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Age and the Head-Up Tilt Test Outcome in Syncope Patients

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Background: The head-up tilt test (HUTT) is a useful diagnostic tool for syncope.
Objectives: We sought to investigate the outcome of the HUTT in syncope patients and identify the relationship between age and different hemodynamic outcomes.
Patients and Methods: In this cross-sectional study, we prospectively enrolled consecutive patients who presented with syncope and underwent the HUTT with a clinical suspicion of neurocardiogenic syncope after the exclusion of orthostatic hypotension cases. The HUTT consisted of consecutive passive and active phases. In the passive phase, the patients were tilted at 70 degrees for 20 minutes; and if negative, the test was repeated with 400 micrograms of sublingual nitroglycerin for another 20 minutes. Positive responses were classified according to the classification of the vasovagal syncope international study (VASIS) and compared for age and gender.
Results: A total of 498 patients were enrolled (age = 44.93 ± 18.77 years; male = 271 [54.4%]). Overall, 291 (58.4%) patients had a positive HUTT, while 256 (88.5%) patients had a positive result during the active phase. The test results were as follows: 107 (36.7%) mixed type (VASIS I), 103 (35.3%) cardioinhibitory (VASIS IIA = 44 [15.1%]; VASIS IIB = 59 [20.2%]), and 80 (27.4%) vasodepressive (VASIS III). There was no relationship between gender and syncope type. The trend of the HUTT result significantly changed with age, and the rate of cardioinhibitory syncope decreased after middle ages (P value for trend = 0.02).
Conclusions: Hemodynamic response to the HUTT was associated with age. Cardioinhibitory response became less frequent with age due to exaggerated vagal activity in the younger patients as compared with the older subjects.

Keywords: Syncope; Tilt-Table Test; Vasovagal Syncope; Diagnosis; Age Groups

1. Background

Syncope is a transient loss of consciousness due to cerebral hypoperfusion (1), and around 40% of the adult population experience at least one syncopal episode during their life (2-5). The most common cause of syncope in all age groups is neurally mediated disorders, and young adults are the most affected population (6). These are benign conditions without any associated increase in mortality and are characterized by vasodilatation or vagally driven bradycardia or asystole, which causes profound systemic hypotension and consequent dizziness, presyncope, and finally, syncope (1, 3). Older people are at a high risk for syncope due to the physiological changes of aging and the presence of more comorbid conditions and, thereby, more medications, which may predispose them to hypotension (7).

However, a definite relationship between age and type of syncope has yet to be fully documented, particularly in the elderly, whose clinical conditions need further clarification (8). The head-up tilt test (HUTT) is widely used and has remained a practical tool in the diagnosis and management of syncope (9). Accordingly, it seems useful to determine whether the basic characteristics of syncope patients such as age and gender may influence the HUTT outcome.

2. Objectives

In the present study, we sought to investigate the outcome of the HUTT in syncope patients evaluated at Tehran heart center. We also studied the influence of age and gender on the response to the HUTT in patients with unexplained syncope.

3. Patients and Methods

3.1. Study Population

The study group consisted of 498 consecutive patients who were diagnosed with unexplained syncope with one or more attacks and were referred for the HUTT between September 2009 and September 2011. All the pa-

tients underwent a thorough evaluation, comprised of a careful medical history and physical examination as well as supine and orthostatic blood pressure measurements, consistent with the European society of cardiology task force on syncope 1. Patients who had signs and symptoms indicative of orthostatic hypotension were excluded. The study protocol and its ethical issues were approved by the research board of Tehran university of medical sciences.

3.2. Head-Up Tilt Test

The HUTT was performed using an electrically controlled tilt table with a foot board for weight bearing, using a Task Force® hemodynamic monitor 3040i (CNSystems Medizintechnik, Graz, Austria). The blood pressure, heart rate, and rhythm were continuously monitored and recorded according to a 2-stage tilt protocol with nitroglycerin (TNG) provocation.

The HUTT was conducted after an initial observation with the patient in the supine position for 10 minutes. The test consisted of 2 consecutive stages. In Stage I, the patient was tilted at 70 degrees for 20 minutes without medication and with control of the heart rate and 3-lead electrocardiography, based on the protocols of the European Society of Cardiology. The blood pressure was continuously and noninvasively monitored during the test. If syncope (or limiting symptoms) developed, the test was halted and the patient was returned into the supine position. Otherwise, the patient was taken into Stage II, where 400 micrograms of sublingual TNG was administered and tilting was continued for another 20 minutes. If syncope (or limiting symptoms) occurred during the active phase, the tilt table was rapidly lowered to return the patient to the supine position, and the study was terminated.

As regards the classification of the collapse pattern, there were 5 potential outcomes for the test: 4 sub-classes of a positive result and 1 negative result. Positive tests were classified according to the classification of the vasovagal syncope international study (VASIS) (4):

1) Mixed type: The heart rate falls at the time of syncope, but it does not fall to under 40 beats per minute (bpm) for less than 10 seconds. The blood pressure falls before the heart rate falls.

2) Cardioinhibitory type:

Type IIA: Cardioinhibition without asystole occurs when the heart rate falls to a ventricular rate below 40 bpm for longer than 10 seconds but asystole of shorter than 3 seconds does not occur. The blood pressure drops prior to the fall of the heart rate.

Type IIB: Cardioinhibition with asystole is defined as the occurrence of asystole for more than 3 seconds. The heart rate fall coincides with or precedes the blood pressure fall.

3) Vasodepressor type: The heart rate does not fall more than 10% from its peak value at the time of syncope.

Finally, the patients were classified based on age into 6 groups (10 - 25, 26 - 35, 36 - 45, 46 - 55, 56 - 65, and > 65 years old), and the percentage of each syncope class within each age group was then compared to determine whether there was a trend of change in the HUTT results. The P value for trend was calculated.

3.3. Statistical Analysis

The categorical data were presented as frequency (percentage) and were compared using the $\chi 2$ test. The continuous variables were presented as mean ± standard deviation and were compared using the Student t-test in case of normal distribution. Otherwise, a nonparametric Mann-Whitney U test was employed. The normality of the continuous variables was tested using the Kolmogorov-Smirnov test. A P value ≤ 0.05 was considered statistically significant. PASW statistics 18 for Windows (SPSS Inc., Chicago, Illinois, USA), was used for the statistical analyses.

4. Results

A total of 498 patients were enrolled in this study and underwent the HUTT. The patients' demographic characteristics and type of syncope are depicted in Table 1. The mean age at referral was 44.93 ± 18.77 years, and 271 (54.4%) patients were male (Table 1). The female subjects were significantly younger than the males (P = 0.001).

The HUTT was positive in 291 (58.4%) of the total study population. In 258 (88.6%) subjects with a positive HUTT, the test became positive during the active phase. There was no significant difference between the negative and positive cases in terms of gender (P = 0.49). There was also no statistical difference between the positive and negative HUTT subjects regarding age (mean age = 44.95 ± 18.72 years vs 42.89 ± 18.67 years, respectively; P = 0.23).

Among the patients with a positive response, those with cardioinhibitory syncope (both types A and B) were significantly younger than the ones in the other groups (P = 0.03). A positive HUTT in the passive phase was significantly more frequent in cardioinhibitory syncope, particularly type IIB, while there was a higher frequency of an active-phase positive HUTT in mixed type syncope (P = 0.03). However, there was no significant difference between the age and gender groups in regard to a positive test response during the active or passive phase. All the physiological measurements at the start of the HUTT were similar between the groups (Table 2). There was no significant difference in the frequency of responses to HUTT between the gender groups (P = 0.41).

As is depicted in Figure 1, the trend of the HUTT result significantly changed with age and the rate of cardioinhibitory syncope decreased after middle ages (P value for trend = 0.02).

Table 1. Characteristics of the Study Population [a]

Parameter	Values (n = 498)
Age, y	44.93 ± 18.77
Male gender	271 (54.9)
Overall positive HUTT	291 (58.9)
Passive-phase positive HUTT	33 (11.3)
Type of Syncope	
Vasodepressive	81 (16.2)
Mixed	107 (21.4)
Cardioinhibitory type A	44 (8.9)
Cardioinhibitory type B	59 (11.9)

[a] Abbreviation: HUTT, Head-up tilt test.

Table 2. Comparison of the Demographic and Clinical Characteristics Between the Syncope Subgroups, Including Cardioinhibitory Syncope Subtypes [a]

Parameter	Cardioinhibitory Type A (n = 44)	Cardioinhibitory Type B (n = 59)	Mixed Type (n = 107)	Vasodepressive (n = 81)	P Value [b]
Male gender	25 (56.8)	26 (44.0)	60 (56.0)	48 (59.2)	0.32
Age, y	43.48 ± 19.28	39.24 ± 15.58	46.72 ± 19.49	47.63 ± 18.85	0.03
Passive-phase positive HUTT	6 (13.6)	13 (22.0)	5 (4.6)	9 (11.11)	0.03
Supine SBP	117.64 ± 13.05	116.03 ± 13.32	117.35 ± 13.72	114.17 ± 15.08	0.41
Supine DBP	76.80 ± 10.83	76.17 ± 10.65	75.44 ± 10.68	74.41 ± 10.12	0.62
Supine heart rate	75.50 ± 13.04	74.63 ± 15.39	73.65 ± 12.41	74.78 ± 15.73	0.88
Start orthostatic SBP	113.75 ± 15.62	113.81 ± 14.88	113.51 ± 12.99	110.96 ± 18.88	0.62
Start orthostaticDBP	73.89 ± 11.08	73.12 ± 10.89	72.22 ± 10.77	70.44 ± 13.33	0.29
Start orthostatic heart rate	75.84 ± 13.79	77.41 ± 15.41	78.15 ± 13.41	78.43 ± 16.33	0.68
End orthostatic SBP	118.68 ± 17.55	118.53 ± 15.91	118.65 ± 20.39	115.51 ± 19.13	0.7
End orthostatic DBP	80.82 ± 13.52	79.62 ± 13.13	78.09 ± 14.64	76.07 ± 12.38	0.3
End orthostatic heart rate	84.66 ± 14.03	91.29 ± 19.39	87.98 ± 16.10	90.42 ± 19.93	0.28
Event SBP	49.55 ± 11.58	50.39 ± 19.62	54.80 ± 16.67	52.11 ± 17.52	0.13
Event DBP	22.16 ± 18.70	25.22 ± 20.70	28.67 ± 18.66	25.60 ± 22.07	0.4
Event heart rate	27.66 ± 6.47	0	47.18 ± 9.46	89.14 ± 29.09	< 0.0001

[a] Abbreviations: DBP, Diastolic blood pressure; HUTT, Head-up tilt test; SBP, Systolic blood pressure.
[b] P value ≤ 0.05 was considered statistically significant.

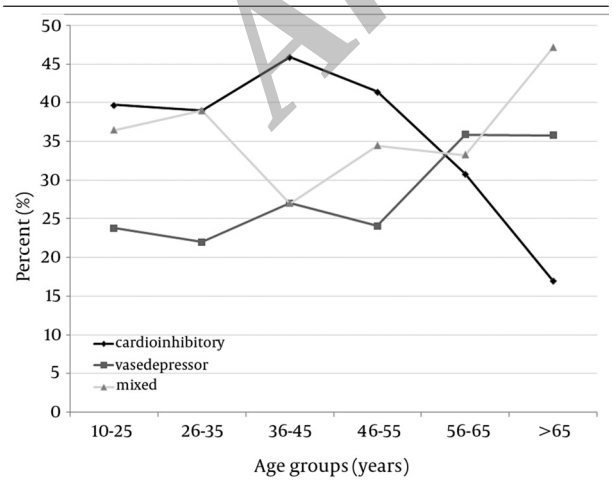

Figure 1. Age-Trend of the Head-Up Tilt Test Results Based on the Percentage Within Each Age Group

5. Discussion

In this study, 498 patients with unexplained syncope were enrolled and a positive HUTT was recorded in 58.4% of the study population. The age of the patients was significantly higher in the vasodepressive group. There was also a significant trend toward a reduction in cardioinhibitory syncope by advancing age. Nevertheless, there was no significant link between gender and the type of syncope based on the HUTT results.

It has been previously observed that age is controversially related to the results of the HUTT. Syncope was previously deemed a frequent condition in young people, particularly women (10). Age and sex have been shown to have no association with the positivity of the HUTT (10). Conversely, age has a significant influence on the response type. Whereas some studies have shown that cardioinhibitory or mixed syncope is more frequently

observed in younger and vasodepressor syncope in older patients, which is similar to the findings of the present study (11, 12), some other studies have not reported age as a predictive variable (13). One possible mechanism for the age-dependent clinical response to the HUTT can be the fact that a low body negative pressure in older subjects, as compared to younger subjects, decreases the movement of the thoracic blood into the lower extremities (14). In addition, older subjects have a reduced power of low-frequency heart rate variability in response to orthostatic stress (15, 16). A higher rate of vasodepressor response to the HUTT among the older subjects in our study may also reflect the inability of the ageing heart and autonomic nervous system to make the proper adjustment in the heart rate to compensate for the stress induced by the HUTT (17-20). Moreover, one study suggested that the age-related differences of a positive vasovagal episode during the HUTT depend on the magnitude of the underlying bradycardic response (21).

Our rate of 42% negative HUTT cases is not comparable to that reported by previous studies (22-25). This might be due to the difference in methods and populations in different studies. Furthermore, some studies have used only the passive HUTT without pharmacological provocation (23). Nonetheless, age significantly influenced response type in the above-mentioned study, and this trend was similar to our findings. However, the specificity of the HUTT varies from 86% to 100% (26, 27), with more controversial sensitivity in different studies (27, 28).

On the other hand, the frequency of cardioinhibitory response progressively decreased from young to old age in our study population. In other words, the frequency of vasodepressor syncope increased with age in this study, which is consistent with some previous works (23, 29, 30). This is a noteworthy finding in that it can provide a better vision for the assessment and management of syncope in different age groups.

This study has some limitations. Certain variables could not be studied because they were not routinely recorded at baseline. It was, therefore, not possible to perform a multivariable regression analysis. Moreover, our center is a referral hospital and patients who experienced recurrent syncope or unusual symptoms were included in the study. Thus, there is a potential for selection bias, which might limit the generalizability of the findings.

The HUTT is a valuable diagnostic tool for vasovagal syncope in all age and sex groups. The results of this study demonstrated that the type of syncope varied by age and that cardioinhibitory response became less frequent with age due to exaggerated vagal activity in the younger patients as compared with their older counterparts. Moreover, the HUTT became positive in the active phase in the patients with cardioinhibitory syncope. Further studies are required to fully describe the effect of age in conjunction with other clinical features on the pathophysiology of syncope.

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Authors' Contributions

Proposal: Rezvan Noormand and Saeed Sadeghian. Drafting: Akbar Shafiee. Data gathering: Rezvan Noormand, Fatemeh Tavakoli, and Alireza Gheini. Supervision and revisions: Saeed Sadeghian, Ahmad Yaminisharif, and Gholamreza Davoodi. Arash Jalali: Statistical analysis. All authors approved the final draft.

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