

# Tilt training increases the vasoconstrictor reserve in patients with neurally mediated syncope evoked by head-up tilt testing

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## Aims

Tilt training is a useful therapeutic option in neurally mediated syncope (NMS). We tested the hypothesis that tilt training will restore orthostatic tolerance by increasing the degree of vasomotor reserve during sustained orthostatic stress.

## Methods and results

In this follow-up study we enrolled 17 patients (age  $31 \pm 22$  years, 11 females) with a clinical diagnosis of NMS and two consecutive positive tilt tests. The head-up tilt test was repeated day after day: one session per day. All patients were instructed to continue a programme of daily standing training at home. Follow-up tilt testing was performed after a period of 6 weeks in 14 patients. ECG and finger arterial blood pressure (Portapres) were recorded during subsequent tilt testing. Left ventricular stroke volume (SV), cardiac output, and systemic vascular resistance were computed from the pressure pulsations (Modelflow). Spontaneous cardiac baroreflex sensitivity was estimated by cross-spectral analysis of heart rate (HR) and systolic blood pressure. In all patients, orthostatic tolerance was restored after  $4.1 \pm 0.9$  tilt sessions, median 4. The follow-up tilt test was also negative in all patients. This was accompanied by a significant rise in systemic vascular resistance to compensate for a postural reduction in SV in the sustained head-up tilt position. No evidence could be provided of altered baroreflex control of HR after tilt training.

## Conclusion

Tilt training restores orthostatic tolerance at least in part by increasing the amount of vasoconstriction that can ultimately be made available during sustained orthostatic stress. The increased vasoconstrictor reserve is preserved after 6 weeks of continued standing training at home.

## Keywords

Tilt training • Neurally mediated syncope • Vasoconstrictor reserve • Baroreflex

## Introduction

Neurally mediated syncope (NMS) is a common medical problem resulting from an abnormal autonomic response with excessive vagal tone and sympathetic withdrawal.<sup>1</sup> Prolonged head-up tilt testing is widely used to reproduce symptoms associated with this syndrome.<sup>2</sup> Despite numerous studies the pathways involved in tilt-induced NMS remain incompletely understood. Until now, the most likely explanation is an insufficient vasoconstriction that can be made available in the sustained upright position.<sup>3</sup> In a recent report, Fu *et al.*<sup>4</sup> showed that the individual variability in

orthostatic tolerance is largely dependent on the degree of neural and vasomotor reserve available for vasoconstriction. Accordingly, impairment of the baroreflex control over sympathetic outflow has been documented in patients with a typical history of NMS.<sup>5–7</sup>

Many different treatment options are available for NMS, but the impact on determinants of hypotension in individual patients is not well established. To date, no definitive evidence exists to show that patients with NMS benefit from pharmacological therapy,<sup>8</sup> and pacing is reserved for the few patients in whom syncope is accompanied by marked asystole.<sup>9</sup> The recently introduced

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therapy of daily repeated tilt testing is different; in that it may affect more than one mechanism in concert in the same patient.<sup>10</sup> Most clinical studies have documented that tilt training therapy restores orthostatic tolerance to a level that prevents syncope in the majority of patients.<sup>11–14</sup> However, it is as yet uncertain how the clinical effects of sequential head-up tilt testing can be explained. In this study, we hypothesized that tilt training will restore orthostatic tolerance by increasing the vasoconstrictor reserve in the sustained head-up tilt position. The purpose was to assess haemodynamic characteristics and baroreflex control of heart rate (HR) and systemic vascular resistance during subsequent head-up tilt testing in patients with a typical history of NMS.

## Methods

### Study population

Twenty-one patients with recurrent NMS were deemed eligible for inclusion into this follow-up study in the period between June 2004 and July 2006. Clinical diagnosis of postural NMS was confirmed by two consecutive positive head-up tilt tests. Prior evaluation excluded primary cardiac and neurological causes of syncope. No medication was used that could affect circulatory control. Three patients were excluded because of incomplete data recording. One patient refused to enter the study. This resulted in a total of 17 patients from whom informed consent was obtained. The study was approved by the local Medical Ethical Committee.

### Baseline diagnostic head-up tilt test

In all selected patients, a first positive diagnostic head-up tilt test was performed on a motorized tilt table with foot support according to the Westminster protocol.<sup>15</sup> Briefly, after a 15 min resting period in the recumbent position the patients were moved to the 60° upright position for a maximum duration of 45 min or until syncope developed. At the time of syncope, patients were returned to the recumbent position (tilt-back). No pharmacological provocation was used to avoid a false-positive diagnosis.<sup>16</sup> Syncope was defined as an abrupt, transient loss of consciousness, and loss of postural tone. The tilt test was considered positive if syncope developed in association with hypotension, bradycardia, or both. Presyncope was defined as the last minute before tilt-back.

### Tilt training programme

Around 1 month after the initial assessment, a second positive tilt test was reproduced at the start of in-hospital daily repeated tilt testing. For further tilt training, the same procedure was adopted as for the diagnostic tilt test. In all patients the target was to obtain two consecutive negative tilt tests. Orthostatic tolerance was considered as normal if the patients could sustain the test for at least 45 min. After discharge from hospital, the patients were instructed to continue a programme of daily standing training at home.<sup>12</sup> We recommended one or two sessions per day, 30 min each. Patients had to stand with their feet 15 cm away from the wall and lean with the upper back against the wall without moving. This tilt training was organized in a safe place, without risk of injury, and with the attendance of a family member. Each session was ended at the occurrence of first symptoms. All patients were asked to return to the hospital for a control tilt test after a period of at least 6 weeks.

### Data acquisition

Data recording was started at the start of in-hospital tilt training. During sequential head-up tilt testing, electrocardiogram (amplifier/programmer: Medtronic 9690, Minneapolis, MN, USA) was recorded and beat-to-beat arterial blood pressure was measured non-invasively with a servo-controlled photoplethysmograph (Portapres, TNO, Amsterdam, The Netherlands), placed on the mid-phalanx of the right middle finger.<sup>17</sup> The hand was positioned at heart level and held in place using an arm sling to prevent hydrostatic pressure differences in upright posture. Finger cuff pressures were compared with intermittent arm-cuff pressures (Colin BP-88S, Komaki, Japan) and used to track arterial blood pressure changes. Electrocardiogram and finger arterial pressure were digitized at 1 kHz using an external A/D converter (DATAQ Instruments Inc., Akron, OH, USA) and stored on a laptop computer. Respiratory rate was derived from changes in the thoracic impedance (incorporated in Colin BP-88S, Komaki, Japan).

### Haemodynamic analysis

A file consisting of consecutive RR intervals (RRI) was created from electrocardiogram.<sup>18</sup> Accordingly, beat-to-beat mean arterial pressure (MAP) was calculated as the true integral of the arterial pressure wave divided by the corresponding beat interval. Beat-to-beat changes in stroke volume (SV) were estimated by modelling flow from finger arterial pressure (Modelflow, TNO Biomedical Instrumentation).<sup>19–22</sup> Cardiac output (CO) was the product of SV and HR, and systemic vascular resistance (SVR) was obtained from MAP at heart level divided by CO. SV, CO and SVR were set at 100% (baseline) immediately after the assumption of the upright posture and variations were expressed as percentages (%) of this baseline. Beat-to-beat data were averaged per minute during the initial 4 min period in the head-up tilt position. Syncope occurred at different time points of the tilt protocol. Therefore, minute averages were further calculated from 5 min recordings referenced to syncope time in each patient; corresponding 5 min time intervals were used in case of a negative tilt test. Baseline HR, MAP, and PP in the supine position were inferred from the last 4 min preceding the start of tilt. The analysis of changes in SV, CO, and SVR from the supine to the upright tilt position was explicitly omitted to avoid unreliable estimations during posture change.<sup>23</sup>

### Baroreflex sensitivity

Calculation of cardiac baroreceptor sensitivity was based on the spectral analysis technique. In brief, beat-to-beat RRI and systolic arterial pressure (SAP) time series were interpolated, resampled at 2 Hz, and divided into 90% overlapping segments of 128 s. Each segment was detrended, Hanning windowed, and fast Fourier transformed.<sup>24</sup> The obtained spectral resolution was 0.0078 Hz. Power spectral density ( $\text{ms}^2/\text{Hz}$  for tachograms and  $\text{mmHg}^2/\text{Hz}$  for systograms) and the SAP-RRI transfer function gain [baroreflex sensitivity (BRS) in  $\text{ms}/\text{mmHg}$ ] were then computed in the low-frequency band (0.04–0.15 Hz) for each window. The reliability of each BRS estimation was evaluated by the squared coherence function. This method is well established and has been validated to other methods such as the sequence method.<sup>25</sup>

### Statistical analysis

Statistical analysis was performed with SPSS version 11.5 for Windows (Scientific Packages for Social Sciences, Inc., Chicago, IL, USA). Owing to the exploratory nature of the study no strict justification of the sample size could be provided. Variables were tested for normality with the Kolmogorov–Smirnov goodness-of-fit test. Spectral powers were transformed by calculating the natural logarithm to achieve

a normal distribution. Cardiovascular data were averaged at fixed 4 min time frames within subsequent tilt-training sessions: (1) 4–0 min supine before head-up tilt; (2) 0–4 min head-up tilt; (3) 5–1 min referenced to syncope time. The first and last sessions of in-hospital tilt training were selected and compared with a follow-up tilt test after 6 weeks of continued standing training at home. Two-way analysis of variance with repeated measures was performed to verify whether cardiovascular responses within a session change between subsequent tilt-training sessions. This was done for each of the parameters separately. Multiple pairwise comparisons were made with Bonferroni correction. This was done separately for each of the tilt phases in the case of a significant interaction. Mauchly's test of sphericity was conducted with Greenhouse–Geisser correction, if necessary. Tests were two-sided. A  $P$ -value  $< 0.05$  was considered statistically significant.

## Results

### Clinical characteristics

Baseline clinical characteristics of all patients ( $n = 17$ ) are shown in Table 1. The response to the diagnostic tilt test was: type 1 (mixed) in nine patients; type 2A (cardioinhibitory without asystole) in two patients; type 2B (cardioinhibitory with asystole) in one patient; and type 3 (vasodepressor response) in five patients. Asystolic pauses were because of sinus arrest in all cardio-inhibitory cases. The mean duration of the diagnostic tilt test was  $21 \pm 13$  min (range 5–44 min; median 24 min) and did not differ significantly

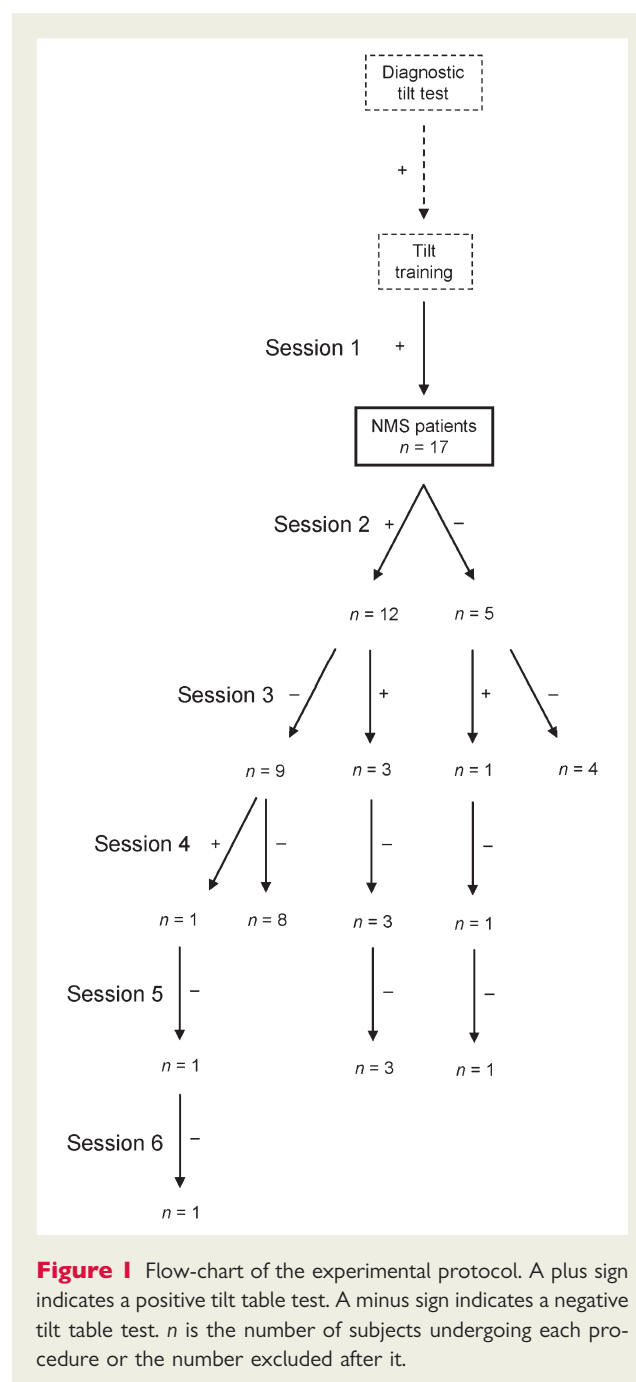
**Table 1** Baseline clinical characteristics of selected patients

	Patients ( $n = 17$ )
Male ( $n$ )	6
Length (cm)	$170 \pm 11$
Weight (kg)	$65 \pm 12$
Age (years)	
Mean $\pm$ SD	$31 \pm 22$
Median	20
Range	14–56
Duration diagnostic test (min)	
Mean $\pm$ SD	$21 \pm 13$
Median	24
Range	5–44
Type of syncope ( $n$ )	
Cardio-inhibitory	3
Mixed	9
Vasodepressor	5
In-hospital tilt-training sessions ( $n$ )	
Mean $\pm$ SD	$4.1 \pm 0.9$
Median	4
Range	3–6
Syncope recurrence before treatment ( $n$ )	
$> 1$ per week	10
$> 1$ per month	15
$> 1$ per year	17

between the different types of tilt responses. On resuming the recumbent position, all patients recovered and returned to a stable sinus rhythm within about 15 s.

### Tilt training and follow-up

Head-up tilt testing was repeated day after day: one session per day. Clinical results of in-hospital tilt training are summarized in Figure 1. The number of in-hospital training sessions ranged from three to six, median four. For all patients, the mean number of sessions to achieve a first negative tilt test was reached after  $2.9 \pm 0.7$  sessions, median three. A second negative test was achieved after



a mean of  $4.1 \pm 0.9$  sessions, median four. During subsequent tilt tests no change in the type of syncope was observed.

Fourteen patients returned to the hospital for a follow-up tilt test after a period of approximately 6 weeks of continued standing training at home. All these patients had continued standing training on a regular basis and the absence of syncope episodes was verified. The follow-up tilt test was negative in all patients.

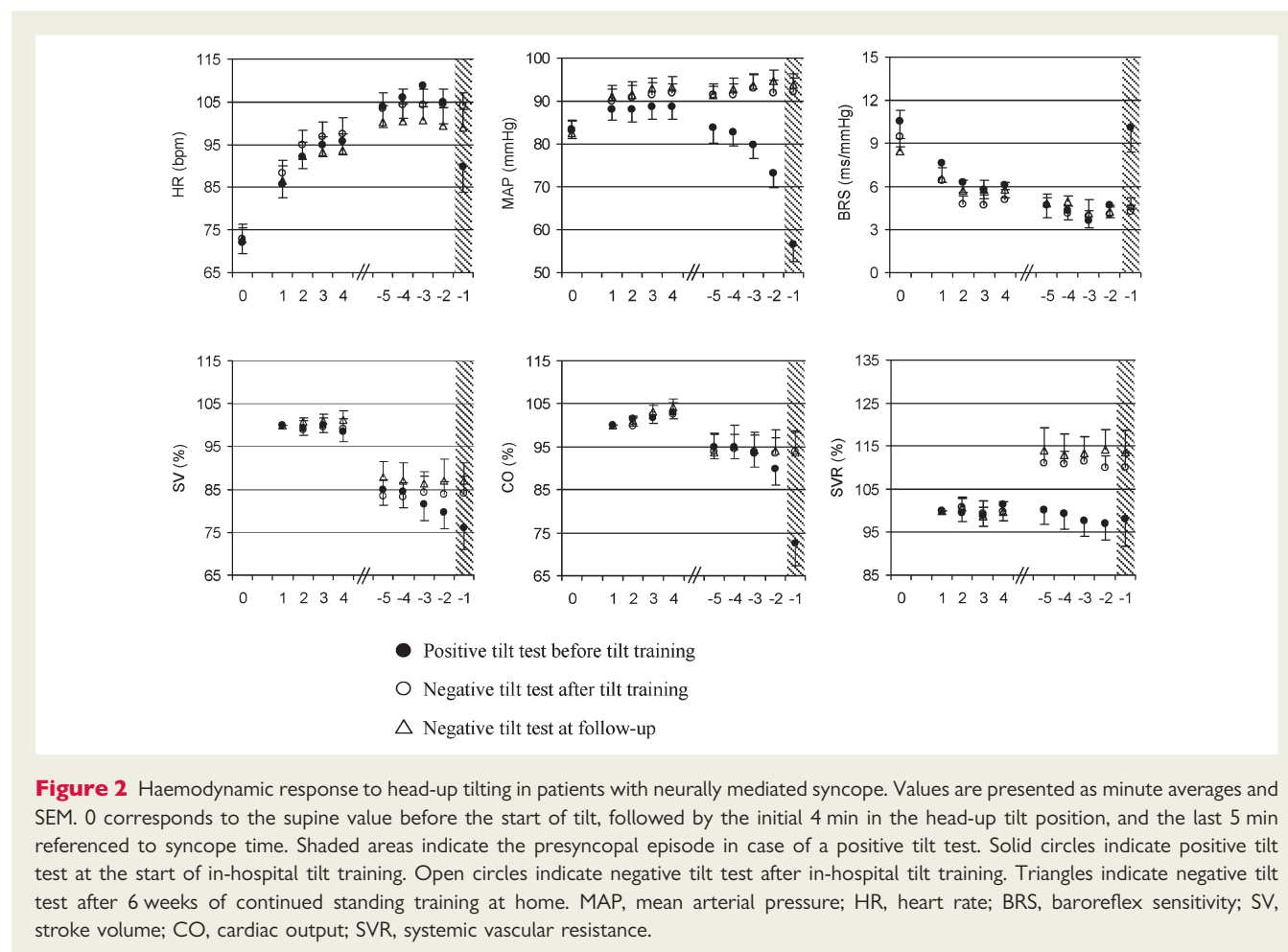
## Circulatory response with postural change

Haemodynamic patterns during subsequent tilt testing are shown in Figure 2. Results are obtained from three different tilt sessions: (1) positive tilt test at the start of in-hospital tilt training, (2) negative tilt test at the end of in-hospital tilt training, and (3) negative tilt test after 6 week continued standing training at home. The corresponding power spectral estimates are summarized in Table 2. We did not find significant differences between subsequent tilt sessions during 4 min periods preceding and following postural change. On average in all sessions, HR in the supine position was  $73 \pm 11$  b.p.m. and increased to  $93 \pm 13$  b.p.m. during the first 4 min in the upright posture ( $P < 0.001$ ). Accordingly, average MAP increased from  $83 \pm 8$  to  $89 \pm 10$  mmHg, whereas BRS decreased from  $10 \pm 5$  to  $6 \pm 3$  ms/mmHg because of the haemodynamic

changes induced by head-up tilt (both  $P < 0.001$ ). The average SAP low-frequency power increased from supine to upright tilt ( $11 \pm 6$  to  $27 \pm 12$  mmHg<sup>2</sup>;  $P < 0.001$ ) and also RRI low-frequency power tended to become higher in the upright posture ( $741 \pm 653$  to  $868 \pm 834$  ms<sup>2</sup>;  $P = 0.108$ ). SV, CO, and SVR were remarkably stable ( $\sim 100\%$ ) during the first 4 min of tilt (Figure 2). During these periods, none of the patients showed symptoms of oncoming syncope.

## Sustained circulatory response in the upright posture

Regardless of the tilt test outcome, there was a relative reduction in SV from  $100 \pm 5\%$  at baseline tilt (0–4 min head-up tilt) to  $85 \pm 14\%$  between 5 and 1 min referenced to syncope time ( $P < 0.001$ ). This was associated with a significant rise in HR from  $93 \pm 13$  to  $103 \pm 16$  b.p.m. ( $P < 0.001$ ). Maximum HR decreased with subsequent tilt testing from  $109 \pm 20$  b.p.m. at the start of in-hospital tilt training to  $105 \pm 14$  b.p.m. after in-hospital tilt training, and to  $101 \pm 17$  b.p.m. after 6 week continued standing training at home ( $P = 0.038$  between tilt training sessions). Despite the rise in HR, there was a reduction in CO relatively to baseline tilt ( $101 \pm 5$  to  $93 \pm 14\%$ ;  $P < 0.001$ ), which was independent of the tilt test outcome. The reduction



**Figure 2** Haemodynamic response to head-up tilting in patients with neurally mediated syncope. Values are presented as minute averages and SEM. 0 corresponds to the supine value before the start of tilt, followed by the initial 4 min in the head-up tilt position, and the last 5 min referenced to syncope time. Shaded areas indicate the presyncopal episode in case of a positive tilt test. Solid circles indicate positive tilt test at the start of in-hospital tilt training. Open circles indicate negative tilt test after in-hospital tilt training. Triangles indicate negative tilt test after 6 weeks of continued standing training at home. MAP, mean arterial pressure; HR, heart rate; BRS, baroreflex sensitivity; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance.

**Table 2** Spectral and cross-spectral data at fixed 4 min time frames throughout the tilt test protocol before and after in-hospital tilt training therapy and after 6 weeks of continued standing training at home (follow-up)

	Positive tilt test before tilt training (n = 17)	Negative tilt test after tilt training (n = 17)	Negative tilt test at follow-up (n = 14)	P-value
4–0 min before head-up tilt				
RRI LF power (ms <sup>2</sup> )	756 ± 601	727 ± 640	739 ± 772	0.559
SAP LF power (mmHg <sup>2</sup> )	10 ± 5	11 ± 5	11 ± 7	0.991
BRS LF gain (ms/mmHg)	11 ± 5	9 ± 7	8 ± 3	0.253
0–4 min head-up tilt				
RRI LF power (ms <sup>2</sup> )	840 ± 690	844 ± 968	933 ± 893	0.434
SAP LF power (mmHg <sup>2</sup> )	27 ± 13	27 ± 10	27 ± 13	0.759
BRS LF gain (ms/mmHg)	6 ± 3	5 ± 3	6 ± 2	0.644
5–1 min referenced to syncope time				
RRI LF power (ms <sup>2</sup> )	384 ± 368	942 ± 926*	985 ± 733*	0.019
SAP LF power (mmHg <sup>2</sup> )	16 ± 8	37 ± 24*	37 ± 17*	0.001
BRS LF gain (ms/mmHg)	4 ± 2	4 ± 2	5 ± 2	0.493

Data are presented as the mean value ± SD. The P-value indicates significant differences between tilt sessions.

BRS, baroreflex sensitivity; LF, low frequency; RRI, R-R interval; SAP, systolic arterial pressure.

\*P < 0.001 compared with a positive tilt test before tilt training.

in CO before tilt training was not compensated for by a proportional increase in SVR, thus leading to a gradual MAP-fall in the period between 5 and 1 min prior to syncope (Figure 2). Orthostatic tolerance was restored because of a substantial rise in SVR from 98 ± 14% before tilt training, to 111 ± 9% immediately after in-hospital tilt-training, and to 114 ± 10% after 6 week continued standing training at home (P = 0.034 between tilt training sessions). Accordingly, significantly higher low-frequency powers of SAP and RRI oscillations were observed after tilt-training therapy during time intervals between 5 and 1 min referenced to syncope time (Table 2). Alternatively, no significant changes in the BRS low-frequency gain were observed between tilt-training sessions.

## The presyncopal episode

During the last minute before syncope, all patients showed marked hypotension with MAP of 57 ± 17 mmHg. HR ranged from 42 to 133 b.p.m. during this period (mean 89 ± 25 b.p.m.). Five of the 17 patients had a HR above 100 b.p.m., whereas four had a HR below 60 b.p.m. During the presyncopal episode in all patients HR decreased compared with its peak value that was reached about 3 min before syncope time (Figure 2). The fall in HR during presyncope was accompanied by a sudden rise in the cardiac BRS together with an abrupt drop in CO. SV in the presyncopal episode was 76 ± 18% of baseline, CO was 73 ± 20%, and SVR remained stable at 98 ± 26%.

## Respiratory frequency

The respiratory frequency was 14 ± 5 breaths per minute in the supine position before tilt and remained stable (15 ± 5 breaths per minute) upon assuming the upright position in all tilt sessions. During a positive tilt test at the start of in-hospital tilt training, respiratory rate increased towards 23 ± 10 breaths per minute within periods between 5 and 1 min before syncope (P = 0.007).

## Discussion

The purpose of this study was to clarify underlying mechanisms by which tilt training improves symptoms in patients with a clinical diagnosis of NMS. The principle findings are that, at the start of therapy, there is a subnormal increase in systemic vascular resistance that cannot compensate for a postural reduction in SV. However, the fall in CO during 5–1 min referenced to syncope time appears independent of the tilt test outcome. These data indicate that daily repeated tilt testing restores orthostatic tolerance by increasing the degree of vasomotor reserve available for vasoconstriction. Increased vasoconstrictor reserve is preserved after 6 weeks of continued standing training at home.

Several authors have described the efficacy of tilt training in increasing orthostatic tolerance in NMS.<sup>11–14</sup> Until now, the impact of tilt training on determinants of orthostatic blood pressure control has not been established well. Di Girolamo *et al.*<sup>11</sup> postulated that tilt training may have desensitizing effects on stretch-activated mechanoreceptors located in the left ventricular wall. Three other studies have investigated the role of HR variability as an adaptive pathophysiological mechanism in tilt training.<sup>26–28</sup> Piccirillo *et al.*<sup>28</sup> reported that patients who have abnormal autonomic nervous function with increased vagal–cardiac tone may benefit from prolonged tilt training by increasing sympathetic neural outflow to the sinus node at rest. Two other studies point to a substantial influence of tilt training on the sympathovagal balance of HR control in the upright position.<sup>26,27</sup> The authors observed a shift towards less sympathetic dominance and lower HR after tilt-training therapy. In the present study cardiac autonomic control was inferred from the spontaneous cardiac BRS. In agreement with Gardenghi *et al.*,<sup>29</sup> who used a stimulus-dependent BRS method, our data show that baroreflex control of HR does not change with tilt training.

The role of an alteration in cardiac baroreflex function, predisposing NMS patients to orthostatic syncope, has been



suggested<sup>5,6,30</sup> or denied<sup>6,31,32</sup> by different studies, mainly based on stimulus-dependent methods. As previously discussed,<sup>33</sup> the data provided by these methods have the important limitation associated with interference by the applied external stimulus. In addition, reflex responses of HR to baroreceptor deactivation may play a greater role than reflex responses to baroreceptor activation in predisposing patients to postural NMS.<sup>30</sup> Our finding of a reduction in maximum HR during subsequent tilt testing is in line with this concept. Indeed, the origin of orthostatic tachycardia depends chiefly on the degree of thoracic hypovolemia, related to splanchnic hypervolemia, and so is the result of baroreceptor deactivation.<sup>34</sup> A possible reconditioning effect of tilt training on the vagal–cardiac baroreflex response to baroreceptor deactivation was not addressed specifically in this study.

Normally, the major cardiovascular adjustment to orthostatic stress is sympathetically mediated vasoconstriction,<sup>35</sup> the level of which is assumed to be dependent on the degree of unloading of both arterial and cardio-pulmonary baroreceptors.<sup>36</sup> Fu *et al.*<sup>4</sup> recently reported that the degree of sympathetic reserve available for vasoconstriction is finite and may be one of the mechanisms underlying the individual variability in orthostatic tolerance. Accordingly, subnormal forearm resistant vessel responses evoked by orthostatic stimuli have been reported in orthostatic intolerant patients.<sup>37,38</sup> The present finding of a blunted vascular resistance response in typical NMS patients is in line with the hypothesis of a diminished vasoconstrictor reserve.<sup>3</sup> However, the reasons for this diminished reserve remain a matter of speculation. Two possibilities exist. First, NMS patients may have a normal range of vasoconstriction, but use a larger fraction of the reserve, even under resting conditions. Second, there may be a reduction in the range of maximal vascular resistance that can be mediated ultimately by adrenergic activity.

Increased resting muscle sympathetic nerve activity (MSNA) has been documented in patients with chronic orthostatic intolerance<sup>39</sup> and typical NMS,<sup>7</sup> rendering less neural reserve available for vasoconstriction during orthostatic stress. In contrast, we did not find any change in the resting low-frequency powers of spontaneous HR and systolic blood pressure oscillations after restoring orthostatic tolerance by tilt training (*Table 2*). This finding provides circumstantial evidence against the hypothesis that excessive resting sympathetic outflow predisposes to orthostatic syncope in NMS patients. Mosqueda–García *et al.* documented that patients with a history of NMS have similar resting MSNA, but impaired sympathetic baroreflex function, when compared with healthy controls.<sup>5</sup> In their study however, most of the patients failed to achieve a steady-state blood pressure adaptation at low tilt levels, suggestive of some form of autonomic failure.<sup>40</sup> Interestingly, Morillo *et al.* reported that, in typical NMS patients, sympathetic baroreflex responses to arterial pressure reductions below baseline are well preserved.<sup>6</sup> Alternatively, attenuated sympathetic baroreflex responses have been shown with the application of a sub-hypotensive lower body negative pressure.<sup>7,41</sup> This raises an issue worthy of note: the differential role of arterial and cardiopulmonary baroreceptor function in NMS patients with a predisposition to orthostatic syncope. Ichinose *et al.* recently reported that the sensitivity of beat-to-beat sympathetic baroreceptor reflex control is impaired in the early phase of development of

orthostatic syncope.<sup>42</sup> This could explain why low-frequency oscillations in MSNA are reduced in the setting of an increased sympathetic outflow prior to postural NMS.<sup>43</sup> In our patients, the low-frequency oscillations in systolic blood pressure, which mirror those in MSNA,<sup>44</sup> were significantly reduced in the hypotensive episode preceding NMS (*Table 2*). These data suggest that one or more control systems governing sympathetic neural outflow are modulated prior to the sympathetic withdrawal that is associated with syncope. It is likely that baroreceptor influences on sympathetic vasomotor function are inhibited within the central nervous system because of reflexes arising from emotional stress, as well as vagal, somatic, and/or sympathetic afferents. However, the precise mechanisms remain to be determined.

The concept of vasoconstrictor reserve can be regarded as paralleling that of chronotropic reserve, i.e. the major determinant of residual CO. Normally, a rise in HR during orthostatic stress is aimed at maintaining CO within normal physiological limits.<sup>45,46</sup> In our patients a greater rise in HR was found about 3 min before syncope, compared with the corresponding time intervals after tilt training (*Figure 2*). The reduction in CO, however, was similar before and after tilt training, rendering impaired chronotropic reserve unlikely before training. In the last minute before syncope, failure to maintain CO appears to involve a combined reduction in SV and HR (*Figure 2*). Reflex bradycardia is likely to be the result of excessive vagal tone, indicated by a sudden rise in spontaneous cardiac BRS.<sup>47</sup> The associated reduction in SV is suspected to reflect venous pooling of blood because of sympathetic withdrawal.<sup>46,48</sup> It is speculated that sympathetic silence at the time of syncope could lead to rapid changes in splanchnic blood flow and/or ventricular contractility, both affecting orthostatic tolerance through the underlying effects on SV.<sup>49,50</sup> Finally, the increased respiratory rate before syncope suggests a period of hyperpnea and/or hyperventilation. The consequent reduction in cerebral blood flow could further predispose to the development of reflex syncope.<sup>51</sup>

The present study had some limitations. A first limitation involves the lack of a formal control group. This is a general shortcoming in studies on tilt training because initial tilt testing, which is required for inclusion in the study, may already be an intervention.<sup>52</sup> Besides, head-up tilt testing has some diagnostic limitations related to the reproducibility.<sup>53,54</sup> According to the guidelines of the European Society of Cardiology,<sup>55</sup> the overall reproducibility of an initial positive tilt test (31–92%) is lower than for an initial negative test (85–94%). In the present study, effects of tilt-training therapy were only assessed in patients with a reproducible positive tilt test. This strategy was held to exclude false-positive responders from further analysis. Another point of critique on daily orthostatic training is that it may only be effective in highly motivated patients.<sup>56</sup> This drawback explains why some patients abandon tilt training and are reluctant to undergo prolonged therapy. Maximum compliance to therapy can be achieved by initiating a programme of in-hospital tilt training because it restores orthostatic tolerance in only a few days.<sup>52</sup> In addition, patients should be instructed to return to the hospital for a long-term follow-up. We did not address specifically the impact of age on the tilt-training response in this study, although we have shown previously that age could affect the haemodynamic response in NMS.<sup>57</sup>

Finally, sympathetic tone was assessed indirectly from HR and blood pressure measurements, analysed in the frequency domain, rather than more direct methods such as MSNA recordings.

In conclusion, this is the first study to provide a physiologic explanation for the clinical effects of tilt training in patients with typical NMS. Rather than suppressing the final trigger, daily repeated tilt testing appears to restore orthostatic tolerance by increasing the amount of vasoconstriction that can ultimately be made available during sustained orthostatic stress. We recognize that patients with recurrent NMS often suffer severe physiological burden too. Information about the benign nature of the disorder, reassurance, counselling, and coaching on appropriate postural manoeuvres to prevent presyncope from progressing to syncope, may also produce a powerful impact on syncope recurrence. More than one mechanism may operate in concert in the same patient.

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