

## Early Heart Rate Increase Does Not Predict the Result of the Head-Up Tilt Test Potentiated With Nitroglycerin

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**Introduction and objectives.** The magnitude of the change in heart rate during the first few minutes of the head-up tilt test has been used to predict the test's result. The aim of this study was to investigate whether the heart rate increase during the head-up tilt test potentiated with nitroglycerin is related to the development of syncope.

**Patients and method.** The study included 158 consecutive patients with syncope, with stable sinus rhythm, and without structural cardiac disease who were undergoing a head-up tilt test with nitroglycerin. The heart rate increment induced by the tilt maneuver and by nitroglycerin administration was calculated, and its relationship to clinical variables and to the test's results was analyzed.

**Results.** The head-up tilt test gave positive results in 117 patients (74%). The heart rate was 68.7 (11.3) bpm in the decubitus position and 85.1 (15.4) bpm during the first 6 min of tilting. There was strong inverse correlation between the heart rate increase induced by tilting and age ( $r = -0.63$ ;  $P < .001$ ), but the increase (16.8 [9.3] bpm in patients with syncope vs 14.9 [11.3] bpm in those without;  $P = .3$ ) did not predict the result of the test. The heart rate increase induced by nitroglycerin was also similar for patients with and without syncope during the pharmacologic phase of the test (27.3 [12.6] bpm and 26.7 (13.4) bpm, respectively;  $P = .8$ ).

**Conclusions.** The magnitude of the heart rate increase during the first few minutes of tilt-testing and after nitroglycerin administration is inversely related to age but does not predict the result of the head-up tilt test with nitroglycerin.

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

### El incremento temprano de la frecuencia cardíaca no predice el resultado de la prueba de basculación potenciada con nitroglicerina

**Introducción y objetivos.** El incremento acentuado de la frecuencia cardíaca en los primeros minutos de la prueba de basculación ha sido utilizado como predictor del resultado final de ésta, en protocolos sin potenciación farmacológica o con isoproterenol. El objetivo del estudio es evaluar si este incremento se relaciona con la aparición de síncope durante la prueba de basculación potenciada con nitroglicerina.

**Pacientes y método.** Análisis retrospectivo de 158 pacientes consecutivos sometidos a prueba de basculación potenciada con nitroglicerina por síncope, sin cardiopatía y en ritmo sinusal. Se calculó el incremento de la frecuencia cardíaca secundario a la basculación y el debido a la nitroglicerina, relacionándolos con las variables clínicas y el resultado de la prueba.

**Resultados.** La prueba de basculación fue positiva en 117 pacientes (74%). La frecuencia cardíaca pasó de  $68,7 \pm 11,3$  lat/min en decúbito a  $85,1 \pm 15,4$  lat/min en los primeros 6 min posbasculación. El incremento de frecuencia presentó una fuerte correlación negativa con la edad ( $r = -0,63$ ;  $p < 0,001$ ), pero no se relacionó significativamente con el resultado ( $16,8 \pm 9,3$  lat/min en el grupo con prueba positiva frente a  $14,9 \pm 11,3$  en el negativo;  $p = 0,3$ ). El aumento de la frecuencia cardíaca inducido por la nitroglicerina ( $27,3 \pm 12,6$  y  $26,7 \pm 13,4$  lat/min, respectivamente;  $p = 0,8$ ) tampoco predijo el resultado del test durante la fase farmacológica.

**Conclusiones.** Los incrementos de frecuencia cardíaca en los primeros minutos después de la basculación y la administración del fármaco se relacionan fundamentalmente con la edad y no tienen utilidad para predecir el resultado de la prueba de basculación potenciada con nitroglicerina.

**Palabras clave:** Síncope. Diagnóstico. Prueba de basculación. Frecuencia cardíaca. Nitroglicerina.

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### INTRODUCTION

The head-up tilt test (HUTT) is widely used for the diagnosis of vasovagal syncope. This test is simple and non-invasive, but normal protocols take a long time to complete (35-60 min).<sup>1</sup> With the aim of reduc-

**ABBREVIATIONS**

HR: heart rate.  
 NTG: nitroglycerin.  
 HRbaseline: heart rate before tilting.  
 HRmax: maximum heart rate during tilting.  
 inct-Tilt: increase in HR with tilting (difference between HRmax and HRbaseline).  
 inc-NTG: increase in HR due to NTG (difference between HR post-NTG and HR pre-NTG).  
 HUTT: head-up tilt test.

ing this time, it has been suggested that the values obtained for certain variables during the first few minutes after tilting can be used to predict the final result. Some authors have analyzed whether the rapid and sustained increase in heart rate (HR) observed at the beginning of the test can predict the final result when following non-pharmacological and isoproterenol-potentiated HUTT protocols.<sup>2-5</sup> However, the value of this variable is unknown when sublingual nitroglycerin (NTG) (a commonly used drug) is the potentiating agent (HUTT-NTG). The aim of the present study was to determine whether the increase in HR during the first 6 minutes after tilting is related to the appearance of syncope during HUTT-NTG. With this protocol, the majority of positive responses are obtained in the first few minutes following the sublingual administration of the drug.<sup>6</sup> The secondary aim was therefore to determine whether the increase in HR produced by NTG predicts the result of the pharmacological phase of the test.

**PATIENTS AND METHODS****Patients**

This retrospective analysis involved 158 consecutive patients who were examined at the syncope clinic of a tertiary hospital. All underwent HUTT-NTG for syncope of unknown cause. All patients were subjected to detailed anamnesis, a physical examination, a 12-lead electrocardiogram (ECG) and basic blood tests. All relevant data were prospectively introduced into a database. Patients with (or suspected of having) structural heart disease, an abnormal ECG, clinical or electrocardiographic evidence of arrhythmic syncope, or any non-sinus rhythm as shown by ECG were excluded. Patients examined by HUTT for presyncope, or who had a clear clinical history of a first episode of vasovagal syncope, were also excluded (the latter patients are not subjected to HUTT at our center). Finally, patients receiving treatment with beta-blockers, beta-stimulants or other agents that might influence the HR were also excluded.

**Head-up Tilt Test**

The protocol followed has been previously described.<sup>6,7</sup> Briefly, following venous cannularization the patient was allowed to rest in the decubitus position for at least 10 min. The HUTT test was then begun with an initial tilt of 60° for 20 min. If syncope did not occur, the patient was administered 0.4 µg of sublingual NTG in the form of an aerosol, and the tilt position maintained for another 15 min. The test was considered positive when either syncope or presyncope occurred with asystole, extreme bradycardia, and/or hypotension with a systolic blood pressure (SBP) of <70 mm Hg. Patients showing a non-specific response to NTG (progressive reduction in blood pressure over several minutes with non-specific symptoms) were excluded from the analysis. Patients were monitored using a Task-Force Monitor 3040 (CNSystems, Graz, Austria). This records the ECG, the HR, and the SBP and the diastolic blood pressure (DBP) beat by beat. Data were stored as ASCII files after manual validation.

**Data Analysis**

The data were analyzed using Matlab v. 6.5 (The MathWorks Inc, Natick, Estados Unidos) software. The program detected the moment when tilting began and calculated the mean of the RR intervals in the 5 preceding minutes; from these data the mean baseline HR (HRbaseline) was estimated. The first 6 minutes following tilting were then analyzed, the program calculating the mean RR interval in the 30 s following each beat during this period. The highest mean heart rate calculated was taken to be the post-tilting maximum (HRmax). The difference between the HRmax and the HRbaseline was therefore the increase in HR caused by tilting (inct-Tilt). The increase in HR following the administration of NTG was similarly calculated, comparing the mean HR in the 3 minutes prior to administration of the drug (HR pre-NTG) to the maximum recorded in the 3 minutes following administration (HR post-NTG). The difference between these was defined as the increase in HR caused by the NTG (inc-NTG).

The relationship between the clinical variables and changes in HR was analyzed using the Student *t* and Pearson correlation coefficient tests. Both groups of variables were then related to the results of the HUTT via the  $\chi^2$  test (for qualitative variables) and the Student *t* test (quantitative variables). All calculations were made using SPSS v. 9.0 software.

**RESULTS**

Table 1 shows the demographic and clinical characteristics of the patients and the results of the HUTT-

NTG. The mean age of the patients was 45.9 years; 72 patients (45.6%) were older than 50 years. The majority (74.1%) had presented more than once with syncope (median 3 times). Ninety one patients (57.6%) showed characteristics suggestive of a vasovagal syncope mechanism (which led to HUTT being performed). Positive tests were recorded for 117 patients, the great majority (82.7%) following the administration of sublingual NTG. The proportion of positive tests was higher among women (83.1%) than men (64%;  $P < .01$ ). The patients with positive HUTT-NTG tests were younger than those with negative tests ( $43.9 \pm 21.0$  years compared to  $51.6 \pm 20.8$  years;  $P < .05$ ). The remaining clinical variables showed no significant relationship with the HUTT-NTG results. The mean initial HR was  $68.7 \pm 11.3$  beats/min; this value increased after the first few minutes of tilting to  $85.1 \pm 15.4$  beats/min. A strong negative correlation was seen between the increase in HR induced by tilting and age ( $r = -0.63$ ;  $P < .001$ ). No significant differences were seen in baseline and post-tilting HR between patients with positive and negative HUTT results, nor did the inc-Tilt vary significantly between them (Table 2). An inc-Tilt of  $\leq 18$  beats/min has been described as a predictor of a negative result in other studies.<sup>2</sup> One hundred and one (63.9%) of the present patients showed such a value, but no significant differences were seen between these patients and those with an increase of  $>18$  beats/min with respect to the HUTT-NTG result. Of the 15 patients with a positive result during the baseline phase, 6 (40%) showed an inc-Tilt  $\leq 18$ , whereas 9 (60%) showed a value of  $>18$ . Thus, this variable is of no use either in predicting the result of the test during the baseline phase. The 143 patients with a negative result during the baseline phase received sublingual NTG. Of these, 102 (71.3%) experienced syncope during the pharmacological phase; 41 (28.7%) continued with a negative result. The mean HR before and after the administration of NTG was similar in both of the latter groups. The inc-NTG showed no significant differences with respect to the test result (Table 3). A significant, inverse correlation was found between the inc-NTG and age ( $r = -0.35$ ;  $P < .001$ ), although less strong than that seen between the latter and inc-Tilt. The increases in HR due to tilting and NTG administration were clearly correlated ( $r = 0.45$ ;  $P < .001$ ). Figure shows data for a patient with a markedly increased HR both in the first minutes of tilting and after NTG administration—but who had a negative test result, as well as data for a patient with syncope during the pharmacological phase but with a minimum variation in HR during the test.

## DISCUSSION

The results suggest that the increase in HR in the first few minutes following tilting is primarily related

**TABLE 1. Demographic Characteristics of the Patient Population (n=158) and Results of the Head-up Tilt Test\***

Age, mean $\pm$ SD (years)	45.9 $\pm$ 21.1
Sex, male/female	75/83
High blood pressure, n (%)	42 (26.6)
Diabetes, n (%)	9 (5.7)
Number of syncopes	3 (range, 1-60)
Recurrent syncope, n (%)	117 (74.1)
Vagal signs, n (%)	91 (57.6)
Positive head-up tilt test, n (%)	117 (74)
Baseline phase, n (%)	15 (12.8)
Pharmacological phase, n (%)	102 (87.2)

\*SD indicates standard deviation

**TABLE 2. Heart Rate Before and After Tilting\***

	Positive HUTT (n=117)	Negative HUTT (n=41)	P
HRbaseline, beats/min	68.5 $\pm$ 11.7	69.4 $\pm$ 10.3	.7
Hrmax after tilting, beats/min	85.3 $\pm$ 14.4	84.3 $\pm$ 17.9	.8
Inc-Tilt, beats/min	16.8 $\pm$ 9.3	14.9 $\pm$ 11.3	.3

\*HUTT indicates head-up tilt test; HRbaseline, heart rate before tilting; HRmax, maximum heart rate after tilting; inc-Tilt, increase in HR caused by tilting.

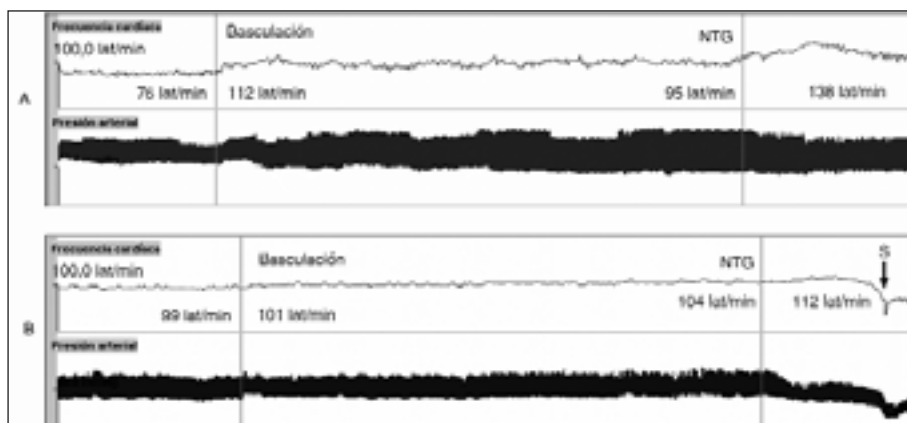
**TABLE 3. Heart Rate Before and After the Administration of Nitroglycerin\***

	Positive HUTT (n=102)	Negative HUTT (n=41)	P
HR pre-NTG, beats/min	80.6 $\pm$ 12.8	80.9 $\pm$ 16.6	.9
HR post-NTG, beats/min	107.8 $\pm$ 20.0	107.6 $\pm$ 23.2	.9
Inc-NTG, beats/min	27.3 $\pm$ 12.6	26.7 $\pm$ 13.4	.8

\*HUTT indicates head-up tilt test; HR pre-NTG, heart rate before administration of nitroglycerin; HR post-NTG, heart rate after administration of nitroglycerin; inc-NTG, increase in heart rate caused by nitroglycerin administration.

to age, and that it is of no use for predicting the result of HUTT-NTG in patients with syncope but with normal hearts. The increase in HR following the administration of NTG also appears to be related to age; the results obtained do not suggest it can predict the result of the test during the pharmacological stage.

It is thought that the activity of the autonomic nervous system is a determining factor in the genesis of vasovagal syncope.<sup>8,9</sup> Although the precise mechanisms leading to the vasodilatory and/or cardioinhibitory response typical of this syndrome are not completely understood, several anomalies in the behavior of the sympathetic and parasympathetic nervous systems have been described in patients with positive HUTT results.<sup>10-15</sup> The observation made in some initial studies<sup>10,11</sup> that patients with a positive



**Figure.** (A) Data from a patient with a marked increase in heart rate in the early minutes of tilting and after the administration of nitroglycerin, but who showed a negative final result. (B) Data for a patient who experienced syncope during the pharmacological phase of the test but only a minimum variation in heart rate. NTG indicates administration of nitroglycerin; S, syncope.

HUTT result show a greater increase in the HR during the first few minutes following tilting led Mallat et al<sup>2</sup> to analyze this possibility in more detail. These authors studied a series of carefully selected patients and found an increment in HR of >18 beats/min during the first 6 minutes after tilting always preceded a negative HUTT result (according to the Westminster protocol; no pharmacological provocation). They obtained similar results in a second series of patients who underwent HUTT potentiated with isoproterenol. In conclusion they suggested that, in patients with an increase in HR of <18 beats/min, the HUTT could be interrupted since it would be negative. This would mean a considerable saving in time. In later studies with less selected patients, poorer predictive results were obtained, but which in general confirmed the idea that patients who experience syncope during HUTT show an early increase in HR greater than that seen in patients with negative results.<sup>3-5</sup> In addition, some authors report an inverse relationship between the increase in HR with tilting and age,<sup>4</sup> a relationship noticed in the present work. This should be taken into account since adjusting for age could nullify any significance in the increase in HR with respect to the final test result.<sup>16,17</sup> In all these studies, HUTT was either performed without pharmacological potentiation or with isoproterenol and according to different protocols. In our hospitals, the "Italian protocol" is often used. This is based on the administration of sublingual NTG after a short period of tilting without drugs.<sup>18,19</sup> Potentiation with NTG seems to increase the sensitivity of HUTT in a manner similar to the administration of isoproterenol, but the patient populations with positive results under one or another methodology do not appear to coincide.<sup>20</sup> It has been observed that HUTT potentiated with NTG provides a greater number of positive results than potentiation with isoproterenol, but only in patients who are >60 years of age.<sup>21</sup> This suggests a different mechanism of action for the 2 drugs, and might explain the recording of different results depending on the technique

used. The literature contains very few data on the relationship between the increase in HR following tilting and the result of HUTT-NTG. In a recent study it was reported that notable increases in HR at the beginning of tilting were more common in younger people, and that these subjects had a high percentage of positive results in HUTT-NTG. Chronotropic incompetence and negative results were more common among patients of advanced age.<sup>22</sup> In this study, however, the possible predictive value of changes in initial HR with respect to the test result was not analyzed. In the present work, a strong, inverse relationship was also seen between age and the increase in initial HR, as well as a higher percentage of positive test results among younger patients. However, the inc-Tilt was not a significant predictor of the test result. This suggests that age, and not the increase in HR, is the variable most strongly related to the onset of syncope during HUTT-NTG. The fact that the majority of patients with a positive result for this test experienced syncope during the first few minutes after the administration of NTG<sup>6</sup> led us to examine whether the increment in HR caused by the drug might be related to the test result. In a healthy population, Gisolf et al.<sup>23</sup> recently showed that the behavior of the HR and the blood pressure during the first 5 minutes after NTG administration did not differ significantly between those who experienced syncope during tilting and those who remained asymptomatic. In the present work, the inc-NTG showed a marked, negative correlation with age, but was not significantly related to the appearance of syncope during the pharmacological phase of the test.

## CONCLUSIONS

Unlike that described by other authors with respect to HUTT without pharmacological or isoproterenol potentiation, the magnitude of the increase in HR in the first few minutes of HUTT-NTG does not appear to predict the result of the test. A small increase in



HR at the beginning of HUTT-NTG does not guarantee that the test will be negative, and should not be used as an indication for interrupting the procedure. Further studies are required to independently establish the effect of age and the provocation technique on the predictive value of the early increase in HR during tilting.

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