

## Clinical Characteristics and Head-Up Tilt Test Results With Three Protocols in 1661 Patients With Syncope

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Because of the absence of a uniform protocol for the head-up tilt table test (HUT), we compared 1,661 consecutive patients with syncope referred for HUT. The influence of age and gender on the results (positive response rate and patterns) obtained with three different protocols, Westminster, isoprenaline and nitroglycerin (groups A, B and C) was analyzed. The proportion of women was larger in the youngest age group. A positive response to HUT was observed in 592 patients. The positive response rate to the HUT was higher in groups B and C than in group A, and the rate diminished with age in groups A and C, because of the decrease in mixed-positive responses, but not in group B. The rate of positive responses was similar in groups A and C, but different in group B; no influence of gender on these results was observed. The results with the Westminster and nitroglycerin protocols were similar, but the rate of positive responses was higher in the latter.

**Key words:** *Gender. Syncope. Tests.*

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### INTRODUCTION

Syncope is a common medical problem whose diagnosis is established from clinical data. The head-up tilt-table test (HUT) is often used as a diagnostic tool and is accepted and recommended by all cardiologists.<sup>1</sup> Almost all groups use one of three HUT protocols: Westminster drug-free protocol, HUT with isoproterenol or HUT with nitroglycerin. Although different responses occur during HUT<sup>2</sup> depending on age,<sup>3-5</sup> the influence of sex and age in the different

### Características clínicas y resultados del test de tabla basculante utilizando tres protocolos en 1.661 pacientes con síncope

Ante la ausencia de un protocolo estandarizado y único, presentamos un análisis de 1.661 pacientes consecutivos remitidos para estudio con test de tabla basculante (TTB) desde septiembre de 1990 y analizamos la influencia de la edad y el sexo en sus resultados utilizando 3 protocolos: Westminster, isoproterenol y nitroglicerina (grupos A, B y C). La proporción de mujeres es mayor en el grupo de menor edad. El TTB fue positivo en 592 pacientes. El porcentaje de respuestas positivas (RP) fue más bajo en el grupo A que en los grupos B y C. En los grupos A y C, éste se redujo con la edad a expensas de las RP mixtas, pero no en el grupo B. Los porcentajes de cada tipo de RP son similares en los grupos A y C, y diferentes en el grupo B, sin que el sexo influya en este resultado. Existe una gran similitud entre los protocolos A y C, pero este último obtiene un mayor porcentaje de RP.

**Palabras clave:** *Sexo. Síncope. Tests.*

protocols has received little attention.<sup>6-8</sup> The aims of this study were to *a)* compare results of HUT using the three most common protocols; *b)* determine whether there were differences in the three protocols according to sex, and *c)* investigate the influence of age on positive responses in each protocol.

### PATIENTS AND METHODS

#### Study design

In a manner compliant with the usual standard ethical criteria of our institution, we included all patients with syncope who were referred to our cardiology service for HUT from September 1990. Patients underwent prior medical examination and blood test results were all normal. Neither

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## ABREVIATURAS

TTB: test de tabla basculante.  
RP: respuesta positiva.

electrocardiogram (ECG) nor chest x-ray suggested any cause of the syncope or were sufficient to provide a definitive diagnosis. The study was done in accordance with the usual procedures in our service.<sup>8</sup> Patients were divided into four arbitrary age groups, representing four different stages in life, for later analysis.

## Tilt table test

After giving written informed consent, patients underwent HUT. Each patient was included in one of the three diagnostic protocols depending on the date of the examination. From September 1990 to April 2000 patients underwent HUT according to the Westminster protocol<sup>9</sup> (Group A), except those patients examined during 1994, for whom the isoproterenol protocol<sup>10</sup> was used (Group B). From April 2000 all patients were studied with the nitroglycerin protocol<sup>11</sup> (Group C).

## Statistical analysis

Continuous variables that did not show a normal

TABLE 1. Demographic characteristics of the study group

	Group A (n = 1.091)	Group B (n = 158)	Group C (n=412)	P
Age, years	45 (24-63)	42 (22-56)	48 (26-62)	NS
Sex, women	492 (45%)	72 (45.3%)	206 (50%)	NS
Number of previous syncope episodes	3 (1-5)	3 (1-5)	3 (2-6)	NS
Duration of symptoms, months	13.5 (3-60)	13 (3-60)	14 (5-84)	NS

Group A: patients tested with the Westminster protocol. Group B: patients tested with the isoproterenol protocol. Group C: patients tested with the nitroglycerin protocol. Data are expressed as the median (interquartile range).

TABLE 2. Clinical characteristics of the age groups

	Young ( $\leq 20$ years) (n=273)	Young adults (21-40 years) (n=407)	Adults (41-60 years) (n=503)	Old (>60 years) (n=478)
Age, years	17 (14-18)	29 (24-36.5)	51 (43.6-56)	71 (63-74)
Sex, women*	58.2%	56.6%	45.6%	32.7%
Number of previous syncope episodes*	3 (1-5)	3 (1,5-6,5)	3 (1-5)	2 (1-4)
Duration of symptoms, months*	16 (6-36)	24 (6-84)	16 (3-84)	10 (1-48)

\* $P < .0001$ . Data are expressed as the median (interquartile range).

distribution were expressed as the median (interquartile range) and analyzed with the Mann-Whitney and Kruskal-Wallis tests. Comparisons between Groups A, B and C or between age groups were made with  $\chi^2$  test for qualitative variables and the Kruskal-Wallis test for quantitative variables. Data were analyzed with version 11.0 of the SPSS (SPSS, Chicago, Illinois) and  $P$  values  $< .05$  were considered significant.

## RESULTS

Tilt table testing was performed on a total of 1661 consecutive patients (770 women; 46.3%) with a median age of 45 years (range, 23-62 years). Testing was done with the Westminster protocol in 1091 patients, with isoproterenol in 158 and with nitroglycerin in 412. The 3 groups were similar (Table 1) and there were no complications. Grouping by age (Table 2) showed that there were more women in the younger age group ( $P = .0001$ ), that younger patients had had more episodes of syncope than older patients ( $P = .0001$ ), and that their duration of symptoms was greater, especially the young adults ( $P = .0001$ ).

A total of 592 (35.6%) patients had a positive response during HUT. The percentage of positive responses in Group A was lower than in Groups B and C (25.4%, 53.7% and 55.5%, respectively;  $P = .0001$ ). A mixed-positive response was the most common in all three groups, followed by hypotension, cardio-inhibition and «other responses» (Table 3). The proportion of positive responses was similar for Groups A and C but different for Group B (Figure 1).

Analysis according to sex showed the same percentage of positive responses for both men and women ( $P = .09$ ). The overall reduction in the percentage of positive responses in Group A compared to Groups B and C was also present in women (25.7%, 49.3% and 60.8%;  $P = .0001$ ) and men (23.2%, 58% and 50.5%;  $P = .0001$ ). There were no differences in the proportion of positive responses according to sex when the patients were grouped by age ( $P = .2$ ).

Patients with a positive response to HUT were younger than those with a negative response (38 years [range, 20-59] versus 47 years [range, 26-64];  $P = .0001$ ). The percentage of positive responses fell as

**TABLE 3. Type of response during the head-up tilt-table test (HUT) in the study group according to age**

	Total (n=1661)	TTB - (n=1069)	HUT + (n=592)	HUT+mixed (n=303)	HUT+cardio (n=113)	HUT+hypo (n=148)	HUT+other (n =28)
<20 years	273	136 (49.9%)	137 (50.1%)	84 (61.3%)	28 (20.4%)	23 (16.7%)	2 (1.4%)
21-40 years	407	255 (62.6%)	152 (37.3)	68 (44.7%)	33 (21.7%)	42 (27.6%)	9 (5.9%)
41-60 years	503	336 (66.7%)	167 (33.2)	88 (52.6%)	28 (16.7%)	40 (23.9%)	11 (6.5%)
>60 years	478	342 (71.5%)	136 (28.4%)	63 (46.3%)	24 (17.6%)	43 (31.6%)	6 (4.4%)

Data are expressed as the number of patients and (percentage). Mixed indicates mixed response; cardio, cardio-inhibitory response; hypo, hypotensive response; other, other responses.

age increased in the four age groups (50.1%, 37.3%, 33.2%, and 28.4%;  $P=0.00001$ ), due mainly to a reduction in mixed-positive responses ( $P=0.02$ ). The reductions in the other positive responses were not significant (cardio-inhibitory,  $P=0.6$ ; hypotensive,  $P=0.14$ ; others,  $P=0.16$ ) (Table 4). The percentage of positive responses fell with age in Groups A and C but not in Group B (Figure 2).

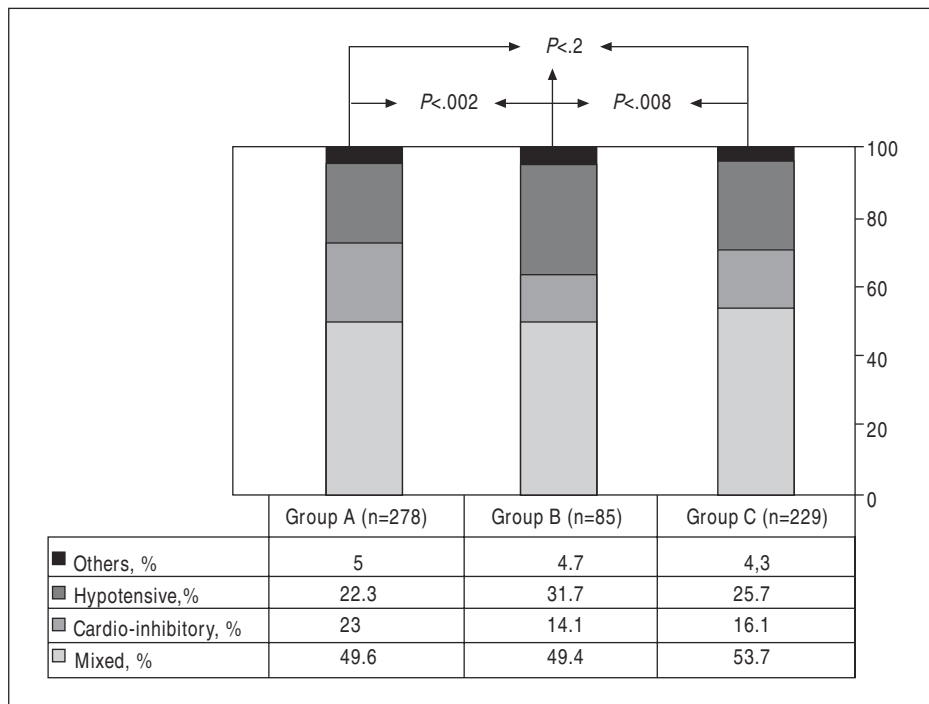
In patients tested with the nitroglycerin protocol there was a nonsignificant age-related increase of a particular type of negative response to HUT sometimes called «exaggerated» by some investigators<sup>11</sup> (1/15, 8/45, 7/57 and 16/66;  $P=0.58$ ).

**DISCUSSION**

The two main findings of this study were the differences in the number and type of positive response to HUT in men and women according to the protocol, and the reduction in positive responses with advancing age in two of the three protocols.

Positive responses were more frequent in patients tested with protocols that used a drug. However, the percentage frequencies of the types of positive response were similar with the use of nitroglycerin and with the Westminster protocol (Figure 1). The differences observed with isoproterenol (absence of a reduction with age and different proportions in the type of positive response) may be partly explained by the presence of false positive responses. The differences between protocols may also represent a certain lack of specificity in older patients, and thus support the need for prospective, randomized studies including control groups, with medium-term follow-up, to confirm the diagnoses.

To date no studies have compared the nitroglycerin protocol over different stages of life; indeed, even though its use is becoming more common its methodology is still being refined.<sup>12</sup> Furthermore, few data exist concerning the use of nitroglycerin for HUT in older patients,<sup>13</sup> in whom it appears to have greater sensitivity than isoproterenol and fewer adverse side-



**Fig. 1.** Differences between percentages in the type of positive response during head-up tilt-table test (HUT) using three HUT protocols. Group A: patients tested with the Westminster protocol. Group B: patients tested with the isoproterenol protocol. Group C: patients tested with the nitroglycerin protocol.

**TABLA 4. Tipos de respuestas divididas según protocolo y grupos de edad**

	< 20 años	21-40 años	41-60 años	> 60 años
<b>Grupo A</b>				
TTB - (n = 813)	107	185	258	263
TTB + mixta (n = 138) (49,6%)	45 (59%)	34 (46,5%)	32 (50%)	27 (41,5%)
TTB + cardio (n = 64) (23%)	19 (25%)	18 (24,6%)	13 (20,3%)	14 (21,5%)
TTB + hipot (n = 62) (22,3%)	12 (16%)	17 (23,2%)	13 (20,3%)	20 (30,7%)
TTB + otras (n = 14) (5%)		4 (5,4%)	6 (9,3%)	4 (6,1%)
<b>Grupo B</b>				
TTB - (n = 73)	14	25	21	13
TTB + mixta (n = 42) (49,4%)	12 (70,5%)	13 (48,1%)	10 (41,6%)	7 (41,1%)
TTB + cardio (n = 12) (14,1%)	2 (11,7%)	3 (11,1%)	5 (20,8%)	2 (11,7%)
TTB + hipot (n = 27) (31,7%)	3 (17,6%)	10 (37%)	8 (33,3%)	6 (35,2%)
TTB + otras (n = 4) (4,7%)		1 (3,7%)	1 (4,1%)	2 (11,7%)
<b>Grupo C</b>				
TTB - (n = 183)	15	45	57	66
TTB + mixta (n = 123) (53,7%)	27 (61,3%)	21 (40,3%)	46 (58,2%)	29 (53,7%)
TTB + cardio (n = 37) (16,1%)	7 (15,9%)	12 (23%)	10 (12,6%)	8 (14,8%)
TTB + hipot (n = 59) (25,7%)	8 (18,1%)	15 (28,8%)	19 (24%)	17 (31,4%)
TTB + otras (n = 10) (4,3%)	2 (4,5%)	4 (7,6%)	4 (5%)	

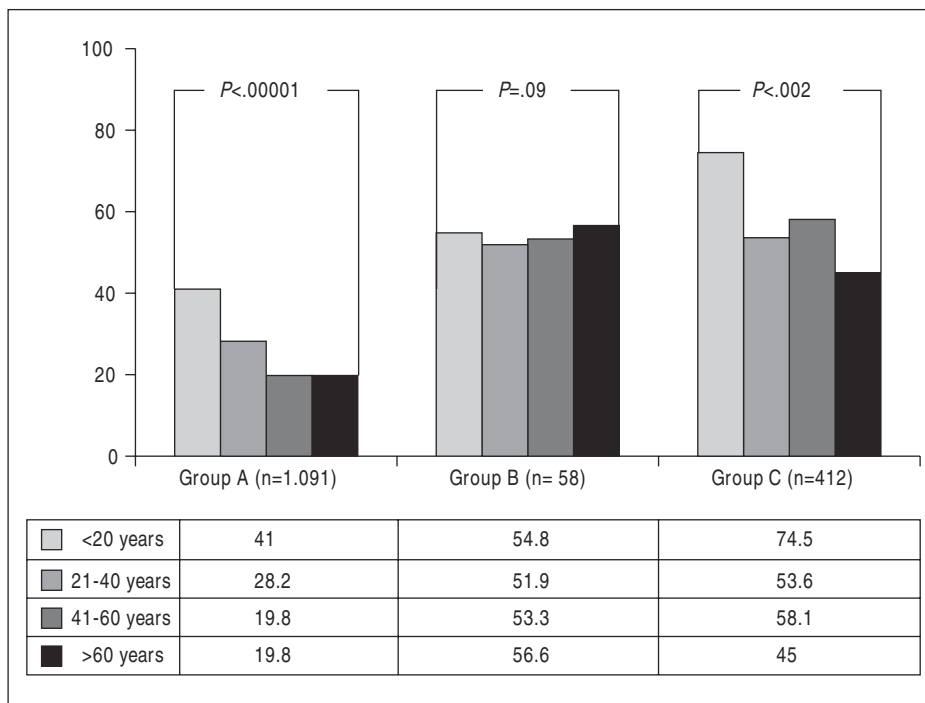
Los datos se expresan como número de pacientes y (porcentaje). Mixta: respuesta mixta; cardio: respuesta cardioinhibitoria; hipot: respuesta hipotensiva; otras: otras respuestas.

effects.<sup>14</sup> Our study demonstrates that the nitroglycerin protocol is associated with more positive responses than the Westminster protocol but, like the latter, the percentage of positive responses decreases with age and the types of positive response are similar. These findings suggest that the nitroglycerin protocol is as “physiological” as the Westminster protocol and support its use in the clinical setting.

As well as previously reported data and the findings

of this study. In addition to the findings of our study, other reasons support the use of the nitroglycerin protocol for HUT: a) provocation with isoproterenol is poorly tolerated by older persons;<sup>14</sup> b) intravenous cannulation is not always recommended for HUT in older patients<sup>15</sup>; c) the cost of nitroglycerin is less than 1% that of isoproterenol, and d) nitroglycerin is safe, well-tolerated and has adequate specificity and sensitivity.<sup>11,14,16</sup>

**Fig. 2.** Percentage of positive responses to the head-up tilt-table test (HUT) with three protocols according to pre-defined age group. Group A: patients tested with the Westminster protocol. Group B: patients tested with the isoproterenol protocol. Group C: patients tested with the nitroglycerin protocol. Mixed: mixed response; Cardio-inhibitory: cardio-inhibitory response; Hypotensive: hypotensive response; Other: other responses. Data are expressed as percentages.



The percentage of «exaggerated» responses varies from 4%-21%, but so far no differences regarding age have been reported. As Bartoletti et al note, the clinical importance of this response is unclear as it is also seen in control subjects (range, 0%-30%).<sup>11</sup> The increased frequency of these responses depending on age may explain, at least in part, the reduced percentage of positive responses with this protocol in our study.

## LIMITATIONS

The study was not randomized. Given the lack of reproducibility of HUT when repeated with the same patient, the different protocols cannot be compared in the same patients. Our data were collected chronologically and methods were largely based on our own experience. No follow-up data are available for our patients and we were unable to quantify false-positive responses.

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