Cardiac Autonomic Patterns Preceding Occasional Vasovagal Reactions in Healthy Humans

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Background—The wide range of clinical presentation of orthostatic vasovagal syncope suggests different underlying changes in the cardiac autonomic modulation.

Methods and Results—To evaluate the beat-by-beat modifications in the neural control of heart period preceding a syncopal event, we studied RR interval variability in 22 healthy subjects who experienced fainting for the first time during a 90° head-up tilt and in 22 control subjects by means of time-variant power spectral analysis. Sympathetic and vagal modulations to the sinoatrial node were assessed by the normalized power of the low-frequency (LF, ~0.1-Hz) and high-frequency (HF, ~0.25-Hz) oscillatory components of RR variability. When the patients were supine, no differences were observed in the hemodynamic and spectral parameters of the 2 groups. During the tilt procedure, RR, LFNU, and HFNU (NU = normalized units) values were relatively stable in control subjects. During early tilt (T1), subjects with syncope had reduced RR intervals compared with control subjects. In 13 subjects with syncope, RR decreased while LFNU and LF/HF increased in the last minute of tilt before syncope (T2). Conversely, in the remaining 9 fainters, LFNU and LF/HF decreased from T1 to T2 and HFNU increased slightly.

Conclusions—Two different patterns may be recognized in the cardiac autonomic changes preceding an occasional vasovagal event, namely, one characterized by a progressive increase of the marker of cardiac sympathetic modulation up to the onset of syncope, the other by a sympathetic inhibition with an impending vagal predominance. The recognition of different pathophysiological mechanisms in fainters may have important therapeutic implications.

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Key Words: syncope □ nervous system, autonomic □ spectroscopy

Vasovagal syncope is a common clinical event, the pathogenetic mechanisms of which are still poorly understood.1

On the basis of experimental observations,2 it has been hypothesized that a possible trigger mechanism in humans might be the inappropriate mechanical activation of ventricular vagal unmyelinated afferents in the presence of reduced ventricular filling. In particular, the stimulation of ventricular vagal receptors would be produced by an enhancement of heart contractility due to an exaggerated cardiac sympathetic activation.

The possibility that an initial cardiac sympathetic overactivity might promote vasovagal reactions is supported by the clinical observation of a transient rise in heart rate before syncope.3 In addition, it has been observed that the administration of exogenous catecholamines4 or nitroglycerin5 before a tilt test promotes neurogenic fainting in susceptible subjects by eliciting a direct or reflex increase in sympathetic activity.

However, the attempt to quantify sympathetic activity before syncope has also furnished variable and sometimes opposite results. For instance, plasma norepinephrine concentrations have been found to be elevated3,6 or diminished7,8 before syncope. Studies based on conventional power spectral analysis of RR variability have indicated increased9,10 reduced11,12 or unchanged13 values of the markers of cardiac sympathetic modulation before a vasovagal event. The heterogeneity of the changes in the sympathetic drive to the vessels before syncope was recently highlighted in a study that used microneurography techniques.14 Indeed, vasovagal events induced by a tilt test were preceded by either a blunted increase (in habitual fainters) or a marked enhancement (in occasional fainters) of the muscle neural sympathetic discharge.14

However, the methodologies used in those studies could not continuously assess the cardiac autonomic changes that precede neurogenic syncope. This is of paramount importance, because the wide range of clinical presentations of vasovagal reactions might reflect different underlying cardiac pathogenetic mechanisms, which in turn imply the necessity

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of differently tailored therapeutic approaches. In fact, the actual onset of syncope can be abrupt, with only few and transient symptoms, or slower, with presyncope signs such as nausea and dizziness preceding the complete loss of consciousness by seconds or even minutes. It is conceivable that these different clinical presentations might be related to different cardiac neural changes preceding the vasovagal event.

We addressed this hypothesis by evaluating RR interval variability in the period preceding the onset of bradycardia in a group of young, healthy subjects who fainted for the first time during a tilt test. Time-variant autoregressive spectral analysis was used to obtain markers of sympathetic and vagal cardiac modulation on a beat-by-beat basis to evaluate continuously the possible complex and rapid changes in the autonomic control of heart rate before syncope.

**Methods**

**Study Population**

This study includes a group of 22 subjects (age, 16±1 years; 11 male, 11 female) who experienced a vasovagal reaction during a 90° head-up tilt test. They were part of a population of healthy volunteers recruited by our laboratory to study the effects of the tilt maneuver. A second group comprises 22 healthy control subjects (age, 20±1 years; 9 male, 13 female) who were asymptomatic on tilt and during 2 or more previous tilt tests.

None of the subjects had ever experienced a syncopeal event. Informed consent was provided by the subjects and their parents.

**Recorded Variables**

Respiratory activity (nasal thermistor; Nikon Kohden TR611) and ECG were continuously recorded on an FM tape recorder (Racial Store 7DS). Arterial pressure was measured at rest and 3 times during tilt by a mercury sphygmomanometer. In subjects with syncope, blood pressure was also assessed, when possible, at the onset of symptoms.

**Protocol**

After an adequate period of adaptation on the tilt table, data recording was initiated for the resting condition (15 minutes). Thereafter, all subjects underwent a 90° head-up tilt test, which was maintained for 15 minutes. The tilt procedure was interrupted whenever criteria for the onset of a vasovagal episode were satisfied.

The experimental protocol was approved by the Ethical Committee of our hospital.

**Definitions**

A vasovagal episode was defined as the occurrence of loss of consciousness or the onset of presyncope signs and symptoms, together with an increase of RR interval >80% of early tilt values and a decrease of systolic pressure >40% of early tilt values.

**Data Analysis**

Analog data were analyzed off-line after analog-to-digital conversion at 300 samples per second per channel. The principles of the software for data acquisition and time-variant spectral analysis have been described elsewhere. Time-variant spectral analysis of heart period variability represents a development of usual autoregressive power spectral analysis. It is based on a recursive least-squares-method algorithm, which makes the autoregressive identification procedure suitable to update the coefficients of the model every new beat. Therefore, power spectral analysis can be performed on a beat-by-beat basis, permitting the evaluation of the changes in the spectral components during unstable conditions like transient ischemia and syncopal events.

The forgetting factor $\omega$ weights the prediction error terms exponentially, thus focusing the model on the most recent data out of the window of interest. This latter is defined by $\omega$, according to the formula $n=1/(1-\omega)$, where $n$=number of beats.

In this study, we used an $\omega$ value of 0.98, that is, a window of interest of 50 beats. The use of a high-pass IIR filter on RR series before time-variant identification accounts for the reduction of total RR interval variance and of the absolute power of the single oscillatory components (see Tables). Moreover, a further reduction in the power of the above-mentioned variables is probably due to the shorter window of interest (ie, 50 beats when $\omega=0.98$) compared with the conventional spectral analysis usually performed on longer segments of data.

As already reported, 2 major oscillatory components can be identified in the power spectrum of RR variability: a high-frequency (HF) component at $0.15-0.40$ Hz, considered a marker of vagal modulation of the sinoatrial node, and a low-frequency (LF) component at $0.04-0.15$ Hz, considered, when normalized, a marker of sympathetic modulation.

The power of the LF and HF oscillatory components is computed both in absolute units (ms²) and in normalized units (NU), obtained by dividing the absolute power of each oscillatory component by total power minus the very-low-frequency component and multiplying by 100. The LF/HF values were calculated as a measure of the relative power of the LF and HF components.

**TABLE 1. Hemodynamic and Spectral Profiles of Control Subjects and Subjects With Syncope at Rest and During the Early Phase of Tilt**

<table>
<thead>
<tr>
<th></th>
<th>SAP, mm Hg</th>
<th>DAP, mm Hg</th>
<th>Resp, cycles/min</th>
<th>RR, ms</th>
<th>HR, bpm</th>
<th>RR Variance, ms²</th>
<th>LF, ms²</th>
<th>LF, NU</th>
<th>HF, ms²</th>
<th>HF, NU</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Control</td>
<td>117±3</td>
<td>75±2</td>
<td>16±1</td>
<td>925±36</td>
<td>67±3</td>
<td>228±78</td>
<td>89.8±35.5</td>
<td>43.33±3.72</td>
<td>61.2±20.3</td>
<td>44.34±4.23</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>117±2</td>
<td>73±3</td>
<td>16±0.4</td>
<td>939±31</td>
<td>66±2</td>
<td>107±23</td>
<td>35.7±7.7</td>
<td>39.64±3.37</td>
<td>46.3±14.4</td>
<td>48.18±3.61</td>
</tr>
<tr>
<td>Tilt</td>
<td>Control</td>
<td>114±4</td>
<td>78±2</td>
<td>15±1</td>
<td>720±28†</td>
<td>86±3</td>
<td>125±59†</td>
<td>49.8±17.5</td>
<td>74.20±2.89†</td>
<td>18.7±13.07</td>
<td>16.35±2.64†</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>109±2†</td>
<td>76±2</td>
<td>16±1</td>
<td>636±16†</td>
<td>95±2†</td>
<td>35±5</td>
<td>19.4±3.4</td>
<td>79.70±2.52†</td>
<td>2.0±0.37</td>
<td>13.60±1.92†</td>
</tr>
</tbody>
</table>

SAP indicates systolic arterial pressure; DAP, diastolic arterial pressure; Resp, respiration; RR, RR interval; and HR, heart rate.

*P<0.05 vs Control; †P<0.05 vs Rest.
reciprocal changes of the sympathetic and vagal modulation of the sinoatrial node discharge (sympathovagal balance). Conventional spectral analysis was also performed on the respiratory signal in the recumbent position and during T1 and T2 to assess the main respiratory frequency.

Statistics
Data are expressed as mean±SEM. Two-way ANOVA for repeated measures and 1-way ANOVA with the Student-Newman-Keuls test for multiple comparisons and Student’s t test for paired observations were used whenever appropriate. Differences were considered significant at values of P<0.05.

Results
As summarized in Table 1, at rest, no differences in hemodynamic and spectral parameters were observed between control subjects and subjects who developed a syncopal attack. During tilt, RR interval decreased in both groups, reaching lower values in subjects with syncope. The frequency-domain analysis assessed a significant increase of LFNU and LF/HF and a concomitant decrease of HF NU in the 2 groups.

The time course of changes during tilt of RR interval and of the spectral markers of cardiac autonomic regulation, as obtained in an asymptomatic control subject and in 2 subjects who suffered from syncope (center and right), are illustrated in Figure 1. These examples of syncope represent the 2 most remote types of patterns in the spectral components observed in subjects who fainted. In the control subject, LFNU and HFNU values remained stable along tilt. The subject with “sudden syncope” had a slight decrease of RR and a progressive increase of HFNU before syncope that was accompanied by a sudden rise of RR and HFNU and a drop of LFNU. Of interest, LFNU exhibited large fluctuations during the entire tilt period. In the example depicted in the right panels of Figure 1, the LFNU index, after an initial plateau, underwent a slow decrease, with a final reduction at the time of syncope. In addition, a marked progressive increase in HFNU was evident in the period preceding the maximal bradycardia. Thus, in this case, the period before syncope was characterized by a slow, progressive inversion of the pattern of the spectral markers LFNU and HFNU, the reduction of the former being accompanied by a gradual increase of HFNU. Consequently, a latency between the maximum of LFNU and the onset of bradycardia could be identified in the example on the right side of Figure 1.

Of the 22 subjects who developed syncope, 13 showed a pattern similar to the example of the central panels of Figure 1 and were grouped as sudden syncope. The 9 remainders, who displayed a time lag between the maximum of LFNU and the onset of bradycardia (range, 12 to 167 seconds), were considered to be “syncope with latency.”

Table 2 summarizes the differences among groups during early tilt (T1), when all subjects were asymptomatic. Only RR

<table>
<thead>
<tr>
<th></th>
<th>SAP, mm Hg</th>
<th>DAP, mm Hg</th>
<th>Resp, cycles/min</th>
<th>RR, ms</th>
<th>HR, bpm</th>
<th>RR Variance, ms²</th>
<th>LF, NA</th>
<th>LF, NU</th>
<th>HF, NA</th>
<th>HF, NU</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tilt (T1) Control</td>
<td>114±4</td>
<td>78±2</td>
<td>15±1</td>
<td>720±28*</td>
<td>86±3</td>
<td>125±59</td>
<td>49.8±17.5</td>
<td>74.20±2.89</td>
<td>18.7±13.0</td>
<td>16.35±2.64</td>
<td>9.36±1.76</td>
</tr>
<tr>
<td>Syncope with latency</td>
<td>104±3</td>
<td>76±3</td>
<td>17±1</td>
<td>617±14</td>
<td>98±2</td>
<td>33±9</td>
<td>21.2±7.6</td>
<td>81.24±4.10</td>
<td>1.4±0.3</td>
<td>12.28±3.46</td>
<td>13.11±3.26</td>
</tr>
<tr>
<td>Sudden syncope</td>
<td>112±3</td>
<td>76±3</td>
<td>15±1</td>
<td>650±25</td>
<td>94±3</td>
<td>36±6</td>
<td>18.2±2.8</td>
<td>78.64±3.29</td>
<td>2.5±0.5</td>
<td>14.52±2.29</td>
<td>8.64±2.26</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
*P<0.05 vs syncope with latency.
interval was lower in the syncope with latency group than in control subjects. Conversely, during the period of tilt immediately preceding the loss of consciousness (T2), the 2 groups of patients with syncope both had lower RR interval values than control subjects (Table 3). In addition, the syncope with latency group was characterized by reduced values of LFNU and of LF/HF in comparison with the sudden syncope subjects (Table 3). In the 3 groups, RR interval decreased during T2 compared with T1. A reduction of blood pressure values from T1 to T2 was present in both groups of patients with syncope.

Figure 2 shows the individual and mean changes observed in spectral markers by comparing T1 and T2 in the 3 groups. During tilt, subjects belonging to the sudden syncope group had a progressive increase in the spectral marker of cardiac sympathetic modulation LFNU, an inhibition of the vagal index HFNU, and hence, an enhancement of LF/HF indicating a shift of the sympathovagal balance toward sympathetic predominance up to the syncopal episode. Conversely, subjects with syncope with latency exhibited a progressive increase of HFNU attended by a reduction of LFNU and LF/HF, suggestive of an impending predominance of the vagal modulation of the sinoatrial node discharge.

Discussion
In this study, we addressed the hypothesis that the wide variety of clinical presentations of vasovagal events may somehow reflect different or even opposite changes in the cardiac autonomic profile of the fainting subjects.

It was found that individual spectral profiles preceding fainting could be ascribed to 2 different patterns. One was characterized by a progressive increase of cardiac sympathetic modulation up to the sudden onset of bradycardia, and the second displayed a gradual inhibition of sympathetic and a concomitant enhancement of vagal modulation of the sinoatrial node discharge.

Autonomic Changes During Tilt
Our results show that both asymptomatic control subjects and subjects who developed syncope exhibited similar hemodynamics and spectral indices of cardiac autonomic modulation in resting conditions. During the early phase of tilt, when all the subjects of the study were still asymptomatic, the subjects who would develop syncope had similar blood pressure but reduced RR values compared with asymptomatic control subjects (Table 1). This finding is in keeping with a recent observation by Mallat et al23 indicating that a marked increase of heart rate during the first 6 minutes of tilt may predict the occurrence of vasovagal events.

The possibility of performing spectral analysis on a beat-by-beat basis allowed us to focus on the last 60 seconds preceding the onset of bradycardia. Compared with asymptomatic control subjects, in all subjects with syncope, the progression of tilt was characterized by wide fluctuations of

<table>
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<tr>
<th>TABLE 3. Hemodynamic and Spectral Profiles of Control Subjects and of the Two Groups of Subjects With Syncope During the Late Phase of Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP, mm Hg</td>
</tr>
<tr>
<td>Late tilt (T2)</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Syncope with latency</td>
</tr>
<tr>
<td>Sudden syncope</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
*P<0.05 vs syncope with latency; †P<0.05 vs sudden syncope; ‡P<0.05 syncope with latency vs sudden syncope.
the indices of cardiac autonomic control, suggestive of a marked instability of the cardiac neural modulation. In addition, the time-variant approach permitted highlighting of 2 different trends of the spectral markers of cardiac autonomic modulation that might remain hidden\textsuperscript{10} when usual algorithms were used\textsuperscript{10} and that might account for the conflicting findings in the evaluation of plasma catecholamine levels reported in the period preceding vasovagal events.\textsuperscript{1,6–8} The 2 representative patterns are discussed separately below.

Progressive Sympathetic Activation

In 13 subjects with syncope, the spectral marker of sympathetic modulation, LF\textsubscript{NUL}, suddenly dropped to nearly zero concomitantly with the onset of bradycardia, thus suggesting a persistent predominance of the sympathetic drive to the heart up to the vasovagal event. In those subjects, the neural control of the sinoatrial node activity followed a peculiar time course characterized by an increase of cardiac sympathetic modulation in the early phase of tilt compared with the recumbent position and, in most cases, by its further enhancement in the period immediately preceding the onset of fainting. The vagal modulation of heart period, as inferred from the power of the HF\textsubscript{NU} component, decreased during the last minute that preceded syncope.

This pattern is in accordance with previous findings obtained by conventional spectral analysis in patients with isoproterenol-independent orthostatic syncope\textsuperscript{9} and in trained athletes.\textsuperscript{10} It must be pointed out that in the group of asymptomatic control subjects of this study as well, there was a slight increase of LF\textsubscript{NUL} and LF/HF and decrease of HF\textsubscript{NU} with the progression of tilt. Thus, in subjects with occasional sudden syncope, the cardiac neural changes attending passive orthostatism seem to be qualitatively similar to those of normal subjects but quantitatively different.

A possible relationship between high values of LF and susceptibility to neuromediated syncope can also be inferred from a study by Lipsitz et al.\textsuperscript{24} These authors observed an increased rate of syncopal attacks during passive orthostatism in young subjects, with higher LF values compared with elderly subjects.

In keeping with the possible existence of a cardiac sympathetic overactivity immediately before syncope is the observation of echocardiographic signs of sympathomediated enhancement of cardiac inotropism during the 1 to 4 minutes preceding the syncope.\textsuperscript{25}

The data obtained in our group of subjects with sudden syncope lend further support to the experimental findings by Oberg and Thoren,\textsuperscript{2} who reported that the activation of vagal ventricular receptors and the consequent reflex bradycardia could be observed only when a pronounced tachycardia at the beginning of hemorrhage had indirectly suggested the presence of a remarkable sympathetic activation to the heart.

However, the activation of vagal ventricular afferents by sympathetic overactivity is likely to be only one of the mechanisms involved in the genesis of vasovagal episodes with cardioinhibition. Central influences elicited by emotional stress or severe pain can also generate neural mechanisms leading to syncope.\textsuperscript{1} Furthermore, low-pressure cardio-pulmonary baroreceptors have been hypothesized to be more sensitive to orthostatic stress in habitual fainters.\textsuperscript{26} Finally, the occurrence of vasoinhibitory fainting in patients with heart transplants\textsuperscript{27,28} further suggests the existence of mechanisms different from the activation of vagal ventricular receptors. Among them, Dickinson\textsuperscript{29} proposed the anomalous activation of venoatrial stretch receptors as a possible trigger of the sequence of events occurring in vasovagal fainting.

Progressive Sympathetic Inhibition

In 9 of the fainters of our study, the autonomic profile during tilt was characterized by an initial marked predominance of LF\textsubscript{NUL}, which, after having reached a maximum, slowly decreased before dropping down at the onset of bradycardia. Therefore, the period between the maximum sympathetic activation and the onset of the vagal inhibitory reflex seemed to be distinguished by a slow, progressive inversion of the sympathovagal modulation with a consequent cardiac sympathetic inhibition.

This pattern suggests that neuromediated syncope in occasional fainters may be promoted by an alternative pathophysiological mechanism independent of an exaggerated enhancement of sympathetic activity to the heart.\textsuperscript{7}

Indeed, in a group of fainters, Morillo et al\textsuperscript{22} found reduced values of LF and LF/HF during the first 5 minutes of a 60° tilt, suggestive of a failure in vagal withdrawal and a blunted sympathetic activation. Similarly, another study\textsuperscript{11} based on time-frequency mapping of RR variability concluded that subjects prone to vasodepressor syncope were characterized by an elevated cardiac parasympathetic activity that persisted during orthostatic stress.

A failure to enhance the sympathetic tone to the vasculature or to maintain it during standing,\textsuperscript{3} long-lasting tilt,\textsuperscript{14} or lower-body negative pressure\textsuperscript{31} maneuvers has been reported in patients with both occasional and recurrent orthostatic syncope by use of microneurographic techniques. Moreover, a decreased cardiac norepinephrine spillover was observed in patients who experienced a vasovagal syncope during cardiac catheterization.\textsuperscript{7} Finally, an overall diminished cardiovascular sympathetic activity, as inferred from reduced plasma norepinephrine levels, has been documented before syncope in patients undergoing both passive orthostatism\textsuperscript{5} and lower-body negative pressure.\textsuperscript{32}

Limitations of the Study

This study was restricted to spectral analysis of heart rate variability. Important neural control mechanisms known to be altered in patients with syncope, such as high- and low-pressure baroreceptor reflex control of heart rate,\textsuperscript{13,14,33} were not directly addressed.

Moreover, we focused on a highly selected population, that is, on a group of otherwise healthy subjects who fainted for the first time during a gravitational stress. Thus, our findings might not be directly extendable to other types of vasovagal reactions, such as emotional syncope, or to patients with recurrent syncope.

Conclusions

This study showed that in a group of healthy subjects, a marked cardiac sympathetic activation may precede a vaso-
vagal event induced by gravitational stress. It also reported, in other cases, a slow inversion of the cardiac sympathovagal balance with progressive sympathetic inhibition.

We hypothesize that if these occasional fainters should develop recurrent vasovagal reactions, the capability of recognizing different cardiac pathophysiological mechanisms underlying neurogenic syncope might help to select between different drug classes, such as β-adrenergic receptor antagonists or α-adrenergic receptor agonists.

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References
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