Recurrent vasovagal syncope: comparison between clomipramine and nitroglycerin as drug challenges during head-up tilt testing

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Aims
To compare the responses between clomipramine, a centrally acting substance, and nitroglycerin, with mainly peripheral action, when each drug is used during tilt test for the induction of vasovagal syncope (VVS).

Methods and results
Hundred patients with recurrent episodes of classical VVS underwent two tilt tests in a randomized sequence. One test included 20 min of tilt at 60° with intravenous administration of 5 mg clomipramine (clomipramine tilt), whereas the other test included an initial 30 min period of passive 60° tilt, followed by sublingual spray administration of 400 μg nitroglycerin (nitroglycerin tilt). Fifty asymptomatic subjects served as controls. Following clomipramine tilt, a positive response occurred in 73 patients (73%), a negative response in 23 (23%), and drug intolerance in 4 (4%). With nitroglycerin tilt, these percentages were 52, 48, and 0%, respectively. Significant differences were observed regarding positive responses (clomipramine vs. nitroglycerin: 73/100 vs. 52/100, respectively, \( P < 0.05 \)), as well as negative responses (23/100 vs. 48/100, respectively, \( P < 0.05 \)). A high concordance rate was observed in positive responses.

Conclusion
In the evaluation of patients with recurrent classical VVS, clomipramine tilt is associated with an increased positive yield relative to nitroglycerin tilt. This suggests that central mechanisms may be more important than peripheral ones in VVS pathogenesis.

Keywords
Tilt testing • Vasovagal syncope • Clomipramine • Nitroglycerin

Introduction
Although vasovagal syncope (VVS) is a benign condition, it may cause disabling symptoms that diminish quality of life and lead to physical injury. Central as well as peripheral mechanisms have been implicated in its pathogenesis, while their relative contribution is not fully elucidated.

Head-up tilt testing—despite its limitations—is the most specifically able test to determine a definite diagnosis of VVS. The reported sensitivity and specificity of this test depend on the technique used, the sensitivity ranging from 26 to 80% and the specificity being ~90%. Among the newer protocols that have been developed for a more accurate diagnosis of VVS, the clomipramine test and the sublingual nitroglycerin test have shown a sufficient degree of accuracy. Clomipramine acts mainly through central serotonergic mechanisms, whereas nitroglycerin mainly through peripheral vasodilatation.

The relative diagnostic value of the two tests has not yet been systematically tested. In an attempt to see whether central or peripheral mechanisms are more important in the pathogenesis of VVS, we assessed patients with VVS by both tests, in a randomized sequence.

In the absence of a gold standard for the diagnosis of VVS, the diagnostic value of tilt testing may be more appropriately determined when studying patients where a strong clinical suspicion of vagal syncope exists. As a typical history of VVS has been proposed to be the gold standard for diagnosing VVS, patients with typical history of VVS were studied in the present investigation.
Therefore, we directly compared the positive and negative responses to tilt between clomipramine- and nitroglycerin-sensitized tests (i) in patients with recurrent episodes of classical VVS and (ii) in healthy controls. We also assessed clinical variables possibly linked to each positive-tilt test result, including history indicative of central nervous system-related symptoms (fear, emotional distress, sudden unexpected or unpleasant sight, sound, or smell).1,9

Methods

The patient study group consisted of 100 consecutive patients with recurrent episodes of classical VVS (at least two episodes during the last 6 months). Classical VVS was diagnosed according to the guidelines if precipitating events such as fear, pain, emotional distress, instrumentation, or prolonged standing were associated with typical prodromal symptoms. Although patients with classical VVS often do not need a tilt test (as opposed to patients with a more ambiguous history), they were used as gold standard patients for the purpose of this study. The control study group comprised 50 asymptomatic control subjects who were recruited from outpatient medical clinics and were matched for age and sex with the patient group. Exclusion criteria were an initial evaluation consistent with cardiovascular disease and any disease that might affect the circulation or circulatory control, including orthostatic hypotension during the first 5 min of orthostasis.

The study design was approved by the Ethics Committee of the participating centres and informed consent was obtained from all subjects. According to the study design, each patient and control subject underwent two head-up tilt tests, one potentiated by intravenous clomipramine and the other by sublingual nitroglycerin. The two tests were performed on two successive days in a randomized sequence. All patients and the other by sublingual nitroglycerin. The two tests were performed on two successive days in a randomized sequence. All head-up tilt tests were performed in the same conditions, i.e. in the morning, after overnight fasting, in a quiet, dimly lit room, at a comfortable temperature. An intravenous infusion line was inserted at least 20 min before beginning of the test. An electronically controlled tilt table with a foot-board support was used. Blood pressure, heart rate, and rhythm were closely monitored throughout the tests.

A positive response to tilt testing was considered a sudden (in less than 5 min), symptomatic systolic hypotension (less than 80 mmHg), with or without bradycardia (Figure 1). Reproduction of symptoms was needed for considering a test to be positive. Positive responses were classified according to the modified VASIS classification into Type 1 (mixed), Type 2a (cardioinhibition with asystole), 2b (cardioinhibition without asystole), and Type 3 (vasodepressor).

The clomipramine test included 20 min of tilt at 60° with intravenous administration of 5 mg clomipramine during the first 5 min of tilting. The sublingual spray nitroglycerin test included an initial 30 min period of passive 60° tilt, followed by sublingual spray administration of 400 μg nitroglycerin and an additional 15 min tilting period. A relatively prolonged passive phase was chosen for this test so as to increase its sensitivity.3

Following these, we directly compared the positive and negative responses to tilt between clomipramine- and nitroglycerin-sensitized tests as well as the relation of positive tests to the following clinical variables: total syncopal episodes up to the day of study inclusion, number of syncopal episodes during the last 6 months preceding the diagnostic evaluation, age, sex, and history indicative of at least one episode of central nervous system-related symptoms.1

The statistical analysis was performed by Statistica 6.0 software package (Statsoft). Mann–Whitney and χ² tests were used for comparison between groups. A non-parametric correlation test (Spearman’s test) was used to assess for relations between clinical parameters and each test’s positive results. A P-value less than 0.05 was considered statistically significant. Continuous data are presented as mean ± one standard deviation.

Results

The clinical characteristics of patients and controls are shown in Table 1.

In patients, following clomipramine tilt, a positive response occurred in 73 (73%), a negative response in 23 (23%), and drug intolerance in 4 (4%). With the nitroglycerin tilt, the respective responses were observed in 52, 48, and 0% of the patients (Table 2). Of the total of 125 positive responses, 112 (90%) were associated with complete loss of consciousness, evenly distributed between the two drug tests. Near syncope, associated with sudden symptomatic hypotension, reproducing patients’ symptoms, was observed in the remaining cases. Significant differences were observed regarding positive responses (clomipramine vs. nitroglycerin: 73/100 vs. 52/100, P < 0.05) as well as negative responses (23/100 vs. 48/100, respectively, P < 0.05).

Table 1

<table>
<thead>
<tr>
<th>Clinical characteristics of patients and controls</th>
<th>Patients (n = 100)</th>
<th>Controls (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>42 ± 24</td>
<td>38 ± 17</td>
</tr>
<tr>
<td>Men/women</td>
<td>43/57</td>
<td>25/25</td>
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<tr>
<td>Mean number of syncopal episodes</td>
<td>5.9 ± 7</td>
<td>0</td>
</tr>
<tr>
<td>Mean number of syncopal episodes during the last 6 months</td>
<td>3.2 ± 2</td>
<td>0</td>
</tr>
<tr>
<td>Syncope related to fear, stress, etc</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>
The positive-tilt test responses, categorized by drug challenge, test sequence, and haemodynamic type, are shown in Table 3. When we compared separately first and second tilt tests, clomipramine tilt was also associated with the same trend for a higher positivity rate than nitroglycerin tilt (first test: 37/50 for clomipramine vs. 28/50, respectively, \(P : 0.06\) and second test: 36/50 vs. 24/50, respectively, \(P : 0.05\)). Among the 52 patients with a positive nitroglycerin tilt, only two had a negative clomipramine tilt, which was performed as a second test in both cases. Among the 73 patients with a positive clomipramine tilt, 50 had a positive nitroglycerin tilt, too. Drug intolerance (gastrointestinal symptoms) was observed in four patients (4%) during clomipramine tilt and in no patient during nitroglycerin tilt.

In controls, following clomipramine tilt, a positive response occurred in 5 (10%), a negative in 44 (88%), and drug intolerance in 1 (2%). With the nitroglycerin tilt, the respective responses were 6 (12%), 44 (88%), and 0 (0%). Nine of 11 positive responses, irrespective of the drug challenge used, were observed during the first conducted tilt test. In the remaining two subjects, a positive response was observed during a clomipramine tilt that was performed as a second test.

Considering a typical history of VVS as the gold standard for diagnosis, the diagnostic performance of both tests is shown in Table 4. It is important to note that all patients with positive tests have reproduced their clinical symptoms; no difference was observed between clomipramine and nitroglycerin in this regard.

Regarding the relation of positive tests to the clinical variables assessed: (i) the number of total syncopal episodes up to the day of study inclusion and the age of the individual was not related to the positive response to any of the tests, (ii) the number of syncopal episodes during the last 6 months preceding the diagnostic evaluation was related to a positive nitroglycerin tilt result; patients with more than three syncopal episodes during the last 6 months had a 66% positive yield of nitroglycerin tilt, whereas only 38% of those with less than three events gave a positive response to this test, (iii) male or female sex was not related to any tilt test result, and (iv) a history indicative of central nervous system-related symptoms was associated with positive clomipramine tilt test result; patients with a history indicative of centrally mediated syncope had an even more increased positive response rate (35/40, 88%) to this test.

## Discussion

In this study, the results of two recently developed tilt-test protocols with drug provocation, the clomipramine and nitroglycerin test, were directly compared in a gold standard population of patients with classical VVS—possibly not identical, but at least representative of a more mixed VVS population—and a matched group of healthy controls. We found that—when evaluated in
the same patients by a randomized sequence—the use of clomipramine, a centrally acting substance, is associated with an increased positive yield relative to nitroglycerin, the action of which is mainly peripheral. Similar responses between tests were observed when they were performed in healthy controls. A high concordance of positive results was observed. A positive clomipramine tilt was correlated with previous history of centrally induced syncope, whereas a positive nitroglycerin tilt was related to the number of recent syncopal episodes.

Vasovagal syncope: central or peripheral mechanisms?
The mechanism of nitroglycerin-induced VVS7,11,12 and clomipramine-induced VVS9 have been previously studied. The differences between the effects of clomipramine and nitroglycerin could be explained by the differences in their pharmacological properties. Although the precise mechanism by which both drugs increase the sensitivity of tilt testing is complex,13 nitroglycerin mainly acts by inducing preferential peripheral venodilation that aggravates the decrease in venous return to the heart.14 Clomipramine enhances central serotonergic activity by blocking the re-uptake of serotonin in the synapse space and, thereby, increasing stimulation of serotonin receptors.15 The increased positive yield with clomipramine may be attributed to the fact that central serotonergic mechanisms play a key role in the induction of VVS in more patients with VVS than peripheral venodilation does. However, the high concordance rate between positive tests points to a less 'simple' reflex than generally considered. Indeed, VVS is a syndrome related to more than one and—sometimes—apparently opposing pathophysiological mechanisms (as for example those related to heart rate variability,16 muscle neural sympathetic discharge,17 and baroreceptor activity18). Interestingly, patients with previous history indicative of central nervous system-related symptoms had a very high rate of positive clomipramine tilt test response, a finding that confirms the clinical relevance of the test in this subgroup of patients with VVS.

Spontaneous syncope, tilt test result, and drug challenge
Our finding that the positive response to nitroglycerin tilt was related to the number of recent, spontaneous syncopal events implicates that peripheral venodilation-induced VVS may be a prevalent problem during the exacerbation periods of the syndrome (i.e. related to hot environment, dehydration, etc).

Nitroglycerin-sensitized tilt testing (and, also, the ‘classic’ passive as well as isoproterenol-potentiated tilt)19,20 has recently been shown not to be able to exactly duplicate the haemodynamic type of patients’ spontaneous syncopal episodes. This may be due to the fact that challenge drugs modify the response during tilt testing. A drug that is directly linked to the patient’s specific susceptibility might be helpful in overcoming this problem. Clomipramine, which is strongly related to centrally induced syncope, may be such a substance, especially in the subgroup of patients with central nervous system-related VVS (almost half of our classical VVS patient population); this is a hypothesis that would be interesting to be further investigated.

Implications of the study
The increased diagnostic accuracy of clomipramine tilt testing in our study population implies that central mechanisms may be more important than peripheral ones in the pathogenesis of VVS. A patient subgroup specifically sensitive to clomipramine is patients with a history of centrally induced syncope. The high concordance rate between positive clomipramine and nitroglycerin tests implies that a possible combination of the two tests might not increase the diagnostic performance of tilt testing. This means that clomipramine test can be used as a single test instead of performing more than one drug challenges. This test, apart from its increased diagnostic utility, offers a pathophysiological oriented tool that could possibly aid towards more specific (and, possibly, more effective) types of therapy. The use of clomipramine during tilt testing may improve considerably the diagnostic value of this test.

Limitations of the study
A possible limitation of this study is that clomipramine tilt needs an intravenous line for its administration. Despite having waited for at least 20 min after venepuncture, it cannot be excluded that venepuncture per se might have some additional effect in triggering a ‘central’ response. This effect cannot be completely excluded with this design. However, an intravenous line was inserted for all tests, including nitroglycerin tilt, in an effort to minimize potential differences in results that are due to venepuncture.

The diagnostic value of clomipramine test needs to be further evaluated in patients with uncertain syncope and those without ‘central’ triggers. Also, before this test being accepted by the scientific community, our results need to be confirmed by other groups.

Conflict of interest: none declared.

References
Comparison between clomipramine and nitroglycerin during head-up tilt testing


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