Enhanced Reflex Response to Baroreceptor Deactivation in Subjects With Tilt-Induced Syncope

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OBJECTIVES
We sought to evaluate whether changes in resting baroreflex control of heart rate are a distinctive feature of healthy subjects with a history of syncope prone to a positive tilt-test response.

BACKGROUND
The mechanisms involved in the pathogenesis of vasovagal syncope (VVS) are still poorly understood; in particular, the contribution of arterial baroreflex control of heart rate is matter of discussion.

METHODS
A passive tilt-table test was performed in 312 consecutive, otherwise healthy subjects (age 36 ± 15 years) with unexplained syncope and 100 control subjects. At baseline, spontaneous baroreflex sensitivity (BRS; ms/mm Hg) and the baroreflex effectiveness index (BEI) were assessed using the sequence method.

RESULTS
The study population showed normal baroreflex function. Tilt-induced VVS in 94 subjects who were younger than both the tilt-negative and control subjects (30 ± 14, 38 ± 15, and 37 ± 14 years, respectively; p = 0.00005) showed greater BRS (17.4 ± 9.8, 13.2 ± 7.9, and 12.8 ± 5.2 ms/mm Hg, respectively; p = 0.0001), but had a similar BEI (0.59 ± 0.18, 0.56 ± 0.19, and 0.58 ± 0.2, respectively; p = NS). On Cox multivariate analysis, the occurrence of VVS during tilt was inversely related to age (hazard ratio 0.97; p = 0.0004) and directly related to the BRS slope of sequences, implying a baroreceptor deactivation (hazard ratio 1.05; p = 0.02), but not of sequences characterized by arterial baroreceptor stimulation.

CONCLUSIONS
Subjects with tilt-induced VVS showed greater resting BRS but had a normal BEI. The enhanced reflex tachycardic response to arterial baroreceptor deactivation at rest may represent a characteristic feature of subjects prone to tilt-induced VVS. © 2003 by the American College of Cardiology Foundation

Vasovagal syncope (VVS) is the most frequent neurally mediated syncope, and susceptible subjects can often be identified by means of passive tilt-table testing (1). The causes of this susceptibility to orthostatic stress are not completely known, but its clinical hallmark (i.e., hypotension with or without bradycardia) strongly suggests the involvement of autonomic nervous system abnormalities. The circulatory adjustments to orthostatic stress lead to an increase in heart rate, cardiac contractility, and vascular tone in order to stabilize arterial pressure at the level of the brain. Arterial and cardiopulmonary reflex changes are involved in these adjustments (2). The role of an alteration in the arterial baroreflex control of heart rate, predisposing subjects to VVS, has been suggested (3–7) or denied (3,8–12) by different studies, mainly based on classic laboratory methods, most of them including small numbers of subjects.

New perspectives in this field may be offered by the sequence method, which is based on the time-domain detection of sequences of consecutive heart beats characterized by an increase in systolic arterial pressure (SAP) and shortening of the R-R interval, or a reduction in SAP and shortening of the R-R interval (13). This method makes it possible to concentrate on the feedback effects of changes in SAP on the changes in R-R intervals by separating them from the feedforward effects of R-R intervals on SAP (14,15).

We sought to assess whether rest arterial baroreflex control of heart rate in a large number of otherwise healthy subjects with a history of syncope has a role in predisposing them to tilt-induced VVS.

METHODS
Patient selection. Between August 1997 and December 2000, we enrolled all of the consecutive subjects referred to the Institute of Cardiology, Bari University, with a history of syncope, whose symptoms did not allow any definite diagnosis. These subjects were free of any structural heart disease, arrhythmias, diabetes, neurologic diseases, and any drug treatment. Carotid sinus massage performed before tilt testing had to be negative. One hundred subjects with a previous normal response to a 45-min tilt test were enrolled...
Abbreviations and Acronyms

BEI = baroreflex effectiveness index
BRS = baroreflex sensitivity
BRS-down = baroreflex sensitivity for sequences with reduction in systolic arterial pressure and shortening of the pulse interval
BRS-up = baroreflex sensitivity for sequences with increase in systolic arterial pressure and lengthening of the pulse interval
SAP = systolic arterial pressure
VASIS = VAsovagal Syncope International Study
VVS = vasovagal syncope

as controls; a stratification was used to match the approximate age and gender distributions in cases and controls. The study was approved by our local Ethics Committee, and all subjects gave their written, informed consent to participate.

Tilt-test protocol and measurements. All subjects underwent a passive tilt-table test, performed between 9:00 AM and 12:00 PM in a quiet and dimly lit room with a constant room temperature of about 24°C, after they had abstained from any food and drink for 4 h. After a supine rest period of 10 min, the subjects were tilted upright to 70° on an electrically driven table equipped with a footboard support for up to 45 min or until the onset of symptoms. During the tilt test, they were securely bound to the table by means of two straps placed around the legs and waist and were asked not to speak, except to report symptoms. During the baseline and tilting periods, heart rate, respiratory activity (measured by an impedance pneumograph; Hewlett-Packard, model 78354C, Andover, Massachusetts) and noninvasive blood pressure (Finapres, model 2300, Ohmeda, Englewood, Colorado) signals were continuously and simultaneously recorded at a sampling frequency of more than 250 Hz, as previously described (16). Surface electrocardiographic leads I, II, and III were also continuously monitored. The times of all symptoms reported during the test were recorded.

Baroreflex sequence analysis. The beat-to-beat time series of SAP and R-R intervals recorded during the 10-min baseline period were automatically scanned using software capable of identifying the sequences (identified as baroreflex sequences) of three or more consecutive heart beats in which the R-R intervals and SAP concurrently increased (up-sequences) or decreased (down-sequences), as previously described (13). For each sequence, the lag between the RR and SAP values was set at 0 beats, and the minimum acceptable between-beat change was set at 1 mm Hg for SAP and 4 ms for R-R intervals (17,18). The slope of the regression line between the R-R intervals and SAP values was computed for each sequence and taken as a measure of baroreflex sensitivity (BRS; ms/mm Hg). This was computed for all of the baroreflex sequences as a whole and separately for sequences of consecutive beats characterized by either a progressive increase in SAP and lengthening of the pulse interval (BRS-up) or a progressive reduction in SAP and shortening of the pulse interval (BRS-down). In addition, from each recording, the baroreflex effectiveness index (BEI) was evaluated as the ratio between the total number of baroreflex sequences and the total number of beat series in which SAP progressively increased or decreased, irrespective of whether these changes were or were not followed by reflex changes in the R-R interval (SAP ramps) (19).

Definitions and classifications. Syncope was defined as a transient loss of consciousness, and presyncope as a sensation of near-fainting (e.g., wooziness, dizziness, light-headedness) associated with a fall in SAP of >50 mm Hg. The surface electrocardiograms and the time series of the R-R intervals and arterial pressure values during tilt were reviewed by two investigators (M. V. P. and F. M.) in order to analyze hemodynamic collapse patterns. Episodes of VVS were classified according to the VAsovagal Syncope International Study (VASIS) criteria as type 1 (mixed), types 2A and 2B (cardioinhibitory), and type 3 (vasodepressor) (1).

Statistical analysis. Continuous variables are expressed as the mean value ± SD. The Student t test was used to compare continuous variables, and the chi-square test to compare categorical variables. The differences between the control subjects and the patients with and without tilt-induced VVS were assessed using analysis of variance. The correlation between BRS values and age was evaluated using Pearson product-moment correlations. Analysis of covariance followed by the Newman-Keuls post-hoc test was used to correct for differences in age and evaluate differences in the data relating to the three groups. Kaplan-Meier curves were used to describe the event-free tilt-table tests of the subjects stratified on the basis of the values of the variables (divided into quartiles). The log-rank test was used for statistical comparisons. The association between the data and tilt outcome was assessed by means of Cox multivariate regression analysis; the hazard ratio and 95% confidence interval were also computed. Tests were considered statistically significant at p < 0.05.

RESULTS

Of the 826 subjects analyzed because of a history of syncope, 312 fulfilled the study criteria and were enrolled. There were no differences in the baseline characteristics, respiratory rate, or hemodynamic or sequence analysis data between the subjects with a history of syncope taken as a whole and control subjects (Table 1).

Tilt outcomes. Of the 312 study subjects, 216 completed the 45-min tilt test without experiencing syncope or presyncope, and 96 had a positive response (31%), 94 of whom were classified as having VVS (the remaining two subjects were found to have a psychogenic response and, therefore, were excluded from further analysis). On the basis of the VASIS classification, 71 positive responses were defined as type 1 (76%), 7 as type 2A (8%), 5 as type 2B (6%), and 8
Table 1. Clinical Characteristics and Sequence Analysis Data of the Study Subjects and Control Group

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Study Subjects</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36 ± 15</td>
<td>37 ± 14</td>
</tr>
<tr>
<td>Males (%)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 ± 0.10</td>
<td>1.68 ± 0.11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 4</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>Symptomatic episodes over the last year (n)</td>
<td>3 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>Mean R-R interval (ms)</td>
<td>894 ± 149</td>
<td>882 ± 116</td>
</tr>
<tr>
<td>Mean SAP (mm Hg)</td>
<td>126 ± 17</td>
<td>123 ± 17</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>15 ± 5</td>
<td>15 ± 4</td>
</tr>
</tbody>
</table>

Baroreflex sequence analysis

- **BRS-up (ms/mm Hg)**: 14.3 ± 9.3 vs. 13.0 ± 8.8
- **BRS-down (ms/mm Hg)**: 14.5 ± 8.6 vs. 12.8 ± 8.0
- **BRS (ms/mm Hg)**: 14.5 ± 8.8 vs. 12.8 ± 8.2
- **R-R intervals in baroreflex sequences (%)**: 30 ± 15 vs. 32 ± 16
- **BEI**: 0.57 ± 0.19 vs. 0.58 ± 0.2
- **Total SAP ramps (n)**: 105 ± 41 vs. 107 ± 35
- **SAP ramps in BRS-up sequences (n)**: 30 ± 16 vs. 30 ± 16
- **SAP ramps in BRS-down sequences (n)**: 31 ± 18 vs. 33 ± 18

Data are presented as the mean value ± SD, except for males (%).

BEI = baroreflex effectiveness index; BRS = baroreflex sensitivity; BRS-down = baroreflex sensitivity for hypotension/bradycardia sequences; BRS-up = baroreflex sensitivity for hypertension/bradycardia sequences; SAP = systolic arterial pressure.

as type 3 (10%). Symptoms occurred an average of 15.6 ± 10.6 min after the beginning of tilting, and the average time to syncope was shorter than the average time to presyncope (12.6 ± 9.1 min vs. 17.5 ± 11.2 min; p < 0.03).

**Baroreflex function in the VVS group.** In comparison of control subjects and patients with a negative tilt test, the patients with a positive response were characterized by greater rest BRS and younger age, but did not differ in terms of gender or baseline supine hemodynamic parameters (Table 2). There were also no differences in the number of R-R intervals in the baroreflex sequences, the total number of SAP ramps, or the number of BRS-up or BRS-down sequences (Table 2).

Kaplan-Meier analysis revealed a significant overall difference in the tilt outcome as a function of age and BRS (Fig. 1). Both variables had a major impact on the tilt outcome and on the time of symptom onset, with younger patients and those with higher BRS values being more likely to have early symptomatic vasovagal responses to tilt testing. Furthermore, BRS maintained its outcome predictive value when BRS-up and BRS-down were considered separately (p = 0.002 and p = 0.0002, respectively).

As expected, there was a significant negative correlation between patient age and BRS (r = −0.51; p < 0.0001). After adjustment for age, overall BRS and BRS-down remained significantly associated with the occurrence of a vasovagal response to tilting, but this was not the case for BRS-up, the values of which were still higher in subjects with tilt-induced VVS as compared with the other groups, but the difference was no more statistically significant.

Table 2. Comparisons Between Patients With and Without Tilt-Induced VVS and Control Subjects, With and Without Age Adjustment

<table>
<thead>
<tr>
<th></th>
<th>Tilt-Induced VVS (n = 94)</th>
<th>Negative Tilt Response (n = 216)</th>
<th>Control Group (n = 100)</th>
<th>ANOVA (p Value)</th>
<th>ANCOVA (Age-Adjusted p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>30 ± 14</td>
<td>38 ± 15</td>
<td>37 ± 14</td>
<td>0.00005</td>
<td>—</td>
</tr>
<tr>
<td>Males (%)</td>
<td>54</td>
<td>56</td>
<td>55</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.12</td>
<td>1.67 ± 0.09</td>
<td>1.68 ± 0.11</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Mean R-R interval (ms)</td>
<td>906 ± 158</td>
<td>888 ± 145</td>
<td>883 ± 116</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Mean SAP (mm Hg)</td>
<td>125 ± 17</td>
<td>126 ± 18</td>
<td>123 ± 17</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>15 ± 3</td>
<td>15 ± 4</td>
<td>15 ± 4</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>BRS-up (ms/mm Hg)</td>
<td>16.8 ± 10.1</td>
<td>13.2 ± 8.8</td>
<td>13.0 ± 8.8</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>BRS-down (ms/mm Hg)</td>
<td>17.7 ± 9.7*</td>
<td>13.2 ± 7.7</td>
<td>12.8 ± 8.0</td>
<td>0.00002</td>
<td>0.007</td>
</tr>
<tr>
<td>BRS (ms/mm Hg)</td>
<td>17.4 ± 9.8*</td>
<td>13.2 ± 7.9</td>
<td>12.8 ± 8.2</td>
<td>0.00001</td>
<td>0.038</td>
</tr>
<tr>
<td>R-R intervals in baroreflex sequences (%)</td>
<td>30 ± 15</td>
<td>29 ± 15</td>
<td>32 ± 16</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>BEI</td>
<td>0.59 ± 0.18</td>
<td>0.56 ± 0.19</td>
<td>0.58 ± 0.2</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Total SAP ramps (n)</td>
<td>102 ± 40</td>
<td>106 ± 41</td>
<td>107 ± 35</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>SAP ramps in BRS-up sequences (n)</td>
<td>30 ± 16</td>
<td>29 ± 16</td>
<td>30 ± 16</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>SAP ramps in BRS-down sequences (n)</td>
<td>31 ± 18</td>
<td>31 ± 18</td>
<td>33 ± 18</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>

*p < 0.05 versus negative tilt response and control groups (ANCOVA followed by the Newman-Keuls test). Data are presented as the mean value ± SD.

ANOVA = analysis of covariance; ANOVA = analysis of variance; VVS = vasovagal syncope; other abbreviations as in Table 1.
Cox multivariate analysis showed that age was inversely related to the occurrence of VVS during tilt testing, whereas pooled BRS did not reach statistical significance (Table 3). However, when the BRS-up and BRS-down sequences were analyzed separately, the latter remained directly related to the occurrence of tilt-induced VVS (Table 3).

**DISCUSSION**

The pathophysiology of VVS is complex and far from being fully elucidated. Cardiopulmonary as well as arterial baroreflex changes play a major role in maintaining blood pressure homeostasis during changes in body position, but whether their abnormal function has a role in favoring VVS is debated (1). The present study demonstrates that an enhanced arterial baroreflex control of heart rate characterizes subjects prone to tilt-induced VVS. Although the majority of investigators who addressed this issue did not find clear evidence of alterations in the arterial baroreflex control of heart rate in subjects with tilt-induced syncope (3,8–12), a few have reported an abnormality which, however, in most cases, consisted in a reduction (3,4,6) rather than an increase (5,7). The reasons for the discrepancies between the results of these studies and ours are likely to be multifold, and a major contribution may come from different methodologic approaches. In most of these studies, the number of subjects enrolled was quite small (4,5,9,10,12); the clinical conditions of the subjects were different (8) or they were receiving pharmacologic treatment (8,11); sometimes, there was no clear history of previous syncopal episodes (12); or a control group was lacking (3). Finally, another major reason for discrepancies is the use of different tilt-test protocols and the measurement of baroreflex control of heart rate through different methods. In particular, most of the studies have

![Kaplan-Meier curves analysis. Age (top) and baroreflex sensitivity (bottom) were examined in relation to their ability to predict an event-free 45-min tilt-table test. For this analysis, age and baroreflex sensitivity values were arbitrarily divided into quartiles.](image)
used laboratory estimates of the baroreflex control of heart rate based on application of external stimulation. As previously discussed (13), data provided by this method are fairly reproducible and have the important limitation associated with interference by the applied external stimulus. In addition, most studies have selectively focused on the heart rate effects of baroreceptor stimulation, and only two studies (3,6) have also evaluated the heart rate response to deactivation of arterial baroreceptors, but the possible different role of these two components of the cardiac baroreflex was not specifically addressed.

Our study is different in that it included a large number of subjects (to the best of our knowledge, the largest sample so far recruited in a study of syncope), and the use of strict entry criteria made it possible to select subjects without any confounding interference with the determination of the tilt outcome, which might have influenced the autonomic control of heart rate. Another point of interest is the sequence technique we used to analyze BRS. This method is based on the assessment of spontaneous baroreflex control of heart rate, through computer analysis of spontaneous fluctuations in blood pressure and heart rate occurring around the so-called "arterial baroreflex set-point." It provides reproducible BRS values and offers a separate estimate of the gain of reflex changes in heart rate in response to activation and deactivation of arterial baroreceptors (17). This type of information is of primary interest in the case of tilt-induced VVS, because the rapid change in body position from supine to upright causes a fall in venous return that leads to a decrease in cardiac output and, thus, arterial pressure. Under these conditions, it might be expected on theoretical grounds that arterial baroreceptor deactivation should play a greater role than baroreceptor activation in terms of maintaining blood pressure homeostasis, which makes the response to baroreceptor deactivation likely to be the most informative parameter when investigating the autonomic control of heart rate (and thus also of cardiac output) in subjects with VVS.

Indeed, our study, to the best of our knowledge, is the first to provide clear evidence of the occurrence of a different heart rate response to arterial baroreceptor deactivation at rest in subjects with tilt-induced VVS. Enhanced BRS-down was an independent factor predisposing to tilt-induced VVS (1 ms/mm Hg change in BRS-down was associated with a significant 5% change in the hazard ratio). In other words, in subjects prone to fainting during tilting, the deactivation of arterial baroreceptors causes a greater withdrawal of vagal influences directed toward the sinus node and consequently a greater increase in heart rate, as compared with subjects who do not faint under tilt-table testing. On the other hand, in the multivariate model, enhanced BRS-up displays a tendency to act in the opposite direction, thus suggesting a possible different role of increased and decreased vagal cardiac drive in response to baroreceptor activation and deactivation, respectively, in subjects with tilt-induced VVS. These novel findings offer new perspectives in assessing the mechanisms involved in the pathophysiology of tilt-induced VVS, which may convincingly explain the exaggerated and sustained increase in the heart rate of subjects who faint during the first minutes of tilting, as reported by Mallat et al. (20). The role of BRS in the pathophysiology of VVS is further supported by the fact that subjects who will no longer faint during follow-up are characterized by a reduction in BRS values (5,21).

Our study was not designed to investigate whether increased BRS is the result of an alteration occurring at the peripheral (arterial baroreceptor or sinus node) or central level (central nervous system) within the baroreflex arc. However, the data provided by sequence analysis do allow us to make some speculations. We can reasonably exclude the possibility that the enhanced sensitivity of reflex heart rate responses to arterial baroreceptor deactivation is associated with an abnormality in the effectiveness of baroreflex modulation of the sinus node, because there was no difference in the BEI scores of our three groups. A difference in the degree of baroreceptor stimulation and deactivation does not seem to play a key role, because the number of SAP ramps and arterial pressure values were similar in the three groups. Finally, the involvement of an abnormal sinus node response is unlikely, because the R-R interval values in the baroreflex sequences and heart rate were similar in the VVS and VVS-free groups.

If peripheral abnormalities are unlikely, central or other reflex mechanisms may play a role. Although the respiratory rate is known to be capable of dramatically modifying BRS (16), it does not seem to play a role in explaining our findings, because the breathing rate was similar in the subjects who fainted and in those who did not. It is therefore necessary to consider other factors modulating the central integrating mechanisms of arterial baroreflexes, such

### Table 3. Cox Multivariate Analysis for Tilt-Induced VVS

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Chi-Square</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Age (yrs)</td>
<td>11.8</td>
<td>0.97 (0.95–0.99)</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td>BRS (ms/mm Hg)</td>
<td>2.4</td>
<td>1.01 (1.0–1.04)</td>
<td>NS</td>
</tr>
<tr>
<td>Model 2</td>
<td>Age (yrs)</td>
<td>12.5</td>
<td>0.97 (0.95–0.99)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>BRS-up (ms/mm Hg)</td>
<td>2.3</td>
<td>0.96 (0.93–1.01)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>BRS-down (ms/mm Hg)</td>
<td>5.2</td>
<td>1.05 (1.01–1.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI = confidence interval; other abbreviations as in Tables 1 and 2.
as anxiety, cardiopulmonary baroreflex, and chemoreflex influences, as well as the reflex influences arising from skeletal muscle receptors and other reflexogenic areas. In particular, cardiopulmonary reflex could play a key role. A reduction in plasma volume, considered an important predisposing factor in VVS (7), could lead to deactivation of cardiopulmonary baroreceptors and therefore a withdrawal of central inhibition of baroreflex function (22).

Tackling together these considerations, it can be hypothesized that the increased sensitivity of baroreflex control of heart rate during baroreceptor deactivation at rest represents a marker of susceptibility to tilt-induced VVS. However, our data cannot clarify whether these findings represent an epiphenomenon rather than a primary cause of VVS.

We also have to acknowledge that the sequence method may obviously have limitations due to the fact that reflex control of heart rate (as explored by this time-domain technique) does not allow us to collect data on the reflex changes occurring at the levels of peripheral resistance and blood pressure, nor does it offer information on the interactions between arterial and cardiopulmonary reflexogenic areas (13).

Another interesting finding of our study is the role played by age in favoring the occurrence of tilt-induced VVS—the older the subjects, the less likely the chance of fainting. It is worth noting that age has a considerable influence on the reflex control of heart rate, as it is known that BRS values decline with aging (23). The inverse relationship between age and the likelihood of developing syncope during tilt testing is not a completely new finding (24), which emphasizes that age should also be taken into account when investigating whether changes in the baroreflex control of heart rate characterize subjects prone to tilt-induced VVS. In the present study, BRS (particularly the heart rate response to arterial baroreceptor deactivation) was demonstrated to be an independent predictor of the tilt response, as well as the time to symptom onset. These results are in agreement with those of el-Sayed and Hainsworth (7), who not only found increased BRS in subjects with a positive tilt test, but also a negative correlation with the time to symptom occurrence.

Finally, the exaggerated tachycardic response to arterial baroreceptor deactivation may represent a marker of cardiovascular instability and account for the occurrence of large oscillations in heart rate and SAP observed before the onset of syncope (12,25). Although the analysis of BRS during tilt testing, particularly in the minutes preceding syncope occurrence, might have allowed interesting results to be obtained, this was not performed in the present report. Our study was not aimed at addressing the complex mechanisms involved in the genesis of VVS, but rather at evaluating whether changes in BRS may characterize at rest subjects prone to tilt-induced VVS. However, it should be considered a first important step toward the assessment of the more complex changes in reflex cardiovascular control occurring immediately before tilt-induced syncope.

Furthermore, our study does not pretend to address all forms of VVS, but rather focuses on the analysis of baroreflex control of heart rate in the subset of subjects undergoing tilt-induced VVS. Abnormalities in autonomic circulatory control are likely to be involved also in blood injury-induced syncope, as well as in the other conditions not explored in the present report.

Conclusions. Our study of a large population of subjects prone to VVS found that they have higher values of resting arterial baroreflex control of heart rate. In particular, the enhanced tachycardic reflex response to baroreceptor deactivation was the component critically involved in predicting VVS during tilt testing.

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