Do subjects with vasovagal syncope have subtle haemodynamic alterations during orthostatic stress?

Giuseppe Fucà, Maurizio Dinelli, Lorella Gianfranchi, Sabrina Bressan, Catia Lamborghini, and Paolo Alboni*

Division of Cardiology and Arrhythmologic Centre, Ospedale Civile, 44042 Cento (FE), Italy

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Aims There are conflicting reports on the presence of subtle haemodynamic alterations during orthostatic stress in subjects with vasovagal syncope (VVS). The aim of the present study was to investigate whether young/middle-aged subjects with VVS show abnormal responses to orthostatic stress.

Methods and results Four groups of subjects underwent tilt testing (TT) during the passive phase and, if negative, after nitroglycerin administration: Group I, 20 subjects with a history of syncope and positive passive TT; Group II, 23 subjects with a history of syncope and TT positive after nitroglycerin; Group III, 23 subjects with a history of syncope and negative TT; and Group IV, 20 normal control subjects. Heart rate, systolic, diastolic, and mean blood pressure, stroke volume, cardiac output, and total peripheral resistance were computed from pressure pulsations (Modelflow). The demographic data and the values of the haemodynamic variables in the supine position did not differ significantly among the four groups.

The per cent changes in these variables did not differ significantly among the four groups after 2 and 5 min of TT and among Groups II, III, and IV, 2 min after nitroglycerin administration.

Conclusion Young/middle-aged subjects with VVS have a normal measured haemodynamic response to orthostatic stress; therefore, the vasovagal reflex is not secondary to an impairment of the primary vasoconstrictive mechanism.

KEYWORDS
Autonomic system; Haemodynamics; Syncope; Tilt testing; Vasovagal syncope

Introduction
Vasovagal syncope (VVS) is a common clinical problem. It is uncertain whether subjects with VVS suffer only from an abnormal reflex or also from subtle haemodynamic alterations during orthostatic stress, which can predispose to the vasovagal reaction. Reports are conflicting mainly because most studies have utilized subjects with a negative head-up tilt testing (TT), but with a history of syncopal episodes as a control group. However, these subjects do not constitute a suitable control group, as the diagnostic yield of TT is rather low.

The aim of this study was to investigate whether subjects with VVS show subtle haemodynamic alterations, out of the vasovagal reaction, during orthostatic stress. To this end, we compared the per cent changes in haemodynamic variables during the first few minutes of TT in four groups of subjects with: (i) a history of syncope and positive passive TT; (ii) a history of syncope and TT positive after nitroglycerin administration; (iii) a history of syncope and negative TT during both the passive phase and after nitroglycerin, and (iv) control subjects without a history of syncope and with negative TT.

The investigation was carried out in young/middle-aged subjects, as very young subjects without a history of syncope show high susceptibility to orthostatic stress, with a positivity rate of passive TT of 30%1,2; therefore, comparison of the data obtained during TT in control subjects and in those with a history of syncope is of very limited value. Moreover, epidemiological, haemodynamic, and autonomic-response data9,10,13–19 suggest that VVS that starts in old age has a different pathophysiological substrate and that, therefore, the presence of subtle haemodynamic alterations during orthostatic stress should be investigated separately in elderly subjects.

Methods
Patient selection
Patients referred for the evaluation of syncope were regarded as candidates for the present study if they: (i) had syncope of unknown origin after the first evaluation; (ii) were aged >18 and <65 years; (iii) did not show any sign of cardiovascular or...
neurological disease, arterial hypertension, diabetes, or varicose veins; and (iv) had negative carotid sinus massage. Moreover, they were excluded if during TT they showed: (i) a pattern of orthostatic syncope [gradual decrease in the blood pressure (BP) without slowing of heart rate (HR)] and (ii) an exaggerated response after nitroglycerin administration [syncope due to arterial hypotension without slowing of HR], which is a non-specific response after administration of this drug.21

The study population was made up of 22 subjects with inducible syncope during passive TT (2 excluded for technical reasons) (Group I); 28 subjects without inducible syncope during passive TT, but with inducible syncope after nitroglycerin administration (5 excluded because of an exaggerated response). One patient experienced syncope 2 min after the drug administration; this subject was included in the study, but the haemodynamic variables recorded 3 min after nitroglycerin could not be used for the evaluation of orthostatic response (Group II); 24 subjects with negative TT both during the passive phase and after nitroglycerin administration (1 excluded for technical reasons) (Group III). As a control group, we used subjects without a history of syncope and with negative TT both during the passive phase and after nitroglycerin administration, without any sign of cardiovascular or neurological disease, arterial hypertension, diabetes or varicose veins, negative carotid sinus massage, and aged between 19 and 64 years (Group IV). This group comprised 21 volunteers recruited from the personnel of the department of medicine (1 excluded for technical reasons). Further four control subjects without a history of syncope underwent TT, which was positive (one during the passive phase and three after nitroglycerin administration); therefore, they were not included because they did not meet the inclusion criteria. The study was approved by the local Ethics Committee.

Tilt test protocol
The TT was always performed in the morning in a quiet room (temperature 21–24 °C) after overnight fasting. The procedure was carried out using an electronically controlled tilt-table with a footboard for weight-bearing. No patient was taking cardioactive medication. After a 15 min supine control phase, subjects were tilted upright at 60° for 30 min or until syncope, at which time they were immediately tilted back to the horizontal direction. For Group I subjects, the test was terminated when a syncope was induced. For subjects in Groups II to IV, spray nitroglycerin was administered sublingually (0.4 mg) for an additional 15 min tilt duration or until syncope.

Haemodynamic recording
To assess the haemodynamic values, a Finometer (Finapress Medical Systems, Arnhem, The Netherlands) was used, as described previously.22 This is a non-invasive monitor that measures beat-to-beat arterial blood pressure from an arterial pressure using a three-element model of the arterial input impedance.24 Total peripheral resistance, arterial pressure, and heart rate were calculated from the aortic flow, stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR). Beat-to-beat recording was made; however, the values of haemodynamic variables were reported as the average of six consecutive artefact-free cycles just before tilting, after 2 and 5 min of passive tilting, at the end of passive tilting (if negative), and 2 min after nitroglycerin administration.

Statistical analysis
Per cent changes from the baseline were summarized for each variable as mean ± standard deviation. The analysis of variance was used to test differences among the three or four groups (Kruskal-Wallis test). χ² analysis was used for categorical data. All P-values were two-sided, and a type-I error level of 0.05 was adopted.

Results
Subjects’ characteristics
The clinical characteristics of the subjects in the four groups are reported in Table 1. Age, gender, and weight did not show significant differences among the groups. Time-to-syncope was 19.1 ± 8 min in Group I and 6.5 ± 2 min after nitroglycerin administration in Group II.

Baseline supine haemodynamics
The values of haemodynamic variables in the supine phase are summarized in Table 2. Heart rate, systolic, diastolic, and mean BP, SV, CO, and TPR did not show significant differences among the four groups.

Response to passive tilting
Per cent changes were obtained by comparing the values of haemodynamic variables in the supine phase with those obtained after 2, 5, and even 30 min of passive tilting.

After 2 min of tilting (Figure 1), HR increased in the four groups from 7 ± 16 to 13 ± 13%, and the per cent increases were not significantly different among the groups. Systolic BP increased by 0.8 ± 14 and 0.4 ± 8% in Groups I and III, respectively, and decreased by 2.5 ± 8 and 3.7 ± 8% in Groups II and IV, respectively. The percent changes did not significantly differ between the groups because of the high standard deviation. Diastolic BP increased in the four groups from 2.5 ± 13 to 9.4 ± 18%, and the per cent increases were not significantly different among the groups. Mean BP increased by 4.3 ± 15 and 3.7 ± 11% in Groups I and III, respectively, and decreased by 0.7 ± 8 and 0.9 ± 11% in Groups II and IV, respectively. The per cent changes did not differ significantly between the groups. The stroke volume decreased in the four groups from 15 ± 15 to 23 ± 17% and CO from 10 ± 18 to 14 ± 16%; the per cent decreases were not significantly different between the groups. Total peripheral resistance increased in the four groups from 13 ± 16 to 25 ± 38%, and the per cent increases did not differ significantly between the groups.

After 5 min of tilting (Figure 2), the per cent changes in HR, systolic, diastolic, and mean BP, SV, CO, and TPR did not show significant differences between the four groups. Same results were observed after 30 min of tilting among Groups II, III, and IV.

Response to nitroglycerin
This response could be evaluated in Groups II, III, and IV. Per cent changes were obtained by comparing the values of haemodynamic variables at the end of passive tilting with those obtained 2 min after the nitroglycerin administration (Figure 3). The HR increased in the three groups, and the per cent increases did not significantly differ between the groups. Systolic, diastolic, and mean BP decreased in the three groups, and the per cent decreases were not significantly different between the groups. Stroke volume and CO decreased in the three groups, and the per cent decreases did not differ significantly among the groups.
Presence of subtle haemodynamic alterations during orthostatic stress

Table 1 Subjects’ characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Syncope history and passive TT+</th>
<th>Syncope history and TT+ after nitroglycerin</th>
<th>Syncope history and TT–</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>20</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>11/9</td>
<td>14/9</td>
<td>8/12</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43 ± 14</td>
<td>43 ± 12</td>
<td>47 ± 11</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 13</td>
<td>70 ± 13</td>
<td>77 ± 15</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>No. of syncope episodes</td>
<td>7 ± 6</td>
<td>5 ± 6</td>
<td>/</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; n.s., not significant; TT, tilt testing.

Table 2 Haemodynamic variables obtained during supine position, just before tilt testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Syncope history and passive TT+</th>
<th>Syncope history and TT+ after nitroglycerin</th>
<th>Syncope history and TT–</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127 ± 21</td>
<td>119 ± 21</td>
<td>128 ± 18</td>
<td>133 ± 16</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 ± 15</td>
<td>69 ± 12</td>
<td>71 ± 12</td>
<td>78 ± 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>92 ± 17</td>
<td>89 ± 15</td>
<td>93 ± 14</td>
<td>100 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72 ± 14</td>
<td>72 ± 11</td>
<td>70 ± 16</td>
<td>69 ± 13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>78 ± 21</td>
<td>81 ± 23</td>
<td>92 ± 26</td>
<td>85 ± 20</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.4 ± 1</td>
<td>5.7 ± 1</td>
<td>6.0 ± 2</td>
<td>5.8 ± 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total peripheral resistance (U)</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.4</td>
<td>1 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

TT, tilt testing.

Total peripheral resistance increased by 2.7 ± 28 and 3.0 ± 15% in Groups II and III, respectively, and decreased by 4.0 ± 16% in Group IV; the per cent changes were not significantly different among the three groups.

To further evaluate possible differences in the per cent changes in haemodynamic variables, the analysis of variance was repeated among the three groups, i.e. after pooling subjects with positive TT during the passive phase or after nitroglycerin administration (Groups I and II) into a single group. This analysis was possible after 2 and 5 min of passive tilting. The results were similar, as the per cent changes in the haemodynamic variables did not show significant differences between Groups III, IV, and I plus II.

Discussion

Main finding

The main finding of the present study was that subjects with VVS showed a normal haemodynamic response to orthostatic stress. Indeed, during the first 5 min of passive TT and after nitroglycerin administration, the per cent changes in HR, in the haemodynamic variables that, in normal hearts, mainly explore the venous system (SV and CO) were similar in subjects with VVS and control subjects. The inter-individual variation in the haemodynamic variables during orthostatic stress, which is widely reported in the literature in subjects with VVS, was also seen in control subjects, as shown by the high standard deviation of the per cent changes after 2 and 5 min of passive tilting and after nitroglycerin administration (Figures 1–3). This means that this inter-individual variation is a characteristic of the population and not specific to VVS subjects. In this regard, a large inter-individual variation during orthostatic stress was very recently observed in homozygous twins without a history of syncope and was therefore attributed to environmental factors.25

This study is the first to exclude both very young and elderly subjects. The former show a high susceptibility to orthostatic stress and a high rate of positivity to passive TT, even in the absence of a history of syncope1,2; therefore, adolescents could display different haemodynamic responses to orthostatic stress. This point needs further investigation. We excluded elderly subjects because recent epidemiological studies3–5 have shown that the age of onset of VVS, although varying throughout life, peaks at the age of 20 and after 70 years. Considering that, in subjects in whom VVS starts at the old age, loss of consciousness is frequently associated with autonomic disturbances such as carotid sinus hypersensitivity, post-prandial hypotension, and symptoms of autonomic dysfunction,6,26,27 there appears to be a distinct pathophysiology underlying VVS in the elderly. In this perspective, previous studies comparing haemodynamic responses during orthostatic stress (first few minutes of tilt) in young and old subjects have recorded different responses. In particular, HR has been seen to show a smaller increase,9,10,13,15–17 TPR a larger increase,6,10 and CO, both during the passive phase and after nitroglycerin, a larger decrease6,10,12 in elderly subjects than in young ones.

Previous studies

From the methodological point of view, the studies dealing with haemodynamic responses to orthostatic stress in subjects with VVS can be subdivided into two groups. In some
In other studies, the haemodynamic responses have been compared between subjects with a history of syncope and positive TT and those with a history of syncope and negative TT. In other studies, a control group without a history of syncope has been considered.

Positive vs. negative tilt testing
Conflicting results have emerged from these studies.\textsuperscript{28-37} However, subjects with negative TT cannot be considered a suitable control group, as the sensitivity of TT, although
Figure 2  Per cent changes in haemodynamic variables after 5 min of tilt position. All the per cent changes did not show significant differences between the four groups.
Figure 3  Per cent changes in haemodynamic variables from the end of passive tilt to 2 min after nitroglycerin administration. All the per cent changes did not show significant differences between the three groups.
unknown, appears to be rather low. Therefore, from the methodological standpoint, these studies do not appear to be suited to evaluating whether VVS subjects show subtle haemodynamic responses to orthostatic stress; they can only identify possible factors that predict positivity of the test.

Vasovagal syncope subjects vs. control subjects

In some studies, changes in the haemodynamic variables during the first few minutes of TT or lower-body negative pressure have been compared between subjects with VVS and a control group. All these studies agree that VVS subjects display no difference when studied in the supine position, as in our study. Moreover, in all the studies, the changes in the BP during the first few minutes of TT were similar in the two groups.38–43 With regard to all the other variables, there are conflicting reports. In some studies,39,44 HR increased more in subjects with VVS than in controls, whereas in others,38,40,42,43 the increase in the HR was similar in both groups. The TPR has been used to investigate the changes in the arterial tone; Shen et al.42 observed a decrease in the TPR in VVS subjects and an increase in controls, whereas Novak et al.39 observed a similar increase in both groups. Brown et al.41 measured forearm vascular resistance during the first few minutes of TT associated with lower-body negative pressure and observed a smaller increase in this variable in subjects with VVS than in controls. The venous system has been investigated by measuring SV or left ventricular telediastolic volume or thorax and splanchic volumes. In some studies,39,40,45 the reduction in the SV during the first few minutes of TT was similar in VVS subjects and controls; in one study,46 the reduction in the SV was significantly greater in VVS subjects, and in another study,42 it was greater in controls. When left ventricular end-diastolic volume, evaluated by echocardiography, has been used as a measure of the venous return, the results have been equally conflicting. Indeed, Shalev et al.47 observed a similar reduction in this variable during the first few minutes of TT in the two groups, whereas Mizumachi et al.38 and Yamanouchi et al.40 observed a greater reduction in VVS subjects. Steward et al.44 investigated blood distribution during TT in adolescents, by using impedance plethysmography. They observed a greater decrease in the thoracic blood volume and a greater increase in the splanchic blood volume in VVS subjects than in controls, thus indicating decreased venous return, whereas calf volume did not differ between the two groups. However, the haemodynamic changes observed in adolescents may not closely match those seen in mature adults. There is no clear explanation for the conflicting results obtained in the various studies. Probably, different patient populations were investigated; in particular, in all previous studies, very young subjects and/or subjects >70 years were included. In this regard, it should be mentioned that some studies9,38,46–51 have investigated the sympathetic and parasympathetic systems with the HR variability analysis during TT; these have yielded conflicting reports. However, in a recent study16 involving young and elderly VVS subjects, it was observed that age, and not the TT response, is the main determinant of autonomic behaviour during the entire TT.

Vascular response during mental stress and exercise

Manyari et al.52 measured changes in the forearm venous tone using radionuclide plethysmography during mental arithmetic stress in VVS subjects and controls. The per cent increase in venoconstriction did not differ significantly between the two groups; however, VVS subjects responded to mental stress by displaying a wider range of venous volume changes. Thomson et al.53 measured changes in BP during both isometric (handgrip) and dynamic (cycling) exercise in VVS and control subjects. The increase in the BP during isometric exercise was similar in both groups, whereas during cycling, systolic BP was significantly lower at peak exercise in VVS subjects. However, ~25% of these VVS subjects had a history of exercise-induced syncope. It is possible that, in subjects with this type of syncope, an altered vascular response is present during exercise. In this regard, the recent European guidelines20 classify exercise-induced syncope as a situational syncope and not as VVS. This issue needs further investigation.

Study limitations

The absolute values of SV and CO obtained by Modelflow are not perfectly superimposable to those obtained by intrabrachial arterial recording; however, during orthostatic stress, changes in these variables, as obtained by Modelflow, closely follow the changes observed in the intrabrachial recording.54,55

The results of this study may have been slightly different if more than six beats or a combination of parameters measured had been used to assess the outcome in the same group of subjects.

We did not investigate changes in the autonomic tone during the first 5 min of tilting by utilizing HR variability analysis or other methods. The aim of this study was to investigate whether subjects with VVS show subtle haemodynamic alterations during orthostatic stress; investigating autonomic alterations not responsible for haemodynamic changes was outside the purpose of our study.

The results of this study show that subjects with VVS have a normal haemodynamic response to orthostatic stress; however, we cannot exclude an altered haemodynamic response in the cerebral circulation.

Conclusion

Our data show that young/middle-aged subjects with VVS have a normal measured haemodynamic response to orthostatic stress; therefore, the vasovagal reflex, the pathogenesis of which is unknown, is not secondary to an impairment of the primary vasoconstrictive mechanism.

Conflict of interest: none declared.

References


