OBJECTIVES: To evaluate the sensitivity and tolerability of shortened, glyceryl trinitrate (GTN)-potentiated, head-up tilt test (HUT) in patients older and younger than 65 with unexplained syncope and to compare the specificity of GTN-potentiated HUT (GTN-HUT) in older and younger controls.

SETTING: Syncope units in secondary and tertiary hospitals.

PARTICIPANTS: Three hundred twenty-four consecutive patients with unexplained syncope (100 aged ≥65 (mean age ± standard deviation 73 ± 6; 35 men) and 224 aged <65 (41 ± 15; 111 men)) and 64 controls (29 aged ≥65 (73 ± 6; 13 men) and 35 aged <65 (42 ± 13; 16 men)).

INTERVENTION: Patients and controls were tilted upright to 60° for 20 minutes. If syncope did not occur, sublingual GTN (400 µg) was administered and 60° HUT was continued for 15 minutes. Responses were classified as positive, negative, or exaggerated (slow decrease in blood pressure with a slight decrease in heart rate after GTN).

MEASUREMENTS: Electrocardiogram and arterial pressure were monitored continuously.

RESULTS: GTN-HUT was positive in 60% and 66% (NS), negative in 29% and 33% (NS), and exaggerated in 11% and 1% ($P < .001$) of older and younger patients, respectively. In older and younger controls, the GTN-HUT was negative in 70% and 86% and exaggerated in 28% and 9% of cases, respectively, ($P < .05$). The overall specificity (considering as negative also the exaggerated responses) was 97% in older and 94% in younger subjects. No patient or control experienced serious side effects.

CONCLUSION: The shortened GTN-HUT provides satisfactory positivity rate and specificity in older patients. This test may be considered as a diagnostic tool in assessing recurrent unexplained syncope in older patients. J Am Geriatr Soc 50:1324–1328, 2002.

Key words: syncope; head-up tilt testing; older; glyceryl trinitrate

Syncope is a common syndrome in older people, and its prevalence increases with advancing age. Even when it is indicative of benign conditions, syncope is associated with increased morbidity. Neurally mediated syncope was thought to be a rare cause of loss of consciousness in older people when the diagnosis relied on only clinical data. Over the past decade, with expanded use of the head-up tilt test (HUT), a neurally mediated mechanism has emerged as a frequent cause of fainting, even at older ages. Despite its increasing popularity, this test is still not well standardized. The low positivity rate of the unmedicated Westminister protocol in an unselected population has prompted the use of drugs as provocative agents to increase the sensitivity of HUT. Shortened GTN-potentiated HUT (GTN-HUT) provides an adequate test with good specificity and positivity rate in young patients and has recently been proposed as the standard protocol for the diagnosis of neurally mediated syncope. Nevertheless, its use in older patients with unexplained syncope has not been validated.

The aims of this study were to evaluate the sensitivity, specificity, and tolerability of shortened GTN-potentiated HUT (GTN-HUT) in patients with unexplained syncope aged 65 and older and to compare the positivity rate and specificity of shortened GTN-HUT of this group with that of a group of younger patients.
METHODS

Patient Population

One hundred consecutive patients aged 65 and older and 224 patients younger than 65 with a syncope of unknown origin were studied to determine the positivity rate of GTN-HUT. All patients were referred from the emergency room or from outpatient clinics to the “Syncope unit” of the cardiology or geriatric medicine divisions at three hospitals (Fucecchio, Florence, and Modena). The demographic and clinical characteristics of the two groups are presented in Table 1.

Patients who were on antihypertensive treatment were considered hypertensive. Syncope was categorized as unexplained if no plausible cause was detected after a clinical history was taken and a physical examination that included supine and orthostatic blood pressure measurements, basal electrocardiogram (ECG), and bilateral carotid sinus massage in supine and upright positions was performed. Other cardiac (ambulatory 24-hour ECG monitoring, echocardiogram, electrophysiologic study) and neurologic (electroencephalogram, computed tomographic scan) diagnostic tests were performed when necessary. Patients with carotid sinus syndrome, organic heart disease, sick-sinus syndrome, intraventricular conduction defects, orthostatic hypotension, chronic and paroxysmal atrial fibrillation, or permanent pacemaker were excluded from the study.

To assess the specificity of the GTN-HUT protocol, 29 control subjects aged 65 and older (mean age ± standard deviation 73 ± 6; 13 men) and 35 control subjects younger than 65 (42 ± 13; 16 men) were also included in the study. All control subjects were considered healthy on the basis of medical history, physical examination, and standard ECG. In particular, they had no history of syncopal or presyncopal episodes. No control subject was taking any medications. All patients and control subjects gave informed consent to the diagnostic procedure.

Drug

Sublingual spray GTN (400 μg Natispray, Teofarma srl, Pavia Italy) was used in this study as the provocative test. The spray was preferred to sublingual tablets, which, before absorption, require a prolonged dissolution process.

Recordings

ECG leads I, II, and III were monitored on a multichannel oscilloscope. When symptoms developed, the ECG was recorded at a speed of 25 mm/sec with a Mingograph 7 (Siemens Elena, Stockholm Sweden). Arterial pressure was continuously monitored by the Penaz volume-clamp method using a finger cuff (Finapres Ohmeda 2300, Louisville, CO). An appropriate-size finger cuff was used, and the hand was supported with a sling to keep the finger at heart level while the patient was in a supine and upright position. No invasive instrumentation was used during the test.

Experimental Procedure

To avoid interference of diurnal autonomic variability, HUT was performed between 8:30 and 10:30 a.m. All cardiovascular drugs were withdrawn at least 2 weeks before the study, with the exception of drugs that patients were taking at the time of their syncopal episode for reproducing the clinical setting of spontaneous syncopal episodes. Ten minutes was allowed for stabilization in the supine position before HUT. Patients were tilted upright to 60° for 20 minutes on a motorized tilt-table with footplate support. If syncope or presyncope did not occur within 20 minutes, sublingual GTN (400 μg) was administered and observation was continued at the same angle for an additional 15 minutes. If syncope occurred during the test, the patient was returned to the supine position, and the test was interrupted. The angle of 60° was chosen because, in a previous report, the adoption of this angle guaranteed a high specificity without increasing the proportion of false positive tests.

Definitions

Syncope was defined as a sudden loss of consciousness with inability to maintain postural tone and spontaneous recovery. HUT was considered positive when syncope was reproduced in association with hypotension (decrease in systolic blood pressure >60% of the maximal value in upright position), bradycardia (decrease in heart rate >30% of the maximal value in upright position), or neurohormonal activation (increase in plasma catecholamine concentration).

Table 1. Demographic and Clinical Features of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥65 (n = 100)</th>
<th>&lt;65 (n = 224)</th>
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<tbody>
<tr>
<td>Age, (mean ± SD)</td>
<td>73 ± 6</td>
<td>41 ± 15</td>
</tr>
<tr>
<td>Age range</td>
<td>65–87</td>
<td>8–64</td>
</tr>
<tr>
<td>Men/women</td>
<td>35/65</td>
<td>111/113</td>
</tr>
<tr>
<td>Number of syncopal episodes, mean ± SD</td>
<td>4 ± 5</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>Mean duration of symptoms, months, mean ± SD</td>
<td>95 ± 195</td>
<td>82 ± 136</td>
</tr>
<tr>
<td>Patients with recurrent syncope, n (%)</td>
<td>56 (56)</td>
<td>136 (61)</td>
</tr>
<tr>
<td>Total traumas, n (%)</td>
<td>23 (23)</td>
<td>70 (31)</td>
</tr>
<tr>
<td>Major traumas (fractures), n (%)</td>
<td>6 (6)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Patients with arterial hypertension, n (%)</td>
<td>30 (30)</td>
<td>5 (2)</td>
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SD = standard deviation.
of the maximal value in upright position), or both. According to Vasovagal Syncope International Study (VASIS),\textsuperscript{14} positive responses were classified as type 1 (mixed), types 2A and 2B (cardioinhibitory), type 3 (vasodepressive), exception 1 (chronotropic incompetence), and exception 2 (excessive rise in heart rate). A positive cardioinhibitory response was considered present only when bradycardia or asystole occurred immediately before or at the moment of the loss of consciousness and not when they occurred after syncope. According to Raviele et al.,\textsuperscript{7} we defined as an exaggerated response the gradual development of symptoms (usually minor and different from the spontaneous ones) associated with a slow (>5 minutes) decrease in blood pressure alone and only a slight (<30%) reduction in heart rate during the pharmacological phase. Time to syncope was defined as the interval from the beginning of HUT to the loss of consciousness.

Statistics
Statistical analysis was performed with StatSoft 5.1 software (Tulsa, OK). All data are reported as mean ± standard deviation. The Student’s t test for unpaired data was used to compare continuous variables between groups. The chi-square method was used to compare categorical variables. \( P \leq .05 \) was considered statistically significant.

RESULTS
Patients with Syncope
Positivity rate and specificity of the GTN-HUT are illustrated in Figure 1. The test was positive in 60 (60%) older patients. Five patients had syncope during the unmedicated phase, 55 after GTN administration. The mean time to syncope was 11 ± 1 minutes during the drug-free phase and 4 ± 2 minutes during the GTN-potentiated phase of HUT. The different hemodynamic patterns of positive responses are reported in Table 2. We observed an asystole of longer than 3 seconds in three patients during the syncopal phase. A negative response was observed in 29% and an exaggerated response in 11% of older patients. The positivity rate of HUT was 43% in older patients with a history of a single syncope and 57% in those with three or more syncopal attacks. GTN-HUT was positive in 147 (66%) younger patients: 28 during the unmedicated phase and 119 after GTN (Figure 1). The mean time to syncope was 13 ± 5 minutes during the first phase and 4 ± 3 minutes during the second one. The hemodynamic pattern of positive responses is reported in Table 2. An asystole of longer than 3 seconds was observed in 46 patients during the syncopal phase. A negative response was observed in 33% and an exaggerated response in 1% of younger patients (\( P < .001 \), older vs younger group). The positivity rate of HUT was 54% in younger patients with a history of a single episode of syncope and 74% in those with three or more syncopal attacks. The hemodynamic changes during HUT in patients with a positive response are reported in Table 3. Two patients each in the younger and older groups developed a sustained atrial fibrillation after a prolonged asystole occurring during the test. No other serious side effects were observed during the study, and HUT was completed in all cases.

Figure 1. Distribution of responses to head-up tilt test potentiated with sublingual glyceryl trinitrate in control subjects (left panel) and syncope patients (right panel) (□ <65 years, ■ ≥65 years).

Control Subjects
In 20 of 29 older controls, the GTN-HUT was negative. One subject had a positive response after GTN administration, and eight others had an exaggerated response. In 30 of 35 younger controls, the GTN-HUT was negative. Two subjects had a positive response after GTN, and three others had an exaggerated response (\( P < .05 \), older vs younger controls). No subject with a positive HUT had a cardioinhibitory response in either control group. The specificity was 69% in older and 86% in younger controls. If one categorizes the exaggerated responses as negative responses, the overall specificity of the protocol is increased to 97% in older and 94% in younger individuals.

DISCUSSION
HUT is commonly used to evaluate patients with unexplained syncope. In the recent Guidelines of the European Society of Cardiology,\textsuperscript{15} HUT is indicated in recurrent unexplained syncopal episodes in the absence of organic heart diseases, the presence of single syncope in high-risk settings (e.g., occurrence of or potential risk of physical injury, particularly relevant in an older population), and the presence of organic heart disease after a cardiac cause of syncope has been excluded. The usefulness of HUT has

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>n (%)</th>
<th>( P )-value</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>37 (62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type 2A</td>
<td>5 (8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type 2B</td>
<td>3 (5)</td>
<td>.159</td>
</tr>
<tr>
<td>Type 3</td>
<td>10 (17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exception 1</td>
<td>3 (5)</td>
<td>.926</td>
</tr>
<tr>
<td>Exception 2</td>
<td>2 (3)</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

Table 2. Distribution of Positive Responses During Head-Up Tilt Test in Older and Younger Patients According to Vasovagal Syncope International Study Classification\textsuperscript{14}
been demonstrated also in older people. In the past, the diagnosis of vasovagal syncope was based on clinical history, but the frequent absence of prodromic symptoms in older people reduces the “diagnostic yield” of clinical evaluation. Indeed, after widespread introduction of HUT in clinical practice, the diagnosis of syncopal attacks of vagal origin increased, so that unexplained syncope in the older population has dropped from 40% to 15%. Recently, pharmacological stimulation has been introduced to increase the diagnostic accuracy of HUT, but isoproterenol, the most widely used drug in the United States, cannot be used in approximately 10% of patients because of contraindications and because, in as many as 16% to 24% of subjects, particularly at older ages, onset of side effects imposes an early withdrawal. Furthermore, the positive chronotropic effect of isoproterenol may mask the chronotropic-incompetence response, which is frequently observed in older patients. GTN-potentiated HUT as proposed by Raviele et al. is a promising tool for evaluating older patients with unexplained syncope because it has been proven substantially safe and well tolerated. Recently, comparable positivity rates and specificity have been reported for the shortened GTN-HUT, which differs from the original Raviele protocol in that its unmedicated phase is shorter.

Our study demonstrated that the shortened GTN-HUT had a similar positivity rate in older and younger patients with unexplained syncope, whereas several previous studies of low- and high-dose isoproterenol HUT have reported that the positivity rate decreases with aging. A possible explanation for this difference may be identified in the age-related decline in the responsiveness to catecholamines, but Marchionni et al. have demonstrated that, despite similar pharmacokinetics, the pharmacodynamic response to the vasodilating effect of GTN is greater in older individuals, probably because of the diminished plasma volume typical of this population. This might result in a higher proportion of false-positive responses to the GTN-potentiated HUT in older individuals.

In our study, we distinguished between a positive response (expressive of activation of a neural reflex) and an exaggerated response (considered the result of excessive vasodilatation). The clinical significance of the latter is uncertain, and it is frequently observed in older patients who are more susceptible to the vasodilator effect of GTN. If we consider such responses as negative, at least in terms of lacking demonstration of a neuromediated origin of syncope, the specificity of our protocol becomes quite satisfactory and similar in younger and older individuals. As a consequence, we observed a lower positivity rate in the older population than did Natale et al., who did not classify separately this pattern of response.

According to previous studies, the rate of mixed or vasodepressive responses (types 1 and 3) was higher in older patients, whereas the cardioinhibitory responses (types 2A and 2B) prevailed in the younger ones. Such a difference may be caused by an age-related decline in the parasympathetic drive to the heart. In a study by Kurbaan et al., exception 1 response (chronotropic-incompetence) was associated with older age. In this regard, we did not observe a statistically significant difference between the two age groups. This response is mostly seen in older patients with structural heart disease and may be due to an impaired reflex response or to intracardiac conduction defects. Our patient selection, with the exclusion of those with structural heart disease and suspected sick sinus syndrome, may account for the differences between our findings and Kurbaan’s results. The VASIS classification is based on the different behavior of blood pressure and heart rate observed when symptoms and vasovagal reaction occur. Recently, an analysis of the presyncopal phase has identified a dysautonomic pattern, characterized by a gradual and progressive decrease in blood pressure with a small change in heart rate. The original VASIS classification does not take into account this pattern of response, whose pathophysiological mechanism, in contrast to that of vasovagal syncope, may consist of an inability of the cardiovascular system to adapt to the HUT-related hemodynamic stress. The prevalence of this response in our study was similar in older and younger patients (12% vs 9%, \( P = .573 \)). This is probably because this response is observed preferentially in older patients with coexistent carotid sinus hypersensitivity, who were excluded from our study. The shortened GTN-HUT has been well tolerated in all older patients. This represents an advantage over the standard GTN protocol. Indeed, in the study of Kurbaan et al., 28% of patients aged 75 and older could not tolerate the longer GTN-HUT. No serious adverse events were observed in younger or older patients during HUT. Incidence of atrial fibrillation after asystole was similar in both groups and in all cases was self-limited.

### Therapeutic Implications

GTN-HUT allows for identification of the cardioinhibitory and vasodepressive components of syncope and may be a guide to the selection of the most-appropriate thera-
Conclusions

The shorted GTN-HUT, one of the tests that can be used in the diagnostic assessment of patients with recurrent unexplained syncope, provides a highly satisfactory positivity rate and highly satisfactory specificity even in older patients. Because of its safety and tolerability, this test should be preferred in the evaluation of such patients.

References