Arousal elicits exaggerated inhibition of sympathetic nerve activity in phobic syncope patients

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Alerting stimuli causing arousal have been shown to elicit a reproducible transient inhibition of muscle sympathetic nerve activity (MSNA) in healthy subjects. The aim of the present study was to test whether this inhibitory response to arousal is exaggerated in patients with a history of vasovagal syncope. We studied 24 untreated syncope patients, 12 of whom met the DSM-IV-TR diagnostic criteria for blood/injury phobia and 18 age-matched healthy subjects. MSNA was recorded from the peroneal nerve at the fibular head. Arousal was induced by randomly presented trains of five electrical pulses delivered to a finger. The pulses were triggered on five consecutive R waves of the ECG, with a delay of 200 ms. Patients also underwent cardiological and neurological examinations, tilt test and a structured interview to investigate diagnostic criteria for specific phobia. The syncope patients had significantly lower resting MSNA (29 ± 2 bursts/min) and diastolic blood pressure (BP, 78 ± 2 mmHg) compared to controls (36 ± 2 bursts/min and 84 ± 3 mmHg; P < 0.05), whereas no significant differences were found for resting heart rate and systolic BP. The phobic patient group exhibited prolonged sympathetic inhibitions to arousal stimuli compared to controls and non-phobic patients, whereas no difference was found between tilt-positive and tilt-negative patients or between controls and non-phobic patients. The findings suggest that the degree of inhibition in response to arousal stimuli is related to a subjective factor coupled to fear of blood/injury. The exaggerated inhibition in patients with phobia to blood/injury may be a factor predisposing to syncope in those patients.

Keywords: muscle sympathetic nerve activity; arousal; blood/needle phobia; vasovagal syncope

Abbreviations: BP = blood pressure; MSNA = muscle sympathetic nerve activity


Introduction

Vasovagal or neurally mediated syncope is characterized by an abrupt fall of arterial blood pressure due to peripheral vasodilatation in skeletal muscles and probably also in the splanchnic vascular bed (Dietz et al., 1997; Kaufmann and Hainsworth, 2001). In agreement with this, microneurographic recordings have established that the start of the syncope is associated with cessation of sympathetic vasoconstrictor outflow to skeletal muscle (Wallin and Sundlöf, 1982; Mosqueda-Garcia et al., 1997). Simultaneously, there is often an inappropriate bradycardia (Lewis, 1932). The syncope may be triggered in different ways (e.g. by stimulation of sensory or visceral afferents, changes of posture or emotional reactions) and in some subjects the triggering factor may vary. In accordance with this, syncope patients with phobia to blood and injury have been found to have autonomic dysregulation during tilt, predisposing them to syncope also in the absence of blood/injury stimulus (Accurso et al., 2001). The syncope is often preceded by prodromal symptoms, but may sometimes occur suddenly without warning (Hainsworth, 2004). Interindividual differences in tolerance to trigger factors have been reported (Cooper and Hainsworth, 2002) and there is a characteristic sequence of cardiovascular events preceding the syncope (Julu et al., 2003). However, the central nervous mechanism that transforms a fully compensated circulation to a highly unstable system is still unknown.

Recently, we reported (Donadio et al., 2002a, b) that sensory stimuli giving rise to psychological alertness (arousal) causes a short-lasting inhibition of muscle
sympathetic nerve activity (MSNA). The inhibition displays marked interindividual differences, so that in some subjects the stimuli have little or no effect on MSNA, whereas in others, there is a marked inhibition of one or two sympathetic bursts. In a given individual the degree of inhibition was found to be reproducible over several months (Donadio et al., 2002b).

The aim of the present study was to test if the arousal-induced inhibitory response in MSNA is abnormal in patients with a history of recurrent vasovagal syncope. Our hypothesis was that in such patients arousal stimuli would induce exaggerated inhibitory responses that might contribute to the initiation of syncope.

Material and methods
Patient selection
A total of 39 patients, presenting at the Department of Neurological Sciences with a history of frequent syncope (two or more episodes per month), were screened for this study. A majority of these patients reported emotional stimuli as one possible, or the main, trigger. Patients with blood/injury phobia tended to avoid the phobic stimulus. After information that the planned investigation could contribute to a better understanding of their condition, 24 patients (age 32 ± 2 years; mean ± SE) accepted participation, whereas 15 declined, usually because of fear of the recording needles and/or the long duration of the investigation. Emotional triggers were reported by 19/24 participating patients, and 12/24 patients fulfilled the DSM IV diagnostic criteria for blood/injury phobia (Table 1).

Patients had normal cardiological (with ECG) and neurological (with EEG) examinations and they also underwent a tilt test (75° for 30 min). The tilt test was considered to be positive if the subject experienced presyncopal symptoms associated with blood pressure reductions of more than 20 mmHg for systolic (which usually corresponded to a systolic pressure level of ~70 mmHg) and/or 10 mmHg for diastolic pressure (corresponding to a diastolic pressure level of ~40 mmHg) (measured by the Finapres finger volume clamp method). Endocrinological (fasting blood glucose, glycosylated haemoglobin, renal and thyroid function) and routine haematological evaluations were normal.

The control group consisted of 18 healthy subjects (age 31 ± 1 years).

All patients and controls underwent a structured interview concerning DSM-IV-TR diagnostic criteria for specific phobia to establish whether or not a person displays an excessive fear of a not dangerous object or situation in absence of other psychiatric disorders (Sadock and Sadock, 2003).

Resting MSNA was recorded in all, but to be able to make reliable comparisons of the degree of inhibition of activity induced by the stimuli, subjects with few bursts at rest were excluded from the stimulation protocol. This decision was made during the recording and was based on the experimenter’s impression of the level of resting activity. Three subjects in each group were excluded from the stimulation protocol which was performed in 21 patients (aged 32 ± 2 years), 10 of whom were phobic to blood/injury and in 15 healthy controls (aged 31 ± 1 years).

Table 1 Individual clinical characteristics of subjects studied

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of situations evoking syncope episodes</th>
<th>Tilt test</th>
<th>Phobic criteria DSM-IV-TR</th>
<th>No Burst inhibited</th>
<th>No fainting episodes</th>
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<td>1</td>
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<tr>
<td>2</td>
<td>2 (strong emotions, orthostatic)</td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
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<td>neg</td>
<td>Yes</td>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>2 (orthostatic + hot environment)</td>
<td>neg</td>
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<tr>
<td>6</td>
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<td>7</td>
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<td>2 (violent scene, or/ostathic)</td>
<td>neg</td>
<td></td>
<td>2</td>
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<td>*</td>
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<td></td>
<td>ND</td>
</tr>
<tr>
<td>24</td>
<td>2 (needle/blood phobia, pain)</td>
<td>*</td>
<td>pos</td>
<td>Yes</td>
<td>ND</td>
</tr>
</tbody>
</table>

Subjects who met criteria for blood/injury phobia according to DSM-IV-TR indicated in bold. Situations evoking syncope based on patient’s report. NP = not performed. * = subjects excluded from the stimulation protocol.
The recordings were performed 3–5 h after a light meal. Tobacco, caffeine and alcohol were not allowed for 12 h before the examination. The experimental procedures were approved by the Human Ethics Committee at the Bologna University and all subjects gave their written, informed consent to the study.

**Measurements**

Subjects were semi-reclining (upper body ~60° and lower legs ~45° from the horizontal plane) in a comfortable chair (Fig. 1). ECG was recorded by Ag–AgCl electrodes on the chest and respiratory movements by a strain gauge belt around the lower part of the chest. Arterial finger blood pressure (BP) was monitored continuously by the volume-clamp method (Finometer model, Arnhem, The Netherlands), with the cuff around the middle phalanx of the third finger on the same side as the microneurography recording. Resting arterial BP was measured sphygmomanometrically, ~20 min after the end of the stimulation with the subjects in the semi-reclining position.

Multuni unit post-ganglionic MSNA was recorded with a tungsten microelectrode with a tip diameter of a few microns, inserted into a peroneal nerve, posterior to the fibular head. A low-impedance reference electrode was inserted subcutaneously a few centimetres away. The nerve signal was amplified (×50 000), filtered (band pass 700–2000 Hz) and fed through a discriminator for further noise reduction and audio-monitoring. A mean voltage (integrated) display was obtained by passing the original signal through a resistance–capacitance circuit (time constant 0.1 s). During the experiment, neural activity and arterial pressure were monitored on a storage oscilloscope. When a muscle nerve fascicle had been identified, small electrode adjustments were made until a site was found in which sympathetic impulses with a good signal-to-noise ratio could be recorded. A recording of MSNA was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity that fulfilled the criteria for MSNA, previously described (Sundlo¨f and Wallin, 1977). The filtered and integrated nerve signals were sampled (200 Hz) and stored together with other signals in a personal computer using a locally produced data acquisition system. In addition, all signals were stored on analogue tape.

**Stimulation**

The arousal stimulus consisted of a series of five electrical constant current square wave pulses (0.2 ms duration, 9–35 mA amplitude) triggered with a delay of 200 ms on five consecutive R-waves of the ECG and delivered to the index finger on the hand opposite to the microneurography recording (Fig. 1 and see Donadio et al., 2002b for detailed description). A post-R-wave stimulus latency of 200 ms has been shown to evoke maximal MSNA responses (Donadio et al., 2002a). Prior to the insertion of the microneurography electrodes the strength of the stimulus was adjusted to be as high as possible without causing pain, the aim being that each stimulus during the whole stimulation period would induce a high degree of alertness (arousal). The real stimuli were randomly interspersed with dummy stimuli, consisting of series of five trigger pulses without subsequent electrical shocks (i.e. subjects were unaware of the dummy stimuli). Electrical or dummy stimuli were randomly delivered every 30 s in an irregular fashion, and the same order was used for all subjects. Intervals between real stimuli varied between 30 and 210 s.

**Procedure**

After acquiring a stable recording site, resting MSNA was recorded for 15 min. After the resting period the subject was informed that stimulation was about to start at the predetermined intensity with a randomly delivered sequence of stimulation pulses. During the whole stimulation period the loudspeaker was turned off, i.e. the stimuli were not accompanied by any noise but the experimenter monitored the integrated neurogram on the oscilloscope to detect artefacts caused by muscle tension or movement. Forty-eight electrical and dummy trains were delivered in each experiment. In five patients and three control subjects one to two stimulus trains coinciding with muscle tension or other artefacts were excluded from the analysis.

**Analysis**

**Sympathetic activity**

Resting MSNA was calculated for the last 5 min of the resting period and expressed as burst incidence (bursts/100 heart beats) and burst frequency (bursts/min).

To describe the sequence of events associated with the stimuli, the following definitions were adopted (Fig. 2). The first electrical pulse (EL. STIM 1) of a stimulus was delivered in a heart cycle (between R-waves 0 and 1) denoted cardiac interval 1 (CI 1), and the subsequent four pulses were given in cardiac intervals 2–5. A sympathetic burst generated in the central nervous system during cardiac interval 1 is defined as burst 1 (and those generated during cardiac intervals 2–5 as bursts 2–5).

We quantified the effects of the stimulation on the amplitudes of bursts 0 to 6. Since the electrical artefacts from the stimuli often contaminated bursts −1 to 3 the averaged artefact from the electrical pulses was subtracted from the neurogram and eliminated from the quantitative analysis (Donadio et al., 2002b). As the absolute amplitude of the MSNA is influenced by uncontrollable factors such as the proximity of the recording electrode to the active nerve fibres and the exposed area of the recording electrode, comparisons of amplitude changes among different recordings are only possible using relative or normalized metrics. Therefore, after artefact removal all amplitudes of bursts 0–6 were normalized to the mean amplitude (=100) of the nine
reference bursts immediately preceding the stimuli (bursts −10 to −2) for either real or dummy stimulation in each subject.

Then, in each subject the effects of the stimulus on MSNA mean normalized peak amplitudes for each of bursts 0–6 were calculated as the difference from the average amplitude of the nine reference bursts both for real and dummy stimuli. The mechanisms which determine the strength and occurrence of MSNA bursts are not identical (Kienbaum et al., 2001) but since, in a previous study (Donadio et al., 2002b), the effects of the stimuli were similar for both variables we calculated only total MSNA amplitude. Absent bursts were included and given the value of 0.

Cardiovascular variables

For each electrical or dummy stimulation, the computer determined mean BP and cardiac interval of all individual cardiac cycles −10 to −20. Individual values of BP and cardiac interval were then normalized in the same way as burst amplitude, and for each cardiac cycle the difference between the respective mean value and corresponding mean value of heart cycle −10 to −2 (=100) was determined separately for real and dummy stimuli.

Statistics

All values are expressed as mean±SE. In each group and individual, two-tailed Student’s t-test for paired data was used to compare mean normalized amplitude of bursts −10 to −2 with each of bursts 0–6. Bonferroni corrections (for seven repeated tests) were made in all t-tests using a nominal level of significance at P=0.05. Separate analyses were made for real and dummy stimuli.

Repeated measures analysis of variance followed by Duncan’s test was used to test time-dependent changes from the baseline in mean BP and R–R interval. Comparison between groups in MSNA, mean BP and R–R interval were also analysed using repeated measures analysis of variance and Duncan’s test. For comparisons of resting data between subgroups of patients (tilt positive/negative and phobics/non-phobics) unpaired t-tests were used. Paired t-test was used to compare results of repeated recordings in non-phobic patients. In all tests P<0.05 was considered significant.

Results

Demographic and resting data are given in Table 2. Syncope patients (n=24) had significantly lower resting MSNA (29±2 bursts/min) and diastolic BP (78±2 mmHg) compared to controls (n=18) (36±2 bursts/min and 84±3 mmHg; P<0.05), whereas no significant differences were found for resting heart rate and systolic BP. Twelve patients (50%) met the criteria for blood/injury phobia and 12 (different) patients also presented a positive tilt test (Table 1). There was no significant difference in resting data between patients with and without positive tilt test or between phobics and non-phobics.

In the groups that underwent the stimulation protocol resting activities were similar to those in Table 2, the exception being that the difference in diastolic BP (79±2 mmHg in patients and 85±3 mmHg in controls) did not reach statistical significance (P=0.056). A positive tilt test was present in 10 syncope patients (48%) and 10 (different) patients also met the criteria for blood/injury phobia.

During the preparations for the experiment, 10 patients exhibited syncope or presyncopal reactions with dizziness, sweating, blood pressure reduction and bradycardia. All 10 met the criteria for blood/needle phobia and had previously experienced syncope reactions in association with blood sampling or needle injections. These reactions occurred during the early part of the microneurography procedure (insertion of needles or electrical stimulation of the skin or through the needles). When this happened the subject was put in a head down posture and allowed to recover for 15–20 min, whereupon (after the subject had given his consent) a new recording attempt was made. In most cases the time between fainting reaction and the
actual recording was 80–90 min. Two such episodes occurred in three and three episodes in two patients; no episodes occurred in non-phobic patients or in control subjects (Table 1).

In order to investigate the effects of such syncpe episodes on resting MSNA and on the responses to stimulation, a second recording was made in five non-phobic syncope patients. In these patients, a syncpe or a presyncopal reaction was first induced by prolonged standing (44 ± 9 min) in a room with high ambient temperature (33 ± 1°C) and humidity (50 ± 5%). When the syncopal reaction occurred, the subject was put in a head-down posture and allowed to recover for 15–20 min. After that the nerve recording was made and the stimulation sequence was delivered.

### Stimulation-induced effects on muscle sympathetic nerve activity

**Comparison with reference bursts**

On a group basis and compared to the nine reference bursts before the stimulation, electrical skin stimuli caused a significant reduction of the averaged mean voltage amplitude of bursts 0 and 1 both in patients and in controls (Table 3, Fig. 3). The percent reduction of burst amplitudes was similar in both groups (38 ± 9% and 47 ± 7%, respectively). In patients who met the criteria for blood/injury phobia, bursts 0 and 1 were significantly inhibited, whereas no bursts were inhibited in non-phobic patients even if the amplitude reduction of burst 0 was close to statistical significance ($P=0.058$). The inhibitory effects (bursts 0 and/or 1) were similar in tilt-positive and tilt-negative persons. Dummy stimuli induced no changes of the amplitudes of bursts 0–6 in any group.

On an individual basis in the control subjects, there was a significant inhibition of one or two initial bursts in 53% of the subjects, whereas no burst was inhibited in the remaining 47% (Fig. 4A). In the patient group there was greater variation in the number of inhibited bursts (zero to four). This was not related to the outcome of the tilt test: the number of inhibited bursts was similar in tilt-positive and tilt-negative patients. However, when comparing phobic and non-phobic patients more bursts were inhibited in phobics (Fig. 4B); in non-phobics, on the other hand, the inhibitory effects were similar to those in the controls (Fig. 4A). Figure 5 shows examples of the inhibitory effect in a control subject, a non-phobic and a phobic patient.

Nine of the ten phobic patients who underwent the stimulation protocol had a syncpe or a presyncopal reaction during the early part of the microneurography procedure. When relating the number of fainting episodes with the number of inhibited bursts there was a significant positive correlation (Fig. 6). In the five non-phobic patients, in whom a syncopal reaction was evoked experimentally during the second recording, the results were similar in the two experiments. Thus, both the levels of resting activity and the number of inhibited bursts were similar regardless of whether syncpe had occurred or not (Table 4).

### Comparison between groups

In phobic patients the initial stimulus-induced reduction of sympathetic burst amplitudes had a longer duration than in control subjects and in non-phobics: when comparing controls and phobics the phobic patients had significantly reduced amplitude of burst 2 and when comparing phobics and non-phobics both bursts 2 and 3 had significantly lower amplitudes in the phobic patients. Corresponding comparisons between controls and non-phobics, tilt-positive and tilt-negative patients or between males and females showed no significant differences.

### Stimulation-induced effects on cardiovascular variables

Compared to the prestimulus reference beats, the stimuli induced minor changes in mean BP (Fig. 3). In control subjects and the whole group of syncope patients there were small but significant transient increases of pressure. In the group of non-phobics there was a similar small increase but in the phobics the effect was non-significant. When comparing the effects between the groups there were no significant differences.

Compared to the pre-stimulus heart rate the electrical stimuli induced significant bradycardia both in controls and syncope patients (Fig. 3). In this respect there was no difference between phobic and non-phobic patients. In phobics the bradycardia was followed by

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**Table 2: Demographic characteristics and baseline values in syncope and control subjects**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>MSNA</th>
<th>HR</th>
<th>BP</th>
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<tbody>
<tr>
<td></td>
<td>Males/females</td>
<td>Bursts/min</td>
<td>Bursts/100 HB</td>
<td>beats/min</td>
<td>Systolic mmHg</td>
<td>Diastolic mmHg</td>
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<tr>
<td>-----</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>---------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Patients</td>
<td>24</td>
<td>13 M: 11 F</td>
<td>32 ± 2</td>
<td>29 ± 2*</td>
<td>45 ± 3</td>
<td>66 ± 2</td>
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<tr>
<td>Phobics</td>
<td>12</td>
<td>8 M: 4 F</td>
<td>34 ± 3</td>
<td>32 ± 2</td>
<td>49 ± 4</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>Non-phobics</td>
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<td>31 ± 2</td>
<td>26 ± 3</td>
<td>41 ± 6</td>
<td>66 ± 3</td>
</tr>
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<td>Controls</td>
<td>18</td>
<td>9 M: 9 F</td>
<td>31 ± 1</td>
<td>36 ± 2</td>
<td>52 ± 3</td>
<td>71 ± 2</td>
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</table>

HR = heart rate; SBP = systolic BP; DBP = diastolic BP; BMI = body mass index. *P < 0.05 significant difference between groups.
a short-lasting cardiac acceleration; however, there was no significant difference in responses between the groups.

**Discussion**

The main findings of the present study were (i) patients with recurrent syncope had lower resting levels of MSNA and diastolic blood pressure in the sitting posture than an age-matched control group, (ii) arousal induced by somatosensory stimuli led to an exaggerated inhibition of MSNA in those syncope patients who met the criteria for phobia to blood/injury, (iii) in contrast, in patients who did not meet these criteria, the inhibitory effects of the stimuli were similar to those in the control group.

**Table 3** Group comparison of stimulus induced inhibitory and excitatory effects on MSNA bursts

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<th>Burst number</th>
<th>0</th>
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<th>3</th>
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<td>***</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</table>

Analysis made with seven Bonferroni-corrected repeated t-tests. Significance of burst inhibition compared to baseline (bursts −10 to −2) indicated by the following symbols: — no significant effect; †P < 0.05; ‡P < 0.01; ‡‡P < 0.001. Significance of increased burst amplitude (compared to baseline) indicated by §P < 0.05.

**Fig. 3** Stimulus-induced effects on mean voltage neurogram and cardiovascular parameters. Averaged changes from baseline (bursts −10 to −2) induced by five electrical pulses on total burst amplitude (MSNA amplitude), mean blood pressure (mean BP) and cardiac interval (R–R interval) in controls, non-phobic and phobic syncope patients. All values expressed as percentages of mean values in bursts or cardiac intervals −10 to −2. The bar represents the start of the stimulation. * = significant change from baseline. See the text for explanation.

A short-lasting cardiac acceleration; however, there was no significant difference in responses between the groups.

**Discussion**

The main findings of the present study were (i) patients with recurrent syncope had lower resting levels of MSNA and diastolic blood pressure in the sitting posture than an age-matched control group, (ii) arousal induced by somatosensory stimuli led to an exaggerated inhibition of MSNA in those syncope patients who met the criteria for phobia to blood/injury, (iii) in contrast, in patients who did not meet these criteria, the inhibitory effects of the stimuli were similar to those in the control group.
Resting sympathetic activity

In previous studies of patients with recurrent syncope resting supine MSNA was found to be normal (Mosqueda-Garcia et al., 1997). Also resting supine blood pressure has mostly been normal (Accurso et al., 2001; Cooper and Hainsworth, 2002) but in one study systolic (but not diastolic) pressure was lower than in the control group (Mosqueda-Garcia et al., 1997). Our finding of decreased resting MSNA and blood pressure is probably a consequence of the patients being investigated while sitting in a reclining posture: orthostatic tolerance is known to be reduced in patients with repeated syncope (Mosqueda-Garcia et al., 1997; Accurso et al., 2001; Cooper and Hainsworth, 2002). Since resting sympathetic activity and blood pressure in non-phobic patients were similar irrespective of whether syncope had occurred or not during the experiment (Table 4), it is unlikely that a
The second recording was made after an evoked syncopal episode. Same numbering of subjects as in Table 1.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Resting results</th>
<th>Arousal results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSNA (bursts/100HB)</td>
<td>Systolic BP (mm/Hg)</td>
</tr>
<tr>
<td></td>
<td>First rec</td>
<td>Second rec</td>
</tr>
<tr>
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<tr>
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<tr>
<td>P value</td>
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<td>1</td>
</tr>
</tbody>
</table>

The second recording was made after an evoked syncopal episode. Same numbering of subjects as in Table 1. SE = standard error; rec = recording.

residual effect of the syncope contaminated our resting data in phobic patients.

**Sympathetic responses to stimuli**

The mechanism underlying inhibitory responses in MSNA to sensory stimulation is unclear. Since visual and somatosensory (Donadio et al., 2002a) and auditory (Eder et al., unpublished observation) stimuli have similar effects, the inhibition is probably an unspecific arousal response. If the peripheral conduction delay is compensated for, the inhibition may start almost immediately after the stimulus, indicating that the reaction has a central nervous origin and is not a reflex response to a cardiovascular perturbation. Furthermore, when experiments were repeated after a delay of 1–6 months, the occurrence and the strength of the inhibitory responses were reproducible (Donadio et al., 2002b). Taken together, these findings suggest that the responsiveness is robust and characteristic for the individual.

In the present study we found no differences when comparing sympathetic inhibitory responses among tilt-positive and tilt-negative patients. However, the sympathetic inhibitions were exaggerated in phobic patients both when compared to non-phobic syncope patients and control subjects. The most striking findings were that at least one sympathetic burst was inhibited in all phobic patients and in some patients there was a significant inhibition of three or four bursts. In contrast, no sympathetic inhibition occurred in ~50% of controls and non-phobic syncope patients, and the maximum number of inhibited bursts was two (Fig. 4). Hence, the exaggerated sympathetic inhibitory responses to alerting stimuli are related to phobia rather than to syncope per se.

Sensory stimuli are important components of every day life and adequate responses are essential for our ability to avoid injury. Fear of injury is a normal human reaction, the extent of which varies markedly between individuals. In patients with blood–injury phobia the fear is out of proportion and may impede daily life. Blood/injury phobia is a common disorder with an estimated prevalence of 3–4% in the general population (Agras et al., 1969). The fear can be triggered by seeing blood, by sustaining an injury or by receiving an injection or some other invasive medical procedure. In about 80% of these cases the phobic response is characterized by syncope/presyncope but the underlying mechanism is poorly understood (Ost et al., 1984; Thyer et al., 1985). Although psychological factors involved in emotional fainting have been investigated (Kleinknecht et al., 1997; Kouakam et al., 2002) the step from psychological input to autonomic circulatory control remains elusive.

A possible interpretation of the present results would be that the inhibition of MSNA is part of an autonomic response to arousal, the strength of which reflects a fear-related subjective factor. As suggested by the positive correlation between number of bursts inhibited and syncope episodes, the exaggerated sympathetic inhibition may then be a counterpart of their exaggerated fear of injury: the stronger the fear, the more pronounced the inhibition (Fig. 6).

In nine of the ten phobic patients who underwent the stimulation protocol presyncopal or syncopal reactions occurred in the beginning of the experiment. This raises the possibility that the exaggerated inhibition to stimuli was a lingering consequence of the syncope. However, in the five non-phobic patients who experienced an experimentally induced syncope reaction in the second recording, the number of inhibited bursts was similar, regardless of whether or not the stimulation sequence was preceded by syncope (Table 4). This finding makes it very unlikely that the exaggerated MSNA inhibition in phobic patients is due to syncope; instead it supports the idea of a causal relationship between the degree of fear and the number of inhibited bursts. Patients exhibiting repeated syncope episodes during the study may have had more prolonged after-effects than those who had one episode. This makes it difficult to unequivocally exclude an influence of several
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preceding syncopes on the inhibitory mechanism. Nevertheless, since five non-phobic patients had similar inhibitory effects with and without preceding syncope, such a hypothetical influence does not alter the conclusion, that syncope cannot explain the prolonged inhibition in phobic patients.

Recently, syncope has been described in association with sleep, as a new clinical variant of vasovagal syncope (Jardine et al., 2006). Patients affected by this condition presented fainting episodes during sleep, usually characterized by evidence of exaggerated vagal activity. Some of them also had occasional daytime fainting episodes when seeing blood (Krediet et al., 2004). Our data provide no indication that the mechanism underlying phobic syncope is similar to that giving rise to syncope during sleep. In the present study a fearful stimulus gave rise to exaggerated sympathetic inhibition without prominent bradycardia. On the other hand, the effect of arousal on MSNA during the awake state (i.e. inhibition) is different from that during sleep, when arousal induces an excitatory response (Hornyak et al., 1991).

The present results raise the question whether or not the basic mechanism underlying the MSNA inhibition in control subjects (and non-phobic syncope patients) is similar to that of phobic subjects. A possibility would be that the interindividual differences in response among control subjects are related to ‘physiological’ interindividual differences in fear of blood/injury. Another alternative would be that inhibitory responses in control subjects have a more general background and extend to other potential threat stimuli, including learned fear.

**Cardiovascular responses**

There were no differences in cardiovascular responses between controls, the whole syncope group or any subgroup among the syncope patients. Thus, for an arousal induced sympathetic inhibition to evoke syncope (or even a clear blood pressure reduction), it has to be much more prolonged than in the present study, and/or to act in concert with other mechanisms.

One such factor may be orthostatic intolerance. Accurso et al. (2001) found evidence of weak baroreflex responses: phobic patients had more pronounced blood pressure falls during a head up tilt to 70° than healthy controls. Mosqueda-Garcia et al. (1997) and Cooper and Hainsworth (2002) also found evidence of reduced baroreflex responses in syncope patients but did not specify whether patients had phobia to blood/injury. The latter study also demonstrated markedly blunted MSNA responses to tilt, a finding which may explain why our patients, who were investigated in a sitting position, had reduced resting levels of MSNA.

Another factor of importance may be mental activation (stress): during the first 30–60 s, stress evoked by mental arithmetic or the colour word conflict test is associated with a reduction of MSNA (Callister et al., 1992).

Extrapolating from these findings, phobic patients may be particularly sensitive to arousal stimuli in stressful situations in upright postures. Compared to normal subjects blood pressure and sympathetic activity are low to start with and when a fearful stimulus (blood/injury) occurs the sympathetic inhibition has longer duration than in normal subjects. The combination of these factors may then be powerful enough to trigger a central nervous reaction inducing bradycardia, vasodilatation and syncope (Hainsworth, 2004).

In accordance with this interpretation, previous animal data has shown that a central neuronal ‘programme’ may evoke the characteristic autonomic response of vasovagal syncope. By stimulating hypothalamic centres in the cat involved in the defence reaction, bradycardia, sympatho-inhibition, vasodilatation and hypotension have been evoked (Abrahams et al., 1964; Smith, 1974; Koizumi and Kollai, 1981). Furthermore, amygdala and insula have been implicated in awareness and autonomic arousal of conditioned fear (Critchley et al., 2002; Critchley, 2005) and both structures may play a role for emotionally evoked syncope.

**Methodological aspects**

To demonstrate an inhibitory effect of a stimulus requires a certain level of background activity. There are marked interindividual differences in the number of MSNA bursts at rest and in subjects with few bursts at rest, the stimulus and its effects will often occur in cardiac intervals without activity (Sundlöf and Wallin, 1977). Because of this interindividual variability (and since all subjects received the same number of stimuli) the reliability of the significance analysis will be weaker in subjects with fewer bursts. To reduce this confounding effect we investigated the subjects in the sitting posture [the number of sympathetic bursts at rest is higher in sitting than in lying (Burke et al., 1977)] and excluded subjects whom the investigator judged to have too few bursts at rest. It is unlikely that this bias towards subjects with higher activity has influenced the results in a significant way: the exclusions were few and equal among patients and controls.

In summary, we found that patients with phobia to blood/injury exhibit prolonged sympathetic inhibition to arousal evoked by somatosensory stimulation. We suggest that the inhibition is linked to a subjective factor coupled to fear and that the prolonged inhibition is a component of an autonomic response induced by exaggerated fear in phobic patients.

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