Diagnostic criteria for vasovagal syncope based on a quantitative history

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Aims Our goal was to develop historical criteria for the diagnosis of vasovagal syncope.

Methods and results We administered a 118-item historical questionnaire to 418 patients with syncope and no apparent structural heart disease. The prevalence of each item was compared between patients with positive tilt tests and those with syncope of other, known causes. The contributions of symptoms to diagnoses were estimated with logistic regression, point scores were developed, and the scores were tested using receiver operator characteristic analysis. The accuracy of the decision rule was assessed with bootstrapping. Data sets were complete for all subjects. The causes of syncope were known in 323 patients and included tilt-positive vasovagal syncope (235 patients) and other diagnoses such as complete heart block and supraventricular tachycardias (88 patients). The point score correctly classified 90% of patients, diagnosing vasovagal syncope with 89% sensitivity and 91% specificity. The decision rule suggested that 68% of an additional 95 patients with syncope of unknown cause and a negative tilt test have vasovagal syncope.

Conclusion A simple point score of historical features distinguishes vasovagal syncope from syncope of other causes with very high sensitivity and specificity.

KEYWORDS
Vasovagal; Syncope; Diagnosis; Tilt test; Faint; Point scores; History

Introduction
Vasovagal syncope is the most common cause of syncope and can be troublesome to diagnose. As with other causes of total loss of consciousness, patients have no recollection of their unconsciousness, and the reliability of the diagnosis of the first loss of consciousness is quite low1. Many causes of syncope, although uncommon, have a treatable cause and/or an eventual poor outcome, while vasovagal syncope is not associated with excess mortality. The concern about identifying treatable arrhythmic and other causes, and for some causes, an eventual poor outcome2 coupled with the diagnostic uncertainty based upon the history has led to aggressive investigations of patients with syncope. Frequently, these are expensive,3,4 invasive, and all too commonly inaccurate or inefficient.5–8 Although the cause of syncope is eventually discovered in most patients who are referred to specialists, there is need for a simple diagnostic tool for other settings. These might include primary care offices and emergency wards, and in epidemiologic, therapeutic, and health services studies. In these contexts, the current diagnostic tool, tilt testing, may not be feasible.

We aimed to develop simple diagnostic criteria for distinguishing vasovagal syncope from other causes of syncope in patients with structurally normal hearts, on the basis of a careful history targeted at specific features. We began with patients having positive tilt tests, as is the current conventional practice. We prospectively administered a structured questionnaire to syncope patients with a positive tilt test and quantitatively compared the responses with those of patients with syncope due to other known causes.9 From this, we developed a diagnostic point score to discriminate vasovagal syncope from syncope with other known causes.

Methods
Syncope symptom study
The University of Calgary Conjoint Medical Ethics Review Committee and similar committees in all participating centres approved this study. Patients were enrolled in Calgary, Canada; Hamilton, Canada; and Cardiff, United Kingdom.

Inclusion criteria
Consenting patients were eligible if they had had one or more loss of consciousness. They were recruited from sequentially identified patients in university and private practice cardiology clinics, pacemaker clinics, arrhythmia and syncope clinics, and hospital cardiology wards. They were included in the Syncope Symptom Study if they had a diagnosis established according to preset criteria.
(discussed subsequently), if there was no reasonable diagnostic
confusion, or if reasonable investigations failed to elicit a diagnosis.
That is, they were included if the diagnosis was known, or unknown
despite reasonable attempts to elucidate one.

Exclusion criteria
Patients were excluded if they refused consent, were incapable of
completing the questionnaire, or had more than one plausible
cause of one syncopal spell. Patients with a history of known or sus-
ppected cardiomyopathy, or prior myocardial infarction, had the
cardiac diagnosis confirmed by echocardiography, gated angiogra-
phy, or cardiac catheterization, and were then excluded. The
purpose of the larger study, the Syncope Symptom Study, was to
develop historical diagnostic criteria for several classes of loss of
consciousness.9 There were 671 subjects, of whom 102 had epileptic
seizures and 151 had syncope in the setting of structural heart
disease. The remaining 418 patients with syncope in the apparent
absence of structural heart disease are the subjects of this report.

Gold standard diagnostic criteria
Patients had vasovagal syncope if they had a positive tilt test
performed according to one of several currently acceptable
methods.10–14 We chose not to specify that a particular tilt test
protocol be used. This might have increased the internal validity
of the study, but because each protocol has its own specificity and
positive yield, we left the particular protocol up to the participating
centre to increase external validity. It was deemed positive if it
induced clinically reminiscent pre-syncope or syncope, and hypo-
tension, bradycardia, or both. The specific degree of hypotension
and bradycardia were pre-specified and depended on the protocol.
These and other gold standard diagnostic criteria are listed in
Table 1. All patients without an otherwise proven cause of
syncope had an ECG and a tilt table test. Patients ≥60 years old
usually underwent ambulatory electrocardiography.

Syncope symptom questionnaire
All patients completed a structured questionnaire9 with 118 items
developed from that of Calkins et al.17 It assessed symptom
burden, provocative situations, peri-syncopal symptoms, and related medical history. Completed questionnaires were
checked for completion by study co-ordinators, and incomplete
questionnaires were returned for revision. We cross-checked for
incompatible entries to assess the accuracy of questionnaire
completion.

Study definitions
In this article, we use working definitions, rather than pre-emptorily
linking tilt test results to the term vasovagal syncope. Primary
syncope denotes syncope of no apparent other cause in patients
with either a positive tilt test (tilt-positive primary syncope) or a
negative tilt test (tilt-negative primary syncope). Secondary
syncope denotes syncope due to a known cause other than vasovagal
syncope. We developed a point score that discriminated patients
with primary tilt-positive syncope from patients with secondary
syncope.

Statistical analysis9
First, we compared the prevalence of each variable in the tilt-
positive primary syncope and secondary syncope groups using a
Fisher’s exact test and calculated the likelihood ratio for predicting
the diagnosis of tilt-positive primary syncope. The likelihood ratio of
each variable is its prevalence in the tilt-positive primary syncope
group divided by its prevalence in the secondary syncope group. A
variable with a likelihood ratio >1 is predictive of tilt-positive
primary syncope and a variable with a ratio <1 is predictive of secondary syncope. Binary variables were created from continuous
variables using a cut-point, which was the mean of the entire
sample for symmetrically distributed variables and the median for
variable that were very skewed. Variables with a very low preva-
ience were combined into a composite variable provided that
both the magnitude and significance of the likelihood ratio were
about the same and that the combination made clinical sense. Variables with similar meanings and similar descriptive statistics
were also combined in order to reduce the number of variables
eligible for inclusion in the following logistic regression analysis.
We then developed a manual stepwise logistic regression model
that predicted tilt-positive primary syncope. Variables were eligible
for inclusion in the logistic regression model if they were significant
predictors (P < 0.01) in the univariate analysis and were retained in
the multivariable model if P < 0.05 for the Wald statistic. No inter-
actions between the variables were assessed.
To derive a practical diagnostic decision rule, a point score was
developed by assigning ±1, ±2, ±3 (and so on) points to each of
the factors based on the relative magnitude of the estimated
regression coefficient. Each coefficient was divided by the smallest
absolute value of the coefficient retained in the model, then
rounded to the nearest integer. The points were summed and a diag-
nostic threshold chosen using receiver operating characteristic
analysis.18 Using the diagnostic threshold, the apparent sensitivity,
specificity, and overall accuracy in this test sample were estimated.
When the predictive accuracy of a diagnostic decision rule is
assessed using the same patients from whom it was developed, an

Table 1 Gold standard diagnostic criteria for patient inclusion and working diagnostic definitions used in this study during analysis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Gold standard diagnoses</td>
<td></td>
</tr>
<tr>
<td>Vasovagal syncope</td>
<td>Positive tilt test using a currently acceptable method10–14</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Sustained VT documented during syncope, or ≤48 h of admission for syncope, or if haemodynamically unstable, sustained monomorphic VT was induced during an electrophysiologic study15</td>
</tr>
<tr>
<td>Torsade de Pointes</td>
<td>Documented at the time of syncope or shortly afterwards with classic clinical features</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Established diagnosis of arrhythmia, and typical palpitations immediately preceding a syncopal spell, or awoke from syncope with those symptoms</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>Complete heart block with a wide QRS escape rhythm documented during syncope or shortly afterwards</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Documented autonomic neuropathy with significant orthostatic hypotension and presyncope or syncope during tilt table testing16</td>
</tr>
<tr>
<td>Primary syncope</td>
<td>Syncope of no apparent other cause with either a positive tilt test (tilt-positive primary syncope) or negative tilt test (tilt-negative primary syncope)</td>
</tr>
<tr>
<td>Secondary syncope</td>
<td>Syncope due to a known cause other than vasovagal syncope</td>
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unduly optimistic classification rate might occur. This is referred to as the apparent accuracy. Ideally, the true accuracy should be evaluated using a split sample, but in this case, our sample size for the secondary syncope group was not large enough. Accordingly, we used a bootstrap analysis to estimate the excess error that would be detected if an independent sample was used to evaluate the diagnostic accuracy. Five thousand bootstrap samples were drawn from the original sample. For each bootstrap sample, the logistic regression model with the same variables as those in the adopted model was fitted to re-estimate the regression coefficients and the diagnostic decision rule developed. The accuracy of the new decision rule from the bootstrap sample was then assessed in the original sample. The expected excess error rate was calculated from the 9500 bootstrap samples, then subtracted from the apparent accuracy to obtain estimates of the true sensitivity, specificity, and overall accuracy of the diagnostic decision rule.

We derived classification rules both with and without the variables of symptom burden and durations. Finally, we compared the symptoms of patients with gold standard diagnoses with those with no identifiable cause of syncope by two methods. First, we determined the diagnostic performance of the point score for tilt-positive primary syncope in patients with tilt-negative primary syncope. Secondly, we compared the tilt-positive primary syncope patients with tilt-negative primary syncope patients, both of whom fit the derived diagnostic criteria for tilt-positive primary syncope.

Results

Patient population (Table 2)

Patient enrolment occurred between January 1995 and July 2001. All patients who were approached consented, and only two were disqualified, because they had more than one plausible cause of syncope. There were 235 patients with syncope and positive tilt tests (tilt-positive primary syncope), 95 patients with no apparent cause of syncope and negative tilt tests (tilt-negative primary syncope), and 88 patients with other identified causes of syncope (secondary syncope). Of the latter, 42 had complete heart block, 21 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, six had complete heart block, 21 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valve disease, 235 had a supraventricular tachycardia, six had idiopathic ventricular tachycardia, five had aortic stenosis, three had aortic valv

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tilt-positive primary syncope</th>
<th>Secondary syncope</th>
<th><em>P</em>-value, tilt-positive primary syncope vs. secondary syncope</th>
<th>Tilt-negative primary syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>235</td>
<td>88</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>42 ± 18</td>
<td>63 ± 16</td>
<td>&lt;0.001</td>
<td>49 ± 21</td>
</tr>
<tr>
<td>Females</td>
<td>61%</td>
<td>45%</td>
<td>0.011</td>
<td>54%</td>
</tr>
<tr>
<td>Syncopal spells, n (Median, IQR)</td>
<td>6 (3–20)</td>
<td>2 (1–5)</td>
<td>&lt;0.001</td>
<td>5 (3–12)</td>
</tr>
<tr>
<td>Symptom duration, months (Median, IQR)</td>
<td>100 (13–268)</td>
<td>1 (0–16)</td>
<td>&lt;0.001</td>
<td>29 (3–132)</td>
</tr>
</tbody>
</table>
scores in the tilt-negative and tilt-positive primary syncope patients when compared with the patients with secondary syncope are shown in Figure 3. Finally, we assessed whether any of the 71 original significant predictors discriminated between patients whose point scores were ≥−2, and who had either positive or negative tilt tests. Only four out of 71 variables were statistically significant, with $P < 0.05$. When 71 independent tests are performed, the probability of four or more being significant due to chance alone at the 5% level of significance is 0.48, indicating that there is little evidence of any significant difference between these two groups. Similarly, only two of the 34 variables presented in Table 3 were significant at $P < 0.05$.

**Discussion**

**Clinical implications**

In patients with a transient loss of consciousness, there is substantial diagnostic disagreement among physicians, and
written diagnostic criteria improve inter-rater agreement. Although tilt table testing has provided important diagnostic and physiologic insights, it is not readily available in emergency wards and family physicians’ offices, and by codifying diagnosis, the score may streamline management. Similarly, tilt testing may not be feasible in larger community-based studies of people with syncope who are not patients. Varying the diagnostic cut-off level would allow investigators to vary the sensitivity, specificity, and predictive values of the score depending on the need of the study.

The point score was developed from structured questionnaires prospectively administered to patients with apparently structurally normal hearts, and not from a post hoc chart review. Tilt tests were selected as the entry point for patients with presumed vasovagal syncope, because the tilt table test was developed to mimic some of the physiology of vasovagal syncope; they provoke symptoms reminiscent of the patients’ syncopal spells; and because positive tilt tests are accompanied by hypotension and bradycardia, as is vasovagal syncope.

Features of questionnaire

The classification scheme is simple, and to some extent confirms previous empiric diagnostic criteria. We present derived diagnostic questions and their points in Table 5. The patient has vasovagal syncope if the point score is ≥ −2 and syncope due to other causes if the point score is < −2. Some of the diagnostic factors in favour of vasovagal syncope in the model reflect the situations in which vasovagal syncope occurs. These include prolonged sitting or standing and exposure to medical situations. The age criterion reflects the young age at which vasovagal syncope usually first occurs.

However, these used alone were not necessarily sufficient. Four risk factors for other causes of syncope, asystole or bifascicular block on an ECG, supraventricular tachycardia, and diabetes, usually need to be absent to establish a diagnosis of vasovagal syncope. The classification scheme was not improved with the addition of the criteria for the duration of the history or number of syncopal spells. This suggests that patients can be accurately diagnosed at first presentation and that health care wait lists do not confound the diagnosis.

Other studies

Calkins et al. reported a prospective, evidence-based study of the symptoms of patients with ventricular tachycardia, complete heart block, or tilt test-positive vasovagal syncope.

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Table 4  Point scores for the diagnosis of tilt-positive primary syncope, in the absence of knowledge of the numbers and historical duration of syncope and pre-syncope

<table>
<thead>
<tr>
<th>Feature</th>
<th>Regression coefficient (SE)</th>
<th>P-value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one of bifascicular block, asystole, supraventricular tachycardia, diabetes</td>
<td>−4.93 (0.76)</td>
<td>&lt;0.001</td>
<td>−5</td>
</tr>
<tr>
<td>Blue colour noted by bystander</td>
<td>−4.19 (1.26)</td>
<td>&lt;0.001</td>
<td>−4</td>
</tr>
<tr>
<td>Age at first syncope ≥ 35 years</td>
<td>−2.61 (0.63)</td>
<td>&lt;0.001</td>
<td>−3</td>
</tr>
<tr>
<td>Remembers something about the spell</td>
<td>−1.80 (0.53)</td>
<td>&lt;0.001</td>
<td>−2</td>
</tr>
<tr>
<td>Pre-syncope or syncope with prolonged sitting or standing</td>
<td>0.95 (0.49)</td>
<td>0.05</td>
<td>1</td>
</tr>
<tr>
<td>Sweating or warm feeling before a spell</td>
<td>1.95 (0.56)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Pre-syncope or syncope with pain or medical procedure</td>
<td>2.90 (0.85)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
</tbody>
</table>

Classify as tilt-positive primary syncope for points ≥ −2.
positive and tilt-negative primary syncope patients.

Figure 3 A comparison of point score distributions for populations of tilt-positive and tilt-negative primary syncope patients.

Table 5 Diagnostic questions to determine whether syncope is due to vasovagal syncope or to another cause of syncope

<table>
<thead>
<tr>
<th>Question</th>
<th>Points (if yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a history of at least one tachycardia, diabetes?</td>
<td>-5</td>
</tr>
<tr>
<td>At times have bystanders noted you to be blue during your faint?</td>
<td>-4</td>
</tr>
<tr>
<td>Did your syncope start when you were 35 years of age or older?</td>
<td>-3</td>
</tr>
<tr>
<td>Do you remember anything about being unconscious?</td>
<td>-2</td>
</tr>
<tr>
<td>Do you have lightheaded spells or faint with prolonged sitting or standing?</td>
<td>1</td>
</tr>
<tr>
<td>Do you sweat or feel warm before a faint?</td>
<td>2</td>
</tr>
<tr>
<td>Do you have lightheaded spells or faint with pain or in medical settings?</td>
<td>3</td>
</tr>
</tbody>
</table>

The patient has vasovagal syncope if the point score is ≥ -2.

Negative and positive tilts

The close symptomatic similarity between most patients with negative and positive tilt tests is consistent with the idea that most patients with negative tilt tests have falsely negative tests. Given that the score is 90% sensitive for tilt-positive primary syncope, and that 68% of tilt-negative primary syncope patients fall in the same diagnostic category, it may be that up to 76% of tilt-negative primary syncope patients truly have vasovagal syncope. Patients with negative and positive tests have similar symptom burdens, similar clinical outcomes in the 3 years following the tilt test, and behave similarly in a multivariable predictive model of pre-test variables for post-test outcome.22-24

Limitations

Patients were accrued from tertiary care clinics and acute care facilities, and these findings need to be tested in a broadly based population. There may be some patients with rare presentations of common disorders who went undiagnosed. We did not specify a particular tilt test protocol to be used. Although this might have increased the internal validity of the study, we recognized that each protocol has its own specificity and positive yield, and therefore, left the particular protocol up to the participating centres to increase external validity. Similarly, we did not specify the investigations necessary to diagnose the absence of structural heart disease. By leaving this to individual centres, we hoped to derive diagnostic criteria driven by and relevant to conventional clinical practice. We assessed the optimism error of the diagnostic schemes with bootstrapping, and independent confirmation is desirable. These criteria should be tested in relatively uncommon syndromes such as long QT syndrome and Brugada syndrome. Another strategy to the development of a diagnostic point score would have been to develop it using subjects with what are assumed to be classic histories of vasovagal syncope, but these criteria are not evidence-based and might be self-fulfilling. Accordingly, we started with tilt test criteria and worked independently towards a historical definition. We hoped this would avoid excessive bias. The point score may reflect regional and referral idiosyncrasies of the study population tested, as well as the particular tilt tests used. The limitations of tilt tests as diagnostic tools were reviewed recently.8 The questionnaire was administered to some patients after their relevant diagnostic studies, and this might have reinforced recollection of symptoms specific to the test outcomes. The effect of age on recollection of symptoms is unknown, as is the use of the point score in elderly patients. We do emphasize that the point score is applicable only to patients without structural heart disease. These concerns underlie the importance of assessing the accuracy and utility of the point score in other populations and settings. Indeed, it has been used in a population-based survey of syncope, is an inclusion measure in an ongoing multinational randomized clinical trial, and will be used in upcoming epidemiological studies in community and acute care sectors. Clinicians should use these criteria only as a guide to diagnosis.

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Conflict of interest: none declared.

Appendix

References


