Autonomic and electrocardiographic changes in cardioinhibitory syncope

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Aims Cardioinhibitory syncope (CS) is a neurally mediated response causing bradycardia or asystole. This study reports on changes in blood pressure, heart rate variability (HRV), and ECG patterns before and after syncope with asystole.

Methods and results Thirty-five patients with CS and a matched control group were submitted to 60° head-up tilt for 20 min with the addition of nitroglycerin. Syncope developed after a tilt-duration of 1.082 (range 50–1.734 s). Asystole lasted for 21.3 s (range 3.4–80.2 s) and was preceded by sinus rhythm in 21, junctional rhythm in 10, and atrioventricular block in four. Asystole was followed by sinus rhythm in four, junctional rhythm in 24, atrioventricular block in four, and atrial fibrillation in three. The two groups did not differ with respect to supine heart rate, HRV or blood pressure. Prior to syncope, patients showed significant increases in total and low-frequency HRV with reductions in high-frequency HRV and a progressive shortening of the PR-interval.

Conclusion Syncope was preceded by marked accentuation of sympathetic tone with a sudden shift in heart rate control to vagal dominance. Asystole was accompanied by vagally induced, benign arrhythmia in the majority of the patients.

KEYWORDS Reflex syncope; Arrhythmia; Nervous system; Autonomic; Vagus nerve; Heart rate

Syncope is defined as a transient, self-limited loss of consciousness, the onset of which is relatively rapid, and where the subsequent recovery is usually prompt and complete. The underlying mechanism is a transient global cerebral hypoperfusion. Reflex syncope refers to a neurally mediated response that gives rise to vasodilatation and/or bradycardia. According to the pattern of change in heart rate or blood pressure, reflex syncope can be classified as vasodepressor (vasodilatory hypotension), cardioinhibitory (bradycardia/asystole) or a mixture of the two main patterns. These typical responses are thought to represent a hypersensitive autonomic system over-responding to various stimuli among which 'underfilling' of the left ventricle with subsequent stimulation of vagal afferent nerves is the most likely candidate in relation to head-up tilt. Among the reflex syncope patterns, tilt induced prolonged asystole has been advocated to identify a distinct subgroup in whom permanent pacemaker implantation has been proposed and case reports have suggested that the cardioinhibitory response pattern could be associated with significant arrhythmias. Electrophysiological and haemodynamic changes associated with cardioinhibitory syncope (CS) have so far only been described on the basis of single case stories. Accordingly, the present study is the first to report on haemodynamics, heart rate variability (HRV), and ECG changes before and following syncope in a group of patients with a cardioinhibitory response to head-up tilt compared to those obtained in age and sex matched patients showing a normal response to tilt.

Methods

Study population

Patients with CS were included consecutively from persons referred to our laboratory for tilt testing on suspicion of reflex syncope. The patients had to fulfil the VASIS criteria corresponding to class 2b, i.e. they had to show asystole lasting more than 3 s in response to head-up tilting before or after administration of sublingual nitroglycerin. Twenty women and 15 men out of a total of 1,365 tilt tests performed in the period from May 2004 to November 2006 showed a cardioinhibitory response and where therefore eligible to be included. All patients referred to our clinic are submitted to at standardized tilt test as described below and the sampled data are stored for subsequent analysis. Thus, it was possible to perform a case-controlled study in which the control group consisted of age and sex matched persons referred on suspicion of reflex syncope but showing a normal response to head-up tilting with nitroglycerin administration. None of the patients had significant cardiovascular
disease, and all were free of medication up to and at the time of the tilt table test. All tests were performed between 8 a.m. and 2 p.m. in the non-fasting state at standard room temperature. All had a normal baseline 12-lead ECG and a normal 48 h Holter recording.

Protocol
The participants were submitted to a standardized test consisting of 20 min of head-up tilt to 60° followed by sublingual nitroglycerin (0.4 mg) with continued tilting for 15 min or till the occurrence of syncope. The tilt test was preceded and followed by 10 min of rest in the supine position. RR-intervals and blood pressure were measured continuously from one precordial ECG-lead and by Finometer equipment, respectively. Data were sampled at 1.0 kHz and analysed using commercial software (Chart 5.59, AD Instruments Inc, Colorado Springs, USA).

Recorded variables
The ECG was high-pass filtered with a cut-off frequency of 0.6 Hz and was analysed for RR-, PR-, and QT-intervals in the supine and head-up tilted positions. The QT-intervals were also analysed after rate-correction using the Bazett formula. Data were expressed as the mean of 200 cardiac cycles obtained 1 min prior to and after 5 min following the head-up tilt. The ECG-derived intervals were further analysed on a beat-to-beat basis in the last 25 cardiac cycles leading up to the occurrence of asystole.

Data analysis
Heart rate variability was quantified by mean values (meanNN) and standard deviations (SDNN) of normal RR-intervals in the supine and head-up tilted positions as well as by the SD of the difference between successive normal beats (SDSD) and by frequency analysis using Fast Fourier Transformation (FFT). The FFT employed 1,024 points, with a standard Welch filter and the low- and high-frequency components were from 0.04 to 0.15 Hz and from 0.15 to 0.40 Hz, respectively. Low- and high-frequency variations in heart rate were expressed by normalized units according to current guidelines.1 Heart rate variability data were obtained from 300 cardiac cycles recorded in supine position prior to and after 5 min of head-up tilt. In the supine group, HRV was furthermore analysed on a beat-to-beat basis in the last 300 cardiac cycles leading up to the occurrence of asystole.

Statistics
Data are expressed as mean values and SDs except in cases where a normal distribution could not be assumed. In the latter case, data are given as the median with ranges. Comparisons of continuous normally distributed variables were made with unpaired t-test between groups and by paired t-test within groups using a two-sided significance level of 5%. Comparisons of categorical data were made with the χ² test.

Results
A total of 70 (40 women and 30 men) subjects were included in the study equally divided among those who developed CS to head-up tilt and those who did not (controls). The two groups did not differ with respect to age (32.6 ± 1.8 (CS) vs. 31.5 ± 1.8 years), supine resting heart rate (66.1 ± 1.7 (CS) vs. 69.1 ± 1.6 min⁻¹), supine resting systolic blood pressure (116.4 ± 2.8 (CS) vs. 115.1 ± 2.4 mm Hg), or supine resting diastolic blood pressure (57.0 ± 1.8 (CS) vs. 60.0 ± 2.6 mm Hg). In response to head-up tilt, heart rate increased to 75.7 ± 1.8 min⁻¹ (CS) and 76.8 ± 1.7 min⁻¹ (controls), systolic blood pressure increased to 126.0 ± 3.6 mm Hg (CS) and 128.5 ± 2.6 mm Hg (controls) and diastolic blood pressure increased to 73.3 ± 2.6 mm Hg (CS) and 76.3 ± 2.2 mm Hg (controls). The levels of these haemodynamic variables did not differ significantly between groups in the head-up tilted position. The ECG-derived intervals are shown in Table 1 and were within normal range in both groups. In the final 25 cardiac cycles leading up to asystole, PR-intervals were shortened by 10.1% (r² = 0.917) and RR-intervals by 7.4% (r² = 0.689).

Data describing HRV in the supine and tilted positions are shown in Table 2. The results did not differ between groups in the supine or the head-up tilted positions. In the cardioinhibitory group, significant reductions were found during tilt in SDs of differences between successive normal beats (SDSD) and in normalized high-frequency variations (HFₜ), whereas the ratio between low- and high-frequency variations (LF/HF) increased significantly. In the control group, significant reductions were found during tilt in SDs of normal beats (SDNN) and in both normalized low variations (LFₜ) and HFₜ, whereas LF/HF increased significantly. The relative changes in HRV from the patients who developed asystole are given in Figure 1. Significant increases were found in SDNN from 67.1 to 91.7 ms (P = 0.002) and in LFₜ from 64.9 to

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<th>Table 1 ECG-derived intervals in supine and head-up tilted position</th>
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Standard electrocardiographic intervals obtained in the supine and 60° head-up tilted positions in patients with cardioinhibitory syncope and matched controls with a normal response to tilt. Corrected QT-intervals (QTc) were derived by the Bazett formula. Comparisons were made with the t-test. P-values are given for unpaired comparison between patients with cardioinhibitory syncope and controls, and for paired comparisons between supine and head-up tilted positions in cardioinhibitory syncope (CS) and controls (C).
with significant reductions in HF from 27.9 to 21.6 (P = 0.042).

Patients in the cardioinhibitory group developed syncope after a median tilt-duration of 1,082 (range 50–1,734 s). Seventeen patients developed syncope before administration of nitroglycerin. Asystole lasted for a median of 21.3 s (range 3.4–80.2 s) and was preceded by sinus rhythm in 21, junctional rhythm in 10, atrioventricular block in four. The episodes of arrhythmia before asystole lasted for 11.7 s (range 2.0–30.3 s). Asystole was followed by sinus rhythm in four, junctional rhythm in 24, atrioventricular block in four, and atrial fibrillation (AF) in three. The episodes of arrhythmia after asystole lasted for 65.2 s (range 7.3–611.5 s).

Discussion
This is the first comprehensive study of haemodynamic and electrophysiological changes occurring in conjunction with reflex syncope of the cardioinhibitory type. It shows that it is not possible on the basis of standard haemodynamics or measures of HRV obtained in the supine position to distinguish subjects who develop this reaction from those who have a normal tilt test. Subtle differences could be noted in the ECG-derived intervals in the supine position and similar discrete disparities arose in these intervals and in HRV between the syncope group and the controls during tilt. The majority of patients developed self-terminating arrhythmia either before and/or after the syncope—mostly in the form of sinus arrest and junctional escape rhythm. Cardioinhibition is far less frequent than other patterns of reflex syncope occurring during head-up tilt. Previous studies have reported frequencies between 17 and 4% in patients referred for suspected syncope, which corresponds well with our finding of 2.6%. The cardioinhibitory response has previously been named sinoatrial syncope,9 and malignant vasovagal syndrome10 but both terms seem to be misleading. Cardioinhibition is due not only to failure of the normal sinoatrial rhythm and lack of atrioventricular escape but also to the absence of an idioventricular pacemaker. Asystole during head-up tilt does not necessarily imply a malignant outcome and seems not to be associated with increased risk of recurrence. Baron-Esquivias et al.8 studied the long-term outcome in 330 syncope patients of whom 52 showed a cardioinhibitory response and found no cardiac related deaths during a mean follow-up of 40.7 months nor were they able to detect any difference in syncope recurrence between patients responding to head-up tilt with asystole or the vasodepressor pattern. To confuse matters further, Fitzpatrick et al.11 used the name malignant vasovagal syndrome for a group of middle-aged patients with recurrent syncope without prodromes but irrespective of whether the patients responded with vasodilatation, bradycardia or both during head-up tilt. Even though 10 of 53 patients in that study had signs of structural heart disease, no death occurred during long-term follow-up. Baseline haemodynamics have previously been found incapable of distinguishing patients with vasodepressor response from controls12 and though the patients in that study are not directly comparable to ours, it stresses the

<table>
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<tr>
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<th>SDNN</th>
<th>SDSD</th>
<th>LF (ν)</th>
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<tr>
<td><strong>Cardioinhibitory</strong></td>
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<tr>
<td>Supine</td>
<td>85.0 (8.7)</td>
<td>74.0 (12.2)</td>
<td>57.2 (8.0)</td>
<td>40.1 (3.1)</td>
<td>1.81 (0.29)</td>
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<tr>
<td>Tilted</td>
<td>67.1 (7.3)</td>
<td>38.5 (5.3)</td>
<td>64.9 (3.6)</td>
<td>27.9 (2.7)</td>
<td>5.08 (1.13)</td>
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<td><strong>Control</strong></td>
<td></td>
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<tr>
<td>Supine</td>
<td>86.6 (11.1)</td>
<td>61.0 (6.9)</td>
<td>54.0 (3.3)</td>
<td>36.3 (2.9)</td>
<td>2.44 (0.43)</td>
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<tr>
<td>Tilted</td>
<td>59.2 (8.7)</td>
<td>45.0 (13.8)</td>
<td>66.3 (3.6)</td>
<td>27.3 (3.1)</td>
<td>4.50 (0.94)</td>
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<tr>
<td><strong>Cardioinhibitory vs. control</strong></td>
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<tr>
<td>Supine (P-values)</td>
<td>0.98</td>
<td>0.32</td>
<td>0.77</td>
<td>0.32</td>
<td>0.23</td>
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<tr>
<td>Tilted (P-values)</td>
<td>0.45</td>
<td>0.69</td>
<td>0.70</td>
<td>0.80</td>
<td>0.70</td>
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<tr>
<td>Supine vs. tilted</td>
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<tr>
<td>Cardioinhibitory (P-values)</td>
<td>0.10</td>
<td>0.01</td>
<td>0.40</td>
<td>0.0001</td>
<td>0.004</td>
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<td>Control (P-values)</td>
<td>0.03</td>
<td>0.25</td>
<td>0.001</td>
<td>0.0025</td>
<td>0.009</td>
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</table>

Mean values (standard error) of heart rate variability obtained in a 5 min period in the supine and 60° head-up tilted position. The variability is expressed as standard deviation of normal beats (SDNN), standard deviation of differences between successive normal beats (SDSD), normalized low-frequency (LF(ν)) and high-frequency variation (HF(ν)) and their ratio (LF/HF) obtained by Fast Fourier Transformation. Comparisons were made with unpaired and paired t-test.
point that there are no major recognizable cardiovascular abnormalities associated with the tendency to develop reflex syncope.

Increased vagal activity shortens the atrial refractory period heterogeneously\(^{13}\) and inhibits impulse generation in the sinoatrial node\(^{14}\) and slows conduction through the atrioventricular node.\(^{15}\) Heterogeneously shortened refractory period predisposes to AF, inhibition of the sinoatrial node ultimately leads to sinus arrest and enhanced or asynchronous activity to the atrioventricular node may cause atrioventricular blockade. Reports based on single case stories have found asystole to be accompanied by arrhythmias ranging from AF to junctional or ventricular escape rhythm.\(^{4}\) The arrhythmia encountered in our study and in previous case reports could thus be ascribed to enhanced or asynchronous vagal activity.

Three main questions arise on the basis of previous and current observations: (1) how is the asystole induced, (2) why is the supraventricular arrest not accompanied by idioventricular escape rhythm, and (3) what causes the heart to resume electrical activity.

Reflex syncope during head-up tilt is commonly ascribed to the progressive reduction in central blood volume and thus in cardiac filling leading to activation of vagal afferent fibres from receptors in the left ventricular wall or from central venous low-pressure receptors. Activation of these vagal afferents seems to require preconditioning by high levels of sympathetic activity to the heart in animals\(^{16}\) and the susceptibility to upright tilt-induced syncope can accordingly be facilitated in humans by low-level isoproterenol infusions.\(^{17}\) The activity of the autonomic nerves to the heart during head-up tilt can be inferred from analysis of HRV. These analyses have yielded conflicting results but according to Furlan et al.\(^{18}\) there seem to be two main patterns—one with progressively increasing low-frequency activity and one with a progressive shift from the low to the high-frequency component. In our study, head-up tilting was associated with decreases in high-frequency heart rate variations and by significantly greater shortening of the RR- and PR-intervals in patients who experienced syncope indicating a higher degree of vagal withdrawal in the initial phases. In the minutes leading up to the onset of syncope, HRV increased with a shift towards low-frequency variations accompanied by a progressive shortening of the RR- and PR-intervals indicating a further increase in sympathetic activity, in vagal withdrawal or a combination of these. Thus, the afferent part of the reflex syncope during head-up tilt is probably activated by increased sympathetic tone combined with ‘underfilling’ of the central cardiovascular compartment.

Direct stimulation of the vagal nerve is known to be able to provoke asystole in humans\(^{19}\) suggesting that the cardioinhibitory response itself is brought about by a sudden vagal activation. From animal studies it is known that stimulation of the right vagal nerve has a more pronounced effect on the sinoatrial node whereas the left branch has a stronger influence on the atrioventricular conduction.\(^{20}\) It may thus be hypothesized that the right vagal nerve is preferentially activated in patients with sinus arrest and asystole whereas the left vagal nerve most likely is the more active in patients with atrioventricular block and asystole.

Accordingly, it seems reasonable to suggest that the asystole itself is caused by a combination of sympathetic withdrawal and intense synchronous vagal activation except in cases with atrioventricular block where activity in the left vagal nerve may be dominating.

When the sinoatrial pacemaker fails, a junctional escape pacemaker will usually emerge and if this escape pacemaker fails, more primitive idioventricular pacemakers should maintain cardiac rhythm. It has been known for a number of years that overdrive cardiac pacing may result in asystole with lack of escape in patients with total atrioventricular block when the overdrive-pacing rate is high, if the pacing period is long and if cessation is sudden.\(^{21}\) However, experimental studies have shown that the sinoatrial node is particularly resistant to this frequency-dependent suppression of pacemaker activity and the presence of arrhythmia, when asystole is terminated, points to a continued presence of a high vagal activity to the heart during asystole. A high vagal tone activates the inwardly rectifying muscarinic potassium channel (I\(_{K\text{ACH}}\)) hyperpolarizing the pacemaker tissue and could cause asystole in parallel to the activation of ATP-sensitive potassium channels used in cardioplegia during cardiac surgery.\(^{22}\) The I\(_{K\text{ACH}}\) is inactivated by stretch and this may explain the termination of asystole when patients are brought to the horizontal position and venous return is re-established. It seems unlikely that the termination was caused by vagal withdrawal considering the presence of vagally induced arrhythmia and the absence of postvagal tachycardia\(^{23}\) following asystole. According to the hypotheses, CS may be counteracted by limiting the ‘underfilling’ of the central cardiovascular compartment, reducing the β-adrenergic stimulation of the heart, and/or by blocking the I\(_{K\text{ACH}}\). In experimental studies, the bee venom peptide tertapiin can be used to selectively block I\(_{K\text{ACH}}\),\(^{24}\) but presently there are only non-specific antagonists of I\(_{K\text{ACH}}\) such as amiodarone\(^{25}\) for use in humans.

**Conclusion**

Cardioinhibitory syncope elicited by head-up tilting is often associated with arrhythmias most likely ascribable to an increase in vagal tone. Patients with CS cannot be identified by standard haemodynamics or HRV components in the supine, pre-test position. On the basis of our results and the available literature, it is hypothesized that an increased sympathetic tone prior to the event sensitzes vagal afferents from the central cardiovascular system causing a sudden high vagal efferent activity leading to arrhythmia and asystole. The asystole is sustained by the high vagal tone and is probably terminated by mechanical stretch resulting from re-established venous return in the horizontal position.

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**Reference**

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