Sympatho-vagal responses in patients with sleep and typical vasovagal syncope

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ABSTRACT

Sleep syncope is a recently described form of vasovagal syncope that interrupts sleep. The pathophysiology of this condition is uncertain but a ‘central’ non-baroreflex-mediated trigger has been suggested. In the present study, we tested the hypothesis that patients with sleep syncope have abnormal sympatho-vagal responses to non-baroreflex, but normal responses to baroreflex stimuli. We collected historical data from SS patients (patients with vasovagal syncope with sleep syncope; n = 16) and NSS patients (patients with vasovagal syncope without sleep syncope; n = 35), including demography, and triggers and symptoms during syncope. MBP (mean blood pressure), HR (heart rate) and MSNA (muscle sympathetic nerve activity) in SS patients were compared with NSS patients and matched controls (n = 16) during HG (handgrip), CPTs (cold pressor tests), HUT (head-up tilting) and tilt-induced pre-syncope. Patients and controls were of similar age and gender distribution [SS patients, age 46.0 ± 4 years (69 % female); NSS patients, 47.3 ± 4 years (63 % female); controls, 43.7 ± 5 years (69 % female)]. Compared with NSS patients, SS patients reported more fainting episodes: (i) triggered by phobias (75 compared with 37 %; P = 0.001); (ii) while in the horizontal position (44 compared with 6 %; P = 0.001); and (iii) associated with abdominal symptoms (69 compared with 9 %; P = 0.001). Compared with controls, the MBP response to HG was attenuated in SS patients (P = 0.016), and MSNA (burst frequency and incidence) responses to CPT were attenuated in both syncope groups (SS, P = 0.011 and 0.003 respectively; NSS, P = 0.021 and 0.049 respectively). MSNA responses to HUT did not differ. For both non-baroreflex and baroreflex responses, there were no differences in any of the MSNA indices between the syncope groups. Patients with vasovagal syncope, with or without sleep syncope, have very similar sympatho-vagal responses to both non-baroreflex and baroreflex stimuli. This is consistent with sleep syncope being a subform of vasovagal syncope. Attenuation of sympathetic responses to non-baroreflex pathways may be important in the mechanism of vasovagal syncope.

INTRODUCTION

Vasovagal syncope is usually triggered by emotional or postural stimuli and generally occurs when the patient is conscious and the body is upright. Emotions are thought to act via ‘central’ non-baroreflex pathways which inhibit the brainstem [1], whereas upright posture offloads the baroreceptors and disinhibits sympathetic output [2]. Exactly how these mechanisms lead to syncope is poorly understood. Haemodynamic studies have demonstrated

Key words: baroreflex, sympathetic nervous system, tilt-table testing, vagus nerve, vasovagal syncope.

Abbreviations: BP, blood pressure; CPT, cold pressor test; GTN, glyceryl trinitrate; HG, handgrip; HR, heart rate; HUT, head-up tilting; MBP, mean BP; MSNA, muscle sympathetic nerve activity; NSS, vasovagal syncope without sleep syncope; SS, vasovagal syncope with sleep syncope.

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that patients with vasovagal syncope initially respond normally to the orthostatic stress of tilting, but subsequently develop an exaggerated fall in cardiac output, probably secondary to increased venous (splanchnic) pooling of blood [3–5]. Sympathetic withdrawal and bradycardia occur later. Healthy humans will also eventually develop a vasovagal reaction depending on the degree of orthostatic stress and their vasoconstrictor reserve [6]. This has lead to the view that recurrent fainters should be regarded as normal variants, at the lower end of the spectrum of orthostatic tolerance [7]. But do all fainters fit this spectrum?

We have described previously a group of 13 patients who complained of syncope interrupting nocturnal sleep [8]. They woke up feeling faint, and lost consciousness either in bed or immediately upon standing. Most remembered abdominal discomfort at the onset of the attack. We have termed this condition ‘sleep syncope’. These patients also fainted in response to emotional and postural stimuli in the course of daily living, and during HUT (head-up tilting) in the laboratory. We therefore suggested that sleep syncope should be regarded as a new type of vasovagal syncope [9]. The number of patients reported to date is small, and the sleep episodes usually occur sporadically, so no BP (blood pressure) and very few ECG recordings have been undertaken during attacks. Furthermore, no detailed laboratory results have been published.

We therefore decided to undertake autonomic studies on sleep syncope patients, particularly MSNA (muscle sympathetic nerve activity) responses to both non-baroreflex and baroreflex stimuli. MSNA is a reliable index of vasoconstrictor tone. Non-baroreflex pathways are thought to drive the initial pressor responses to HG (handgrip) [10,11] and CPTs (cold pressor tests) [12,13]. Arterial and cardiopulmonary baroreflexes are off-loaded during HUT and hypotension, and MSNA normally increases [14,15]. We assessed non-baroreflex control from responses to HG and hand-in-ice, and baroreflex control from responses to HUT and tilt-induced syncope. We compared non-baroreflex and baroreflex responses in SS patients (patients with vasovagal syncope with sleep syncope) with those of NSS patients (patients with vasovagal syncope without sleep syncope) and controls. As described above, vasovagal reactions can be triggered by phobic reactions via inhibitory non-baroreflex pathways or baroreflex unloading via orthostatic stress. While supine, baroreflex unloading is an unlikely trigger for a vasovagal reaction. We therefore hypothesized that SS patients would have altered responses to tests that assess non-baroreflex pathways controlling BP compared with control subjects and NSS patients. Furthermore, sympathetic responses to HUT would be similar in all three groups and responses to tilt-induced hypotension would be similar in SS and NSS patients.

MATERIALS AND METHODS

Subjects

Patients were enrolled consecutively over a 4-year period (2002–2006) from the syncope clinic at Christchurch Hospital, Christchurch, New Zealand. Referrals were made by neurologists, cardiologists and general practitioners. After providing written informed consent, patients underwent autonomic and tilt testing according to a protocol approved by the Canterbury District Health Board Ethics Committee. All patients were initially assessed in the clinic and were asked to fill out a questionnaire detailing the history of their episodes of syncope. This included when the episodes started, their frequency and duration, associated symptoms, exact sequence of a typical episode, possible triggers (including specific phobic reactions), posture at the time of syncope, medical conditions and medication. ECGs were undertaken on all patients and were examined for conduction abnormalities. Patients with epilepsy, hypertension, heart failure and cerebrovascular disease were excluded. Only patients with a history typical for recurrent vasovagal syncope were accepted.

On the basis of the history, 26 patients with suspected vasovagal syncope and a life-long history of two or more episodes of sleep syncope were assigned to the SS group, and 64 patients with suspected vasovagal syncope and no sleep episodes were assigned to the NSS group. We selected 22 control volunteers (mainly hospital staff with no history of syncope), who were age- and gender-matched to both of the syncope groups. For analysis, we retrospectively selected only tilt-positive patients (48 out of 64 patients) from the NSS group. We subsequently rejected 10, 13 and six patients from the SS, NSS and control groups respectively, because of unsatisfactory MNSA recordings.

Protocol

On the morning of tilting, all medication was withheld, and patients were allowed a light caffeine-free breakfast. All studies took place at 08.00 hours in the same room at the same temperature (20°C). Patients were positioned supine on a hydraulic tilt table in the horizontal position. Three ECG electrodes were applied to the chest. Respiratory rate was monitored using thoracic impedance derived from the ECG signal. A 3-French cannula was inserted into the right brachial artery. Tungsten electrodes (1–5 μm in diameter) were placed in the right leg for microneurographic recordings of the superficial peroneal nerve according to the methods described by Hagbarth and Vallbo [16]. The signal was amplified (×1000), filtered between 700 and 2000 Hz, and integrated (0.1 s) for the purpose of counting multi-fibre bursts. Bursts were accepted provided they were pulse-synchronized, inversely related to BP during deep breathing, and had a signal-to-background ratio > 3. Burst frequency...
(bursts/min) and burst incidence (bursts/100 heart beats) were counted. Burst area was measured (arbitrary units) using custom-made analysis software. All data were recorded continuously using analogue-to-digital conversion software.

**Autonomic tests**

After ensuring recordings were stable for 20 min, baseline values for MBP (mean BP), HR (heart rate) and MSNA (burst frequency, burst incidence and burst area) were calculated from 5-min averages immediately before each manoeuvre with the patient always resting supine in the horizontal position. We ensured baseline values were consistent by allowing at least 10 min between tests and performing the tests in the same order as listed below.

**Non-baroreflex responses**

First, maximal voluntary (HG) contraction capacity was measured using a dynamometer and the patient was asked to grip at 30% of maximal value for 60 s using the left hand [10]. Secondly, a cold pressor stimulus was achieved by submerging the left hand in a bucket of ice water for 60 s [13]. MBP, HR and MSNA responses to HG and CPT were assessed by averaging levels over the final 20 s of the (60 s) stimulus. Previous studies have shown that, for HG, this period includes major incremental changes in MBP and HR but not MSNA, particularly during the first minute of stimulus, whereas reflex MSNA, driven by muscle metaboreceptors, is more important thereafter [10,11]. For CPT, however, major increases in all variables occur during the first minute [12,13]. Variability in sympathetic baseline levels and responses may occur secondary to age and gender [17,18], and pre-existing cardiovascular disease [19–21]. As described above, we avoided individual variability by screening out MSNA (burst frequency, burst incidence and burst area) and ensuring that baseline levels were achieved before each stimulus. We did not measure muscle bulk or match the groups for arm dominance. Most patients found it difficult to comply with both tests beyond the first 60 s, and after this MSNA recordings were often corrupted by motor unit activity.

**Baroreflex responses**

Finally, patients were tilted to the head-up 60° position with a foot support (HUT), fixing the right leg to the table in a partially flexed position so that it was non-weight-bearing, thus protecting the nerve recording field during tilt-up and pre-syncope. MBP, HR and MSNA levels were averaged over the third minute of tilting. If the patient was stable after 20 min, 0.4 mg of nitrolingual spray [GTN (glyceryl trinitrate)] was given sublingually. Twenty-second averages of all indices were taken during pre-syncope before tilt-down. Pre-syncope was defined as a fall in MBP to 80 mmHg or less, associated with the onset of hypotensive symptoms. When this occurred, patients were immediately tilted back to the horizontal position before loss of consciousness. This usually avoided bradycardia and vagal symptoms, allowing continuous MSNA recordings throughout pre-syncope and recovery. The maximum tilt time for patients and controls was 40 min.

**Statistics**

Comparisons among the three or two groups were undertaken using ANOVA or χ² tests as appropriate. Changes within groups were tested using paired Student’s t tests, and comparisons of these changes were made using repeated-measures ANOVA.

**RESULTS**

**Patients and subjects**

Descriptive features of the patient and control groups are listed in Table 1. Both groups of syncope patients were of similar age and gender to the controls. In the SS group, the average number of sleep episodes was 7.0 over a lifetime (range, 1–20) and 2.5 over the previous year (range, 1–10). Compared with the NSS group, SS patients more often reported a life-time history of fainting (episodes started in childhood, 63 compared with 20%; P = 0.003), total loss of consciousness in the horizontal position (44 compared with 6%; P = 0.001), and fainting triggered by phobic reactions to blood, crowds and enclosed places (75 compared with 37%; P = 0.01). Abdominal discomfort, either pain or the urge to defaecate, was more common during sleep episodes (69 compared with 9%; P = 0.001). Nearly all of the patients in the SS group were tilt-positive (88 compared with 100%; P = 0.094), and fainting times (i.e. time to pre-syncope) were similar to the NSS group (P = 0.67). GTN was administered during tilting in 69% of both syncope groups (P = 1.0). None of the control group fainted during tilting. Medication in the SS group was metoprolol (n = 2), oral contraceptive (n = 2), aspirin (n = 2), antidepressants (n = 1), statins (n = 1) and omeperazole (n = 1); and in the NSS group was metoprolol (n = 4), antidepressants (n = 5), statins (n = 3), oral contraceptive (n = 2) and aspirin (5).

**Autonomic function tests**

Haemodynamic and MSNA results at baseline and at the end of the tilting are shown in Table 2. Values did not differ among the three groups apart from MBP at the end of tilting, which was lower in the syncope groups (P = 0.001). There were no differences between the two syncope groups.

Haemodynamic responses to HG, CPT, HUT and pre-syncope are shown in Figures 1 and 2. During HG, MBP (P = 0.001) and HR (P = 0.001) increased in all groups, but the MBP response was attenuated in the SS group.
Descriptive results for the syncope patients and controls
Values are means (range) or absolute numbers (%). Total sleep, lifetime number of episodes of sleep syncope; SS episodes, number of sleep syncope episodes during the previous year; duration of hx, time between first syncope episode and the study; syncope horizontal, number of patients reporting syncope onset whilst horizontal; abdominal symptoms, number of patients who reported abdominal symptoms (pain or the urge to defaecate) during syncope episodes; lifelong syncope, number of patients who reported episodes starting in childhood; phobic reactions, number of patients who reported syncpe in response to crowds, enclosed spaces and the sight of blood; tilt-positive, number of patients who were tilt positive; tilt time, total time from head-up tilting to the end of tilting (onset of pre-syncope for SS and NSS groups and 40 min of tilting for controls) immediately before tilting back to the horizontal. *P values refer to between-group comparisons for all three groups for age and gender, and between syncope groups for the remainder.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SS patients (n = 16)</th>
<th>NSS patients (n = 35)</th>
<th>Controls (n = 16)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.0 (20–71)</td>
<td>47.3 (61–85)</td>
<td>43.6 (14–77)</td>
<td>0.70</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>68.8</td>
<td>62.9</td>
<td>68.0</td>
<td>0.88</td>
</tr>
<tr>
<td>Total sleep (n)</td>
<td>7 (2–20)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SS episodes (n)</td>
<td>2.5 (1–10)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of hx (years)</td>
<td>17.9 (1–40)</td>
<td>3.9 (0.3–20)</td>
<td>—</td>
<td>0.001</td>
</tr>
<tr>
<td>Syncpe horizontal (n)</td>
<td>7 (44%)</td>
<td>2 (6%)</td>
<td>—</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal symptoms (n)</td>
<td>11 (69%)</td>
<td>3 (9%)</td>
<td>—</td>
<td>0.012</td>
</tr>
<tr>
<td>Lifelong syncope (n)</td>
<td>10 (63%)</td>
<td>7 (20%)</td>
<td>—</td>
<td>0.094</td>
</tr>
<tr>
<td>Phobic reactions (n)</td>
<td>12 (75%)</td>
<td>13 (37%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tilt-positive (n)</td>
<td>14 (88%)</td>
<td>35 (100%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tilt time (min)</td>
<td>24.8 (19–40)</td>
<td>23.9 (8–37)</td>
<td>40</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 2 Haemodynamic and MSNA results for syncope patients and controls at baseline and at the end of tilting
Values are means ± S.E.M. *P values refer to ANOVA between all three groups. MSNA burst area values are not listed because the between-group comparisons of individual time points were not valid.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SS patients (n = 16)</th>
<th>NSS patients (n = 35)</th>
<th>Control (n = 16)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNB (mmHg)</td>
<td>99 ± 6</td>
<td>113 ± 3</td>
<td>113 ± 3</td>
<td>0.09</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67 ± 3</td>
<td>65 ± 2</td>
<td>68 ± 2</td>
<td>0.43</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>27 ± 3</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
<td>0.87</td>
</tr>
<tr>
<td>MSNA (bursts/100 beats)</td>
<td>41 ± 4</td>
<td>46 ± 3</td>
<td>42 ± 3</td>
<td>0.65</td>
</tr>
<tr>
<td>End of tilting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNB (mmHg)</td>
<td>73 ± 4</td>
<td>69 ± 2</td>
<td>102 ± 4</td>
<td>0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>82 ± 6</td>
<td>81 ± 4</td>
<td>90 ± 5</td>
<td>0.35</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>36 ± 4</td>
<td>44 ± 3</td>
<td>52 ± 6</td>
<td>0.053</td>
</tr>
<tr>
<td>MSNA (bursts/100 beats)</td>
<td>44 ± 5</td>
<td>57 ± 4</td>
<td>58 ± 4</td>
<td>0.10</td>
</tr>
</tbody>
</table>

(100 ± 6 to 110 ± 6 mmHg) compared with controls (114 ± 3 to 133 ± 5 mmHg; P = 0.016). During CPT, MBP increased in all groups (P = 0.001; between group, P = 0.32), whereas HR remained constant (P = 0.32). There were no differences between the syncope groups. During HUT, MBP was maintained in all groups during early tilting, but at end of tilting fell below baseline in controls (113 ± 3 to 102 ± 4 mmHg; P = 0.001) and syncope groups (SS group, 99 ± 6 to 73 ± 4 mmHg; P = 0.001; and NSS group, 113 ± 3 to 69 ± 2 mmHg; P = 0.001). The fall in MBP was greater in both syncope groups than controls (SS group, P = 0.01; and NSS group, P = 0.001), and was greater in the NSS group than the SS group (P = 0.031). In all groups, HR increased during early tilting (P = 0.001) and was sustained at the end of tilting (P = 0.001; between group, P = 0.35).

MSNA responses to HG, CPT and HUT are shown in Figures 3 and 4. During HG, all indices of MSNA increased (P = 0.001) in all groups (P = 0.2, 0.57 and 0.54 respectively). During CPT all indices increased (P = 0.001), but compared with control (burst frequency, 27 ± 2 to 45 ± 2 burst/min; and burst incidence, 42 ± 4 to 70 ± 5 bursts/100 beats) responses were relatively attenuated in both syncope groups (SS patients, 27 ± 3 to 42 ± 3 bursts/min and 41 ± 5 to 54 ± 5 bursts/100 beats, P = 0.011 and 0.003; and NSS patients, 29 ± 2 to 49 ± 2 bursts/min and 46 ± 3 to 64 ± 3 bursts/100 beats, P = 0.021 and 0.049). During early tilting, all of the MNNA indices increased similarly in all of the groups (P = 0.001; between group, P = 0.13, 0.35 and 0.35). At the end of tilting, the burst frequency and burst incidence remained above baseline in the control
(52 ± 6 bursts/min and 58 ± 4 bursts/100 beats) and NSS (44 ± 3 bursts/min and 57 ± 4 bursts/100 beats; $P = 0.001$) groups, and fell back to baseline in the SS group (36 ± 4 bursts/min and 44 ± 5 bursts/100 beats; $P = 0.14$ and 0.706). Burst frequency fell more in the SS group than control group ($P = 0.035$), and tended to fall in the NSS group ($P = 0.078$). For other MSNA indices, there were no differences between the syncope and control groups. For both non-baroreflex and baroreflex responses, there were no differences in any of the MSNA indices between the syncope groups.

**DISCUSSION**

The results of the present study can be summarized as follows: (i) both groups of syncope patients (with and without sleep syncope) have decreased sympathetic responses to non-baroreflex stimuli; and (ii) sympatho-vagal responses in syncope patients with and without sleep syncope are similar, with a trend towards further attenuation in the sleep group. These findings support the hypothesis that sleep syncope is a form of vasovagal syncope and may be triggered via a non-baroreflex pathway. The laboratory findings were consistent with the patients’ histories: those with sleep syncope reported vasovagal episodes at other times in response to non-baroreflex (emotional) and baroreflex (postural) stimuli. Furthermore, vasovagal symptoms occurred during sleep episodes (e.g. nausea, feeling hot, sweating and light headedness). Finally, nearly all SS patients had a vasovagal reaction during tilt testing.

Unfortunately, because of the episodic nature of sleep syncope, we have been unable to capture a continuous BP recording during an episode, and, until this is achieved, our understanding of this condition is dependent on careful history taking, ECG event monitoring and post-hoc laboratory investigations [9]. Previously, many laboratory studies have been performed in patients with vasovagal syncope during tilt-induced syncope to assess BP, ECG and MSNA continuously and dissect out the sequence of events. The assumption is that tilt-induced syncope is the physiological equivalent of vasovagal syncope [14,22,23]. To date, no study has used standard autonomic tests for comparing haemodynamic and sympathetic nerve responses in vasovagal patients with controls [24]. BP responses to HG have traditionally been criticized because of poor reproducibility; however, a substantial part of the variation can be eliminated by using continuous BP monitoring, as in the present study, instead of intermittent arm-cuff inflations [25].

There is a major variation in baseline MSNA between individuals and with age [17,18]. Furthermore, MSNA responses to CPT are lower in women [26]. We overcame this potential limitation by matching the control group for age and gender. Hence we were able to demonstrate the similarity between the syncope groups over a wide range of autonomic tests. Our
results for HG and CPT were plausible in that MBP changes were generally concordant with all indices of MSNA (with the exception of burst area in HG), the maximal level was always greatest in controls and least in the SS group. It is possible that our present study was under-powered to detect a significant difference between the syncope groups for some MSNA indices. Patient numbers were limited by the relatively low prevalence of sleep syncope and technical difficulties achieving satisfactory nerve recordings. Thus even though there was a trend for MSNA responses to be relatively more attenuated in the SS group, we emphasize that the pattern of response was always similar in the syncope groups, particularly when they both deviated from controls during CPT. The normal initial response to HUT observed in the present study confirms previous studies: BP was maintained in both syncope groups by similar increases in HR and MSNA, indicating no obvious abnormality in baroreflex control [22,23,27]. As expected, at the end of tilting, MSNA remained increased in controls, but tended to fall back to baseline levels in the syncope groups. MSNA withdrawal was more apparent in the SS group, but, again, the pattern of response was similar in the two syncope groups across most MSNA indices, moving in the opposite direction to controls. MSNA withdrawal may have been harder to demonstrate in some patients, because we tilted them back to the horizontal as soon as they became hypotensive, i.e. before complete withdrawal and increased vagal tone [22,27]. This was undertaken in the interests of patient comfort and to preserve the sympathetic recording field. The rapid return of MSNA activity immediately after returning the subject to the horizontal position is the only way to be sure that the fall off in bursts is real rather than a loss of the recording field [14]. Consequently, we did not reproduce any of the abdominal symptoms reported by patients during their sleep episodes.

Our present finding that MSNA responses to non-baroreflex pathways are decreased in patients with vasovagal and sleep syncope is novel. It may provide an explanation as to the mechanism for vasovagal syncope in the horizontal position when central blood volume is full. In this position, the baroreceptors are relatively loaded, making it unlikely that decreased vasoconstrictor reserve, impaired baroreflex function or even a paroxysmal cardio-inhibitory reflex could be the mechanism [28,29]. In patients with vasovagal syncope, some studies have demonstrated attenuation of baroreflex function, including cardiopulmonary baroreflex control of vasoconstriction [30], and arterial baroreflex control of vasoconstriction or HR [14,31]. However, others have found exaggerated (cardiopulmonary and arterial) baroreflex control of vasoconstriction or HR [32–34]. Therefore the importance of cardio-inhibitory reflexes in humans is uncertain [35,36]. Despite the often quoted ‘biphasic fainting response’, there is very little evidence that exaggerated sympathetic reactions to non-baroreflex or baroreflex stimuli are important [37,38]. Other mechanisms with the potential to temporarily impair sympathetic output (and hence vasoconstrictor reserve) need to be considered. During the first minute of static HG, BP is increased primarily by central command. Descending cortical pathways inhibit cardiogvagal activity in the brainstem thus increasing HR and cardiac output. During the second minute, BP increases further, but more in response to MSNA via the muscle metaboreflex [11]. We found that, in sleep syncope patients, BP response was attenuated during the first minute, but the exact mechanism for this was unclear. The cold pressor response is primarily an increase in vasoconstrictor MSNA activity, following stimulation of thermoreceptor fibres in the skin which connect to the CNS (central nervous system) via spinothalamic afferents [12,13]. In addition, a central response to pain (via nociceptors) may contribute to the increase in MBP by maintaining cardiac output [39]. Although baroreflex control of MSNA persists during cold stimulation, severe hypertension is not sufficient to eliminate the pressor response [40]. This reflex therefore operates via a very potent central pathway for the rapid stimulation of MSNA. We found it was decreased in both syncope groups. We suggest that attenuated
non-baroreflex responses may therefore predispose patients to vasovagal and sleep syncope. This is consistent with studies showing that HG and cold pressor stimuli may increase orthostatic tolerance in some, but not all, individuals [41,42].

Non-baroreflex mechanisms may be particularly important for maintaining BP during sleep when baroreflex function is altered; it has been demonstrated that, during slow-wave sleep, MSNA decreases simultaneously with a fall in BP, but that arousal stimuli are able to increase BP rapidly, via sudden increments of MSNA [43]. Furthermore, recent studies have shown that sudden bursts of MSNA in response to noxious arousal stimuli may be impaired in (awake) phobic patients with vasovagal syncope [44]. This may explain the association we found in the present study between sleep and phobia-triggered syncope. Patients may be predisposed to both forms of syncope because their non-baroreflex excitatory pathways are unable to override progressive hypotension during slow-wave sleep and in response to fear. Thus, in certain situations, these pathways may be as crucial for maintaining MSNA as the baroreflexes.

In conclusion, the results of the present study demonstrate that patients with sleep vasovagal syncope and patients with daytime vasovagal syncope have similar responses to sympathto-vagal function tests. Compared with matched control subjects, they have decreased responses to non-baroreflex-mediated function tests. The trend towards lower responses in sleep syncope patients is consistent with the hypothesis that sleep syncope is at the end of the normal spectrum of vasovagal susceptibility, in which syncope can occur in the supine position despite normal baroreflex function.
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Received 30 September 2008/16 February 2009; accepted 12 March 2009
Published as Immediate Publication 12 March 2009, doi:10.1042/CS20080497