

Head-up Tilt Test Potentiated with Nitroglycerin. What is the Optimal Duration of the Test after Administration of the Drug?

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Introduction and objectives. Numerous variations of the head-up tilt-table test potentiated with nitrates have been reported. After the administration of nitroglycerin, between 10 and 25 min of continued tilting have been recommended. The aim of this study was to assess the optimal duration of the pharmacological phase of the head-up tilt-table test potentiated with sublingual administration of nitroglycerin spray (NTG-TT).

Method. The records of 498 consecutive NTG-TT were reviewed. Our protocol consisted of a 20-min drug-free phase at a 60° angle. If syncope does not develop, 400 g of sublingual nitroglycerin spray is administered and the patient continues to be tilted for a further 25 min. The test results and time to a positive response were analyzed.

Results. The result of NTG-TT was positive in 288 procedures, most of them after nitroglycerin administration (255, 88.5%). The mean time to a positive response was 10.7 ± 6.7 and 5.0 ± 2.4 min during the control and pharmacological phases respectively. Most positive responses were concentrated in the 3 to 5 min after drug administration. The time to syncope after nitroglycerin administration was over 10 min in 9 patients and 15 min in only 2 patients.

Conclusions. The duration of the pharmacological phase of NTG-TT using the described protocol can be reduced to 15 min without loss of sensitivity. A further reduction to 10 min would decrease the rate of positive responses by a small amount and might be considered clinically acceptable.

Key words: *Head-up tilt table test. Nitroglycerin. Syncope.*

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Prueba de basculación potenciada con nitroglicerina: ¿cuánto debe durar la prueba tras la administración del fármaco?

Introducción y objetivos. Existen varios protocolos para realizar la prueba de basculación potenciada con nitratos, y se ha recomendado mantener la basculación entre 10 y 25 min tras la administración del fármaco. El objetivo del estudio es determinar la duración óptima de la fase farmacológica de la prueba de basculación potenciada con nitroglicerina sublingual en forma de aerosol (PB-NTG).

Métodos. Se han revisado los registros de 498 estudios consecutivos de PB-NTG para el diagnóstico de síncope o presíncope. El protocolo consta de una fase de basculación basal a 60° seguida de la administración sublingual de 400 g de nitroglicerina en aerosol manteniendo la basculación otros 25 min.

Resultados. La PB-NTG fue positiva en 288 procedimientos, de ellos, 255 (88,5%) durante la fase farmacológica. El tiempo hasta la aparición del síncope fue de $10,7 \pm 6,7$ y $5,0 \pm 2,4$ min para los positivos en fase basal y farmacológica, respectivamente. El pico máximo de incidencia se produjo entre los minutos 3 y 5 tras la administración de la nitroglicerina. En 9 pacientes el síncope se produjo después del minuto 10 de la fase farmacológica, y sólo en dos después del minuto 15.

Conclusiones. La duración de la fase farmacológica en la PB-NTG con el protocolo descrito se puede acortar a 15 min sin pérdida de sensibilidad. La reducción a 10 min supone una disminución mínima de la tasa de positividad, por lo que se podría considerar aceptable en la práctica clínica.

Palabras clave: *Prueba de basculación. Nitroglicerina. Síncope.*

INTRODUCTION

Since its introduction in clinical practice 15 years, the tilt-table test (TT) has been widely used, but no universally accepted protocol yet exists for its execution.¹⁻⁴ Several pharmacological agents have been used to enhance the sensitivity of the test and/or shorten its

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ABBREVIATIONS

TT: tilt-table test.
 TT-NTG: tilt-table test potentiated with nitroglycerin.
 ECG: electrocardiogram.

duration while maintaining an acceptable specificity.⁵⁻⁸ The administration of isoproterenol increases the number of positive responses^{6,9} but requires intravenous perfusion, has frequent side effects, occasional contraindications, and the use of high doses reduces the specificity of the test.¹⁰ This has motivated a search for alternative drugs to potentiate the appearance of syncope during tilting. The nitrates are often used to obtain a diagnostic effectiveness similar to that obtained with isoproterenol, but with more tolerance and comfort.^{11,12} Several protocols exist based on the agent administered (nitroglycerin in i.v. perfusion, sublingual nitroglycerin in tablets or aerosol, isosorbide dinitrate), the dose, angle of inclination (60° or 70°), and duration of tilting before and after the administration of the drug.^{5,12-20} This last point is of special interest since one of the main limitations to the clinical use of the TT is its duration. The optimal duration of the pharmacological phase has not been clearly established. In various published protocols it ranges from 15 to 25 min^{5,12,14,17} but it has recently been recommended that it be reduced to 10 min.¹⁵ The goal of this study is to determine the optimal duration of the pharmacological phase of the tilt-table test potentiated with sublingual nitroglycerin in aerosol (TT-NTG).

PATIENTS AND METHOD

All the entries of TT made in the arrhythmia unit of the cardiology department of a tertiary hospital from October 1998, when the TT-NTG protocol was first used in our center, to January 2002 were reviewed. Tests made for a diagnostic clinical indication of syncope or presyncope of unknown origin were included in the study and those performed for other reasons during follow-up of the patient or to control pharmacological treatment were excluded. The study protocol of syncope in our center consists basically of an interview, physical examination, and ECG. If these tests are not diagnostic, echocardiogram and Holter monitoring are performed. An electrophysiological study is indicated when structural heart disease or suspicion of arrhythmic syncope exists, otherwise TT is performed. The test was made in the morning, between the 10:00 a.m. and 1:00 p.m., with the patient fasting and in a quiet, darkened room. It was carried out by an experienced nurse with a cardiologist on call. We used a

manual tilt table with a foot support and straps to subject the patient to avoid trauma. After vein cannulation and placement of the electrodes for monitoring, the patient was kept in supine position and relaxed for 10 min. The ECG was monitored continuously during the procedure, and also recorded using a three-channel Holter system for posterior analysis. Blood pressure was measured noninvasively with an automatic sphygmomanometer every 5 min, or more frequently if symptoms or bradycardia appeared. The TT protocol was similar to that described by Del Rosso et al¹⁷ and consisted of a 20-min baseline phase with the patient was tilted 60°. If syncope did not occur, it was followed by a pharmacological phase lasting 25 min after the administration of sublingual nitroglycerin 400 µg in aerosol (Solinitrina spray). Tilting was maintained until a positive result was obtained, intolerance due to other causes was detected, or the protocol concluded (a total of 45 min). At the beginning of each procedure, the demographic and clinical data of the patient were recorded, as well as the test indication. During the tilting phase, heart rate and blood pressure were recorded every 5 min, the patient's symptoms, the time, and the reason why the test was interrupted and any related incidentals. The result was considered positive in the case of syncope or presyncope associated with marked reduction of the heart rate and/or blood pressure, classifying the responses as type I (mixed), II (cardioinhibitor), and III (vasodepressant).²¹ The progressive decrease, during at least 5 min, of blood pressure to values below 70 mm Hg systolic blood pressure associated with symptoms (dizziness, nausea) and little or no accompanying bradycardia was defined as an exaggerated response to nitroglycerin^{5,17} and not considered a criterion of positivity. A descriptive statistical analysis was made of the data. In addition, the relation between the clinical and demographic variables and the phase of the TT in which a positive response was elicited was evaluated using the Chi-square test.

RESULTS

During the study period, 498 studies of TT-NTG were made in our laboratory for the diagnosis of syncope or presyncope. The mean age of the population was 57.0±19.9 years and 61% were men. A total of 477 patients (95.8%) were studied for syncope (recurrent in 71% of cases) and the remaining 21 for presyncope. Most did not have heart disease (433 patients, 86.9%). The result of TT was classified as positive in 288 procedures (57.8%) and was type I in 146 (51%), type II in 43 (15%), and type III in 99 patients (34%). It was negative in 210 (42.2%), of which 23 (4.6% of the total) presented an exaggerated response to nitroglycerin. Positive responses occurred during the pharmacological phase in 255 patients

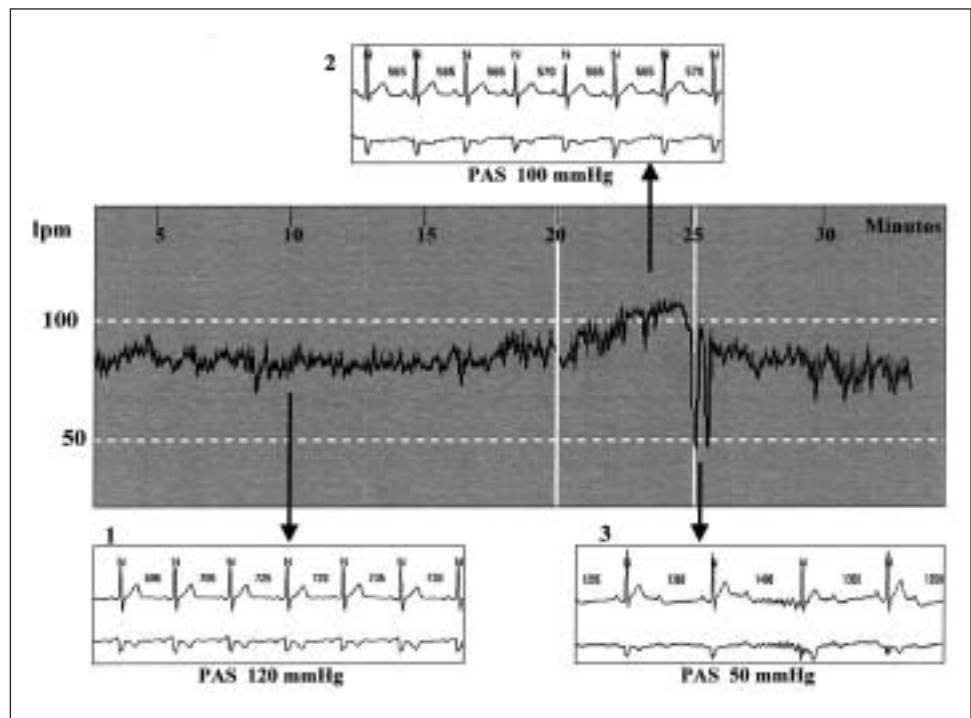


Fig. 1. Recording of the heart rate during a positive tilt-table test. Electrocardiograms and blood pressure at three moments in the test: 1. After 15 minutes of baseline tilting without drugs. 2. Two minutes after administration of 400 μ g sublingual nitroglycerin. 3. At the time of syncope. Note the appearance of 2:1 AV block.

(88.5% of all positive tests). The time to positivity was 10.7 ± 6.7 min for the tests that were positive in the baseline phase, and 5.0 ± 2.4 min for those positive in the pharmacological phase. A typical example of positive TT-NTG in the pharmacological phase is shown in Figure 1. A progressive rise can be observed in the heart rate after administering the drug, and the appearance of the vagal reflex with a sudden decrease in heart rate and syncope within a few minutes. The distribution in time of the positive responses in the pharmacological phase is shown in Figure 2. The peak incidence occurred between minutes 3 and 5 after nitroglycerin administration, ranging from minute 2 to 17. The test was positive after minute 10 of the pharmacological phase in 9 patients (1.8%) and it was positive after minute 15 in only 2 patients. The women had a greater percentage of positive tests in the baseline phase (15.2% versus 8.0% in men; $P < .05$). In contrast, there was no significant relation between the positive phase of TT-NTG and age, history of a single or recurrent syncope, or the presence of structural heart disease. There were no complications or important side effects related with the administration of nitroglycerin. Occasionally, mild headache or nausea appeared, which in no case required the procedure to be discontinued.

DISCUSSION

Our results indicate that most of the positive responses during the pharmacological phase occurred in the first 10 min of the phase with the TT-NTG protocol

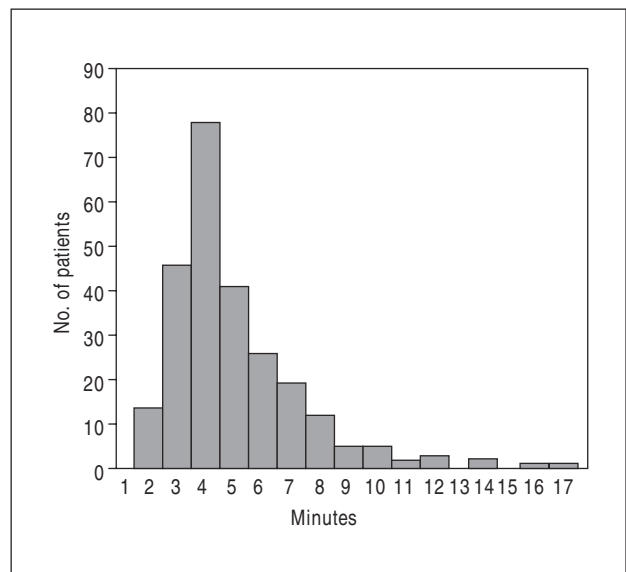


Fig. 2. Temporary distribution of positive responses after sublingual nitroglycerin administration.

described. The patient only exceptionally presented syncope after more than 15 minutes, which is why it is not necessary to prolong the test more.

Diverse TT protocols potentiated with nitrates have been published. In the initial study by Raviele et al,⁵ sublingual nitroglycerin in 300- μ g tablets was used, maintaining the tilt for 20 min after its administration. Syncope occurred in minute 7 ± 8 of the pharmacological phase, with a range between 3 and 17 min, which

was similar to our findings. A study with isosorbide dinitrate demonstrated a greater delay in reaching positivity in the pharmacological phase (9.3 ± 4.4 min), with a range of 5 to 15 min, although the limitation of the phase to 15 min did not allow the incidence of more delayed responses to be evaluated.¹⁴ It has been suggested that aerosol formulations of nitroglycerin have a better bioavailability and more homogeneous absorption because they do not depend on the patient's capacity for salivation and mastication, which can be impaired, especially in older people.²² It is likely that these properties and the larger dose released by the aerosol (400 μ g) shorten the time to positivity of the test, which was 5 ± 4 min in three studies that used this formulation. This is why the authors recommended that the duration of the pharmacological phase be reduced to 15 min.²³ Nevertheless, although most of the positive results occur in the first minutes after nitroglycerin, there is no precise information on the percentage of patients with more delayed responses. The maximum time to syncope during the pharmacological phase was 9 and 25 min in two published series of TT potentiated with nitroglycerin aerosol.^{15,17} In our study, the latest syncope occurred in minute 17 after drug administration and only 9 occurred after minute 10. These figures suggest that the test remains sensitive when the duration of the pharmacological phase is shortened to 15 min, as has been recommended by the European Society of Cardiology in a recent document.²⁴ Reduction of the time to 10 min involves a loss of approximately 2% in the rate of positivity. Although the clinical repercussion of this loss of sensitivity is probably small, it is doubtful that saving 5 min justifies modifying a widely used protocol.

Study limitations

Blood pressure was measured in our laboratory with a sphygmomanometer and it is difficult to exactly assess the behavior of blood pressure in the seconds preceding syncope with this method. For this reason, we did not use a precise quantitative criterion as the criterion of positivity, which could introduce subjectivity into estimates of the duration of the test. However, in cases in which the test was considered positive in the absence of syncope, arterial noises were inaudible and the patient's symptoms were clear when tilting was stopped, which is why we do not think that this fact greatly affected the results of the study. It must also be considered that our protocol included cannulation of a vein to administer atropine in the case of symptoms persisting at the end of the test. It has been suggested that this procedure can modify the results of the test,²⁵ which is why one should be prudent when extrapolating conclusions to protocols in which the test is performed without a venous access.

CONCLUSIONS

The appearance of syncope during TT-NTG with the protocol described (60° tilt, baseline phase lasting 20 min, sublingual nitroglycerin dose of 400 μ g in aerosol formulation) is exceptional beyond minute 15 after drug administration. Therefore, a duration of the pharmacological phase of 15 min can be recommended without a loss of sensitivity. Reducing the pharmacological phase to 10 min produces a small decrease in the rate of positivity and could be acceptable in clinical practice, although it seems reasonable to maintain the 15-min value as a standard, given the interest in using a uniform protocol in all centers performing this type of tests.

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