4 (\( e^{\log \text{ difference}} = 1.59, 95\% \ CI = 0.84–3.03 \)) but statistically significant at week 24 (\( e^{\log \text{ difference}} = 1.75, 95\% \ CI = 1.01–3.06 \)). Down slope BRS also

---

**Figure 1** Study design and recruitment of participants. HUT, head-up tilt-test; HOT, home orthostatic training.
showed larger improvements over baseline for HOT compared with placebo at week 4 (e\(^{log\ difference}\) = 1.79, 95% CI = 1.00–3.22) and week 24 (e\(^{log\ difference}\) = 1.53, 95% CI = 0.88–2.68) (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\(^{log\ difference}\) between HOT and placebo for the change ratio in LF-HRV from baseline was 3.22 (95% CI = 1.06–9.86) for week 4 and 2.11 (95% CI = 0.72–6.17) for week 24. The e\(^{log\ difference}\) for the change ratio in HF-HRV was 3.19 (95% CI = 1.03–10.59) 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 (8–10) for the control group and 25 (18–35) for the HOT group. Five (50%) of the subjects in the placebo arm and six (50%) of the 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 the subjects in the intervention arm reported symptoms of presyncope or syncope during training, but no injuries were sustained.

Five out of the 7 (71%) subjects reported syncope recurrence in the placebo arm compared with 4 of the 10 (40%) subjects in the intervention arm. Two of the 10 subjects (20%) in the control arm and 6 of the 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 (0–2) for the sham training group and 0 (0–4) for the HOT group.

Blinding
Only 3 of the 10 (30%) subjects who completed the study in the HOT group and 2 of the 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 VVS, 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 with placebo throughout the study. Similar improvements were also observed for the frequency domain HRV 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 manoeuvres including active standing. 21

Table 1 Characteristics of participants

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

SD, standard deviation.
*Includes antihypertensive and antianginal medications.
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.\textsuperscript{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 as 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 three or more consecutive heart beats at rest is a measure of baroreflex response (the sequence method).\textsuperscript{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.\textsuperscript{12} recently published the results of an uncontrolled study which demonstrated an improvement in vasoconstrictor reserve with initial in-hospital tilt-training followed by 6 weeks of HOT, 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.\textsuperscript{12} Piccirillo et al.\textsuperscript{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 vs. non-responders. This increase in LF-HRV was not confirmed by

### Table 2 Changes in autonomic variables from baseline observed at weeks 4 and 24

<table>
<thead>
<tr>
<th></th>
<th>Week 4 per baseline</th>
<th>Week 24 per baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ratio (SD)</td>
<td>e^log difference (95% CI)</td>
</tr>
<tr>
<td>Up slope BRS\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td>1.34 (1.90)</td>
<td>1.59 (0.84–3.03)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.84 (2.05)</td>
<td>0.85 (1.42)</td>
</tr>
<tr>
<td>Down slope BRS\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td>1.48 (1.82)</td>
<td>1.79 (1.00–3.22)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.82 (1.93)</td>
<td>0.93 (1.46)</td>
</tr>
<tr>
<td>LF-HRV\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td>1.70 (2.66)</td>
<td>3.22 (1.06–9.86)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.51 (4.01)</td>
<td>0.61 (3.25)</td>
</tr>
<tr>
<td>HF-HRV\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td>2.01 (1.97)</td>
<td>3.19 (1.03–10.59)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.61 (5.37)</td>
<td>0.74 (3.14)</td>
</tr>
</tbody>
</table>

LF, low frequency; HF, high frequency; BRS, baroreflex sensitivity; HOT, home orthostatic training; e^log difference, antilog of mean differences. Values in italic represent statistical significance at the level of P < 0.05.

\textsuperscript{a}Comparisons were made using log-transformed values. Antilog of mean and mean differences between log-transformed values is presented. The mean values with SD therefore represent the unitless ratio between week 4 baseline and week 24 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.

### Figure 3 Changes in HRV over baseline. Mean change in log(LF) and log(HF) HRV 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 weeks 1, 4, and 24 from baseline. LF, low frequency; HF, high frequency.
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 with 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.\(^27\) Reports on HRV have been conflicting, but appear to consistently suggest a lower increase in LF-HRV during HUT in VVS 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 HUT as effective treatments for refractory VVS.\(^7\)–\(^11\) More recently, a handful of small, single-centre, randomized controlled trials have reported a 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 positiveity 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 multicentre placebo-controlled study involving metoprolol, a beta-adrenoceptor antagonist, has been negative.\(^4\) Two multicentre 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 HOT 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 with 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 multicentre, randomized placebo-controlled trial is now indicated as a matter of urgency.

**Acknowledgements**

Special thanks to Mrs Deborah Little for providing data support.

**Conflict of interest:** none declared.

**Funding**

The Home Orthostatic Training in Vasovagal Syncope (HOTVVS-1) study was supported by a research grant from the British Geriatrics Society and the NIHR Biomedical Research Centre for Ageing and Age-related Disease awarded to the Newcastle upon Tyne Foundation Hospitals NHS Trust. The salary of M.P.T. was funded by the Royal College of Physicians/Dunhill Medical Trust Joint Research Fellowship.

**References**


