

Effect of Time Elapsed From Spontaneous Syncope on the Diagnostic Performance of the Head-Up Tilt Table Test

Juan Martínez Sánchez, Arcadi García Alberola, Javier Lacunza Ruiz, Juan J. Sánchez Muñoz, Joaquín Barnés, Juan A. Ruipérez, and Mariano Valdés

Hospital Universitario Virgen de la Arrixaca, Murcia, Spain.

Objectives. The propensity for spontaneous and tilt-induced neurocardiogenic syncope may exhibit temporal variations. Therefore the diagnostic performance of the head-up tilt test could be improved if it were performed soon after the occurrence of spontaneous syncope. The objective of this study was to assess whether the time interval between the last syncopal episode and tilt table testing influenced the outcome of the test.

Patients and method. Three hundred and fifteen patients undergoing diagnostic tilt table testing potentiated with nitroglycerin for suspected neurocardiogenic syncope were included in the study. The time between the last spontaneous syncope and the tilt table test was recorded and its relationship with the results of the test was analyzed.

Results. The tilt table test was positive in 211 patients (67.0%). The time from syncope to test was similar for patients with positive and negative tilt table test results: 28 (1-500) vs 32 (2-700) days (NS). No significant relation was observed between the results of the test and the occurrence of spontaneous syncope during the week, the month or the three months previous to the procedure. However, in men and in patients older than 50 years a higher rate of positive tests was observed if the tilt test was performed within the first month after the last spontaneous syncope.

Conclusions. The time from the last previous spontaneous syncope to the head-up tilt test does not have a significant impact on test outcome in the overall population with suspected neurocardiogenic syncope. However, the rate of positivity might decrease in men and patients older than 50 years if the test is performed later than one month after the spontaneous syncopal episode.

Key words: Syncope. Diagnosis. Head-up tilt test.

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Correspondence: Dr. A. García Alberola.
Pza. del Roble, 36. 30120 La Alberca. Murcia. España.
E-mail: algamur@teleline.es

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Efecto del tiempo transcurrido tras el síncope sobre el rendimiento diagnóstico de la prueba de basculación

Introducción y objetivos. La propensión a sufrir síncope neuromediados parece modificarse con el tiempo, por lo que el rendimiento diagnóstico de la prueba de basculación podría mejorar si se efectúa pronto tras el episodio sincopal. El objetivo del estudio es determinar si el tiempo transcurrido desde el síncope espontáneo hasta la realización de la prueba de basculación modifica la tasa de positividad de la misma.

Pacientes y método. Se incluye a 315 pacientes a los que se practicó una prueba de basculación diagnóstica potenciada con nitroglicerina por sospecha de síncope vasovagal. Se registró el tiempo desde el síncope hasta la realización de la prueba y se analizó su relación con el resultado de la misma.

Resultados. La basculación fue positiva en 211 pacientes (67,0%). El tiempo síncope-basculación fue similar en los pacientes con resultado positivo y negativo (28 [1-500] frente a 32 [2-720] días; NS). Globalmente, no existió una relación significativa entre el resultado de la prueba y la existencia de síncope durante la semana, el mes o los 3 meses previos. Sin embargo, en los varones y en mayores de 50 años, la tasa de positividad fue mayor en los pacientes con un tiempo síncope-basculación inferior a un mes.

Conclusiones. El tiempo transcurrido desde el último síncope espontáneo no afecta significativamente el resultado del test de basculación en una población global evaluada para diagnóstico de síncope, pero la tasa de positividad puede disminuir en varones y en mayores de 50 años si la prueba se efectúa después de un mes del último síncope.

Palabras clave: Síncope. Diagnóstico. Prueba de basculación.

ABREVIATIONS

TTT: tilt table test.

VVS: vasovagal syncope.

T-TTT: time from last spontaneous syncope to tilt table testing.

INTRODUCTION

The table tilt test (TTT) is widely used to evaluate patients with unexplained syncope. A positive result on the test suggests a diagnosis of vasovagal syncope (VVS),¹⁻³ but the test's sensitivity is difficult to determine because there is currently no definitive diagnostic test for this type of syncope. The rate of positive TTT results in patients with recurring syncope of probable neurally mediated origin ranges between 40% and 85%, depending on various clinical factors and the methodology used.⁴⁻⁷ Negative results tend to be highly reproducible, but 15%-35% of the patients with an initially positive result fail to record a positive result on a second test performed days or weeks after the first.⁸⁻¹⁰ Given that the propensity to suffer spontaneous syncope varies over time, with a cyclical pattern being observed in many patients, it has been suggested that chronobiological factors could also lead to variability in TTT results.¹¹ If the likelihood of having VVS and of presenting a positive TTT result does vary over time, then the test's sensitivity could be improved if it were performed shortly after the syncopal episode. No specific studies that examine this possibility have been found in the literature, although some indirect and discordant data do exist. This aspect of the diagnosis and management of syncope is likewise not included in review documents,^{1,11} so clear recommendations as to when a diagnostic TTT should be performed in patients with syncope are currently not available. The objective of the present study was to determine whether time elapsed between the last syncopal episode and TTT influence the outcome of the test.

PATIENTS AND METHODS

Three hundred and fifteen patients referred for assessment of syncope to an outpatient arrhythmia clinic in the study center were recruited consecutively. All patients included in the study received a diagnostic TTT between September 2000 and October 2002. Patients with pre-syncope were excluded from the study. The protocol used to diagnosis syncope included questioning, physical exploration and electrocardiograph (ECG) in all patients. If the ECG is abnormal or there is evidence or suspicion of structural heart disease, the usual complementary tests (echocardiogram,

Holter monitoring and electrophysiologic study) are performed to ascertain the cause of the syncope, and TTT is carried out if the tests prove negative. When heart disease is not suspected and the ECG is normal, TTT is the first diagnostic test performed.

The TTT was performed using the Italian protocol, with a baseline phase of 20 min at 60°, and a further 25 min following administration of 400 µg of sublingual nitroglycerin spray.¹² ECG monitoring was performed continuously throughout the test, together with noninvasive manual blood pressure measurement every 5 min or so where symptoms were present. Occurrence of syncope or pre-syncope in association with extreme bradycardia or hypotension (systolic blood pressure below 70 mm Hg or undetectable) was considered a positive result, and responses were classified as cardioinhibitory, vasodilatory or mixed, using the VASIS (Vasovagal Syncope International Study) criteria.^{13,14} Clinical and demographic data, together with the time elapsed between the patient's last spontaneous syncope and performance of the TTT (T-TTT), were collected prospectively from all patients at the beginning of the test. The T-TTT was highly variable, as patients attending the arrhythmia clinic can be referred from hospital wards, from the emergency department via a rapid (1-5 days) appointments system, as well as from other hospital departments or for consultations, either preferentially (1-2 weeks) or nonpreferentially (weeks or months). A descriptive analysis of clinical and demographic variables was performed. Normally distributed variables were expressed as mean \pm standard deviation (SD), and variables showing a non-normal distribution using the Kolmogorov-Smirnov test were expressed as median (range). The χ^2 test was used to analyze the relationship between qualitative variables. In patients with positive and negative TTT results we compared T-TTT with the Mann-Whitney test, given that the T-TTT values did not show a Gaussian distribution.

RESULTS

Table 1 shows the clinical and demographic characteristics of the 315 patients included in the study. TTT was positive in 211 patients (67.0%), with the majority of positive results (n=186; 88.2%) occurring during the pharmacological phase. Of the patients with positive results, 29 (13.7%) showed a cardioinhibitory response, 66 (31.3%) a vasodilatory response, and 116 (55.0%) were mixed. Women had a higher rate of positive results than men (76.6 vs 59.6%; $P<.01$), and no significant association was found between TTT results and age, presence of heart disease, or number of spontaneous syncope. There were no significant differences in T-TTT between patients with positive and negative TTT results (28 [1-500] days vs 32 [2-720] days, respectively). Table 2 shows the number of patients

TABLE 1. Study population clinical characteristics and tilt table test results (n=315)

Age, years	55.1±20.2	
Sex, men/women	178/137	
Heart disease	50	(15.9%)
Ischemic	38	
Nonischemic	12	
Number of syncopes, median (range)	3	[1-100]
Tilt table test		
Positive TTT	211	(67.0%)*
Baseline phase	25	(11.8%)*
Pharmacological phase	186	(88.2%)*
Cardioinhibitory	29	(13.7%)*
Vasodilatory	66	(31.3%)*
Mixed	116	(55.0%)*
Treatment with beta blockers	44	(14.0%)
T-TTT in days, median (range)	30	[1-720]
Syncope in the previous week	73	(23.2%)
Syncope in the previous month	180	(57.1%)
Syncope in the previous 3 months	249	(79.0%)

Percentage of total positive TTT.

TTT indicates tilt table test; T-TTT, time from last spontaneous syncope to performance of tilt table test.

with positive and negative TTT results according to the time elapsed between syncope and performance of the TTT. The percentage of positive results was similar in all cases, and no statistically significant differences were found, though there was a tendency towards a higher rate of positive results in patients in whom the

TABLA 2. Relationship between TTT result and time elapsed since the last syncope

	Positive TTT	Negative TTT	N
Syncope in the previous week			
Yes	48 (65.8%)	25 (34.2%)	73
No	163 (67.4%)	79 (32.6%)	242
Syncope in the previous month*			
Yes	128 (71.1%)	52 (28.9%)	180
No	83 (61.5%)	52 (38.5%)	135
Syncope in the previous 3 months			
Yes	170 (68.3%)	79 (31.7%)	249
No	41 (62.1%)	25 (37.9%)	66

* $P=.09$ when comparing the percentage of positive results in patients with and without syncope in this time period.

N indicates total number of patients.

Percentages refer to the number of patients in the last column.

syncopal episode had occurred in the previous month ($P=.09$). The TTT phase in which syncope occurred was also unrelated to T-TTT. For example, the percentage of positive TTT results in the pharmacological phase was 89.8% in patients with T-TTT less than 1 month and 85.6% in patients with T-TTT greater than 1 month (NS). Subgroup analysis showed similar results for patients with and without heart disease, and with single or recurring syncope. In men, however, there was a greater frequency of positive results when the spontaneous syncope had occurred in the last month (72/108 [66.7%] vs 34/70 [48.6%] in patients with T-TTT>1 month; $P<.05$). No significant differen-

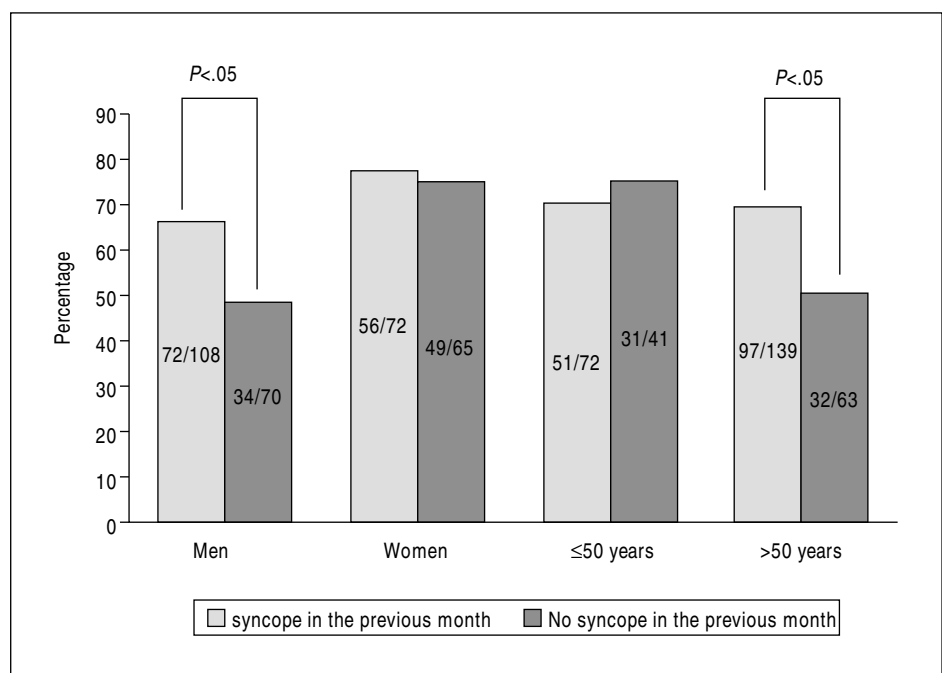


Fig. 1. Positive TTT results by age and sex in patients with and without spontaneous syncope in the month prior to the performance of the test.

ces were found in women (Figure 1). In patients over 50 years of age, a greater rate of positive results was observed when T-TTT was less than 1 month (97/139 [69.8%] vs 32/63 [50.8%]; $P<.05$), whereas no similar significant differences were seen in younger patients (Figure 1). When both criteria were combined, 63.3% of men over 50 (50/79 patients) had positive TTT results when the test was performed within the first month after spontaneous syncope, but the rate decreased to 35.1% (13/37 patients) when T-TTT was over 1 month ($P<.01$). Similar results were obtained when patients with syncope and structural heart disease were excluded from the analysis.

DISCUSSION

These results suggest that, in a general patient population evaluated for syncope, time elapsed from the last syncope to performance of TTT does not greatly affect the rate of positive responses on the test. However, in men aged over 50 the number of positive responses may decrease if there is a delay of more than 1 month between the last spontaneous syncope and performance of the test.

The majority of published studies in which the sensitivity of TTT sensitivity has been assessed do not take into account the time elapsed between spontaneous syncope and performance of TTT. Sheldon et al¹⁵ found no relationship between time with VVS and TTT results, but they did not describe the time elapsed between the last syncope and TTT. In a study of the sensitivity of TTT potentiated with isoproterenol in young people, T-TTT in the group with positive results was 103.0 ± 205.9 days, compared to 19.3 ± 11.1 in the group with negative results. The difference between groups was not statistically significant.¹⁶ However, the large difference in values and the small number of patients ($n=30$) make these results difficult to interpret. In a study to evaluate the sensitivity of isoproterenol-potentiated TTT in 88 patients with typical neurocardiogenic syncope, Pérez Paredes et al¹⁷ performed a multiple regression analysis to find which clinical variables predicted a positive result on the TTT. In a subgroup of patients with positive results in the baseline phase, they found a T-TTT of 4 ± 4 weeks, compared to 16 ± 14 weeks in patients with a negative results ($P<.005$). This was the only variable which significantly predicted a positive result on the test, and they consequently suggested performing the TTT as soon as possible after the syncopal episode, so as to maintain its sensitivity. The difference between their results and those in the present study are probably due to differences between the study populations: in the study by Pérez Paredes et al, subjects were younger and had a typical VVS profile. There were few of this type of patient in our series, as the diagnosis is reasonably obvious and referral to a specific unit for TTT is not re-

quired. There were also important differences in the TTT protocol used: in our study, the baseline phase was shorter (20 min, vs 45 min in the study by Pérez Paredes et al) and was followed by the administration of nitroglycerin, so a comparison of patients with a positive result in the baseline phase in the two studies is not possible. In a preliminary study with a smaller number of patients, our research group found no significant differences in the rate of positive TTT results by time elapsed since the last syncope.¹⁸ When patient numbers were increased, this conclusion appeared to be maintained for the overall group of patients but we found that the number of positive TTT results may decrease in men and those aged over 50 if the TTT is carried out months after the spontaneous syncope. It therefore appears reasonable to schedule the TTT for the first month after syncope in these subgroups. Doing so should help to ensure the test's sensitivity.

The effect of chronobiological factors on the appearance of spontaneous syncopal episodes and TTT results has not been widely studied. It has been observed that patients with a tendency towards recurring VVS often experience those episodes at specific times.¹¹ In a study of 35 patients with VVS and a positive TTT result, 24 h Holter monitoring for spectral heart rate analysis revealed significant changes in the parasympathetic tone in the subgroup of patients in which TTT was negative by the following week.¹⁹ This suggests that spontaneous fluctuations in the vagal tone over time could modify the propensity to present syncope during TTT. The longer term (months or years) implications of this phenomenon are currently unclear, but it could potentially explain why the rate of positive TTT results varies over time in patients with neurally mediated syncope. Our results suggest that this rate might decrease in men over 50 with syncope of unknown cause. Although there is no clear explanation for this effect, syncope mechanisms during TTT have been observed to differ according to patients' sex and age,²⁰ which means that sensitivity to chronobiological factors might also differ across subgroups of patients.

Study limitations

Although data were collected prospectively, the study population was selected using clinical criteria, and the time at which TTT was performed was not decided randomly, making it impossible to rule out the possible effect of undetected variables on results. Furthermore, the sensitivity of TTT as a function of time elapsed since the last syncope should be estimated in patients with a firm diagnosis of VVS, but this is complicated by the lack of a definitive diagnostic test for VVS. Patients with structural heart disease were also included in the study, and syncope in these patients could have a different cause, in spite of a negative evaluation and a positive result on the TTT.

Nevertheless, only a small percentage (16%) of patients had heart disease and their exclusion did not significantly affect results, so including them is not likely to substantially alter the study conclusions. Finally, the relatively small number of patients in which TTT was performed more than 6 months after spontaneous syncope makes it difficult to draw conclusions regarding the rate of positive TTT results in this subgroup.

CONCLUSIONS

This study has shown that, generally speaking, diagnostic TTT need not be performed immediately after VVS, as the time elapsed from the last spontaneous syncope to TTT scarcely modifies the rate of positive results. However, in male patients and those over 50 it appears to be advisable to schedule the TTT for the month following the syncopal episode, to avoid a reduction in the rate of positive results. Further prospective studies are required to confirm the results found here and to establish solid criteria to optimize the timing of TTT in patients with suspected vasovagal syncope.

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