New approach to hypotensive susceptibility in reflex syncope induced by tilt testing

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Abstract

Introduction Why some individuals with similar demographic characteristics develop syncope during tilt testing (TT) and others do not is unknown and low test sensitivity is claimed. We sought an alternative explanation; resting cardiovascular physiology differs in patients with positive and negative TT. Methods We analyzed age, gender, systolic (SBP), diastolic blood pressure (DBP), and heart rate (HR) using three large syncope patient databases comparing tilt-positive with tilt-negative results after excluding orthostatic hypotension. Positive tilt-response, confirming reflex syncope, was defined as reproduction of spontaneous symptoms with characteristic bradycardia and/or hypotension. Impact of demographic, hemodynamic parameters and prevalent hypertension on TT positivity were assessed using logistic regression models. Results Records of 5236 patients (45% males; mean age, 60±22 years; 32% on antihypertensive therapy) were analyzed. TT was positive in 3129 (60%) and tilt-positive patients had lower SBP (127.2±17.9 vs 129.7±18.0 mmHg, p<0.001), DBP (76.2±11.5 vs 77.7±11.7 mmHg, p<0.001) and HR (68.0±11.5 vs 70.5±12.5 bpm, p<0.001) compared with tilt-negative patients. SBP was similar in males and females but males had higher DBP and lower HR than females (p<0.001). In multivariable analysis, tilt-test positivity was independently associated with younger age (p=0.016), SBP[?]128 mmHg (p<0.001), HR[?]69 bpm (p<0.001), and absence of hypertension (p<0.001). Conclusions Patients developing reflex syncope during tilt-testing have lower systolic and diastolic blood pressure and heart rate compared with tilt-negative patients. Tilt-test positivity is independently associated with younger age, lower blood pressure, lower heart rate and absence of hypertension but not with gender. These hemodynamic differences imply hypotensive susceptibility.

Introduction

Tilt-testing (TT) is a surrogate of orthostatic stress, and one of the strongest stressors for precipitation of orthostatic reflex syncope. So far, it is not known why TT is positive in some patients and negative in others who have reflex syncope with similar clinical features and demographic characteristics\sout. Low sensitivity of TT is claimed to be the explanation for these differences in responses. We have sought an alternative explanation in hemodynamic differences.

TT has been shown to be able to induce reflex syncope in 66% of patients presenting a history compatible with reflex syncope[1], but the clinical features and the outcome of patients with positive tilt response are

similar to those of patients with negative response [2]. Patients with negative and positive tests have similar symptoms and symptom burdens[3], similar clinical outcomes in the 3 years following their TTs[4], and have links between symptoms and outcomes.[4-6] Many studies have tried to find variables associated with positive TT with uncertain or contrasting results.[7-13] In general, these studies being small and with other limitations have been unable to give a definite answer, and the applied methodology was inconsistent as, also, was selection of patients and controls. Owing to the inability to identify variables able to explain a positive TT, some authors have suggested that a significant number of patients with a clinical history compatible with reflex syncope may have falsely negative tilt table test results.[3,14]

Recent studies[15,16] have emphasized the primary role of hemodynamic changes in the mechanism of impending reflex syncope during TT. In brief, a decrease in stroke volume precedes and may even trigger reflex bradycardia and vasodilation, leading to ultimate circulatory collapse. Thus, important hemodynamic changes appear to play a major part in the onset of the vasovagal reflex.[16,17] We, thus, conceived that resting cardiovascular physiology may substantially differ in patients with positive and negative TT prompting us to hypothesize that hypotensive susceptibility revealed by TT is favored by a specific baseline hemodynamic pattern. To test this hypothesis, we analyzed a large multi-center population of consecutive patients who underwent TT for suspected reflex syncope.

Methods

Study population

We analyzed individual values of resting supine blood pressure (BP) and heart rate (HR) collected in the years 2003-2019 in three large databases of patients who had undergone TT for unexplained syncope in the tertiary syncope investigation units of hospitals in Florence (n=805) and Lavagna (n=2798), Italy, and Malmö, Sweden (n=1633). We included patients who had undergone TT for diagnosis of syncope, unexplained by the initial assessment[1], with high pre-test probability of a reflex mechanism. We excluded patients with classical orthostatic hypotension (OH), when TT was performed for other than diagnostic reasons (e.g. tilt training), and patients who were investigated for orthostatic intolerance such as postural orthostatic tachycardia syndrome (POTS) but not syncope as the main symptom. Hypertensive patients were included with hypertension being defined by a clinical diagnosis plus hypotensive medication.

Despite the long study period, indications, methodology and interpretation of TT results remained unchanged during this time and were very similar to the recommendations of the current European Society of Cardiology syncope guidelines.[1] TT was performed according to the "Italian protocol" which consists of a 20-minute passive phase at a tilt angle of 70°, followed by a 15-minute nitroglycerine-potentiated phase ([?]400mcg administered sublingually), if syncope was not induced during the passive phase.[18]Positive response was defined as reproduction of spontaneous symptoms in the presence of characteristic hemodynamic pattern of bradycardia and hypotension.[1] In all centers, baseline hemodynamic data were obtained in supine position after 5-10 minutes of rest prior to TT using validated non-invasive beat-to-beat hemodynamic monitors, Task Force Monitor (CNSystems Medizintechnik GmbH, Graz, Austria) in Florence and Lavagna, and Nexfin (BMEYE, Amsterdam, Netherlands) or Finapres Nova monitors (Finapres Medical Systems, PH Enschede, Netherlands) in Malmo.[19,20] The monitors were calibrated before measurement using brachial cuff and oscillometric method according to the manufacturer's instructions. As the monitors render beat-to-beat data, an average value of a hemodynamically stable period of 10 (Florence and Lavagna) or 30 seconds (Malmo) was recorded in the database. The patient information was de-identified before merging the databases, thus, Ethical approval was not required.

Statistical methods

We retrieved the following individual patient data from each database: age, gender, resting systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), and use of antihypertensive drugs for hypertension. The data were subsequently merged into one study population. Continuous data are shown as mean +- standard deviation, whereas frequencies are used to describe categorical data. The method of Kolmogorov and Smirnov was used to check the normality of distributions. Continuous variables were compared by

means of the paired Student's t-test. Paired and multiple proportions were compared by means of Pearson's chi-square test. Stepwise multiple regression analysis was used to identify the independent factors predicting TT positivity. Multivariable logistic regression was adjusted for age, gender, SBP, and HR, whereas presence of hypertension was adjusted for age, gender and HR only. Analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA) and IBM SPSS Statistics software version 26.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at the 0.05 level and all p-values were two-sided.

Results

Study population

The total study population consisted of 5236 patients, 55% of whom were females, the mean age was 60+-22 years. A total of 1655 patients (32%) were on antihypertensive therapy. TT was positive in 3129 (60%) patients and negative in 2107 (40%) patients. TT was positive in 61% of males and in 59% of females.

Comparison between tilt-positive and tilt-negative patients

Tilt-positive patients had lower SBP, DBP and HR compared with tilt-negative patients (**Table 1**). These clinically small but statistically highly significant differences were observed in both males and females (**Figs 1-3**). SBP was similar in males and females; males had higher DBP than females whereas females had higher HR than males (p=0.001 for DBP and HR).

Table 1. Resting hemodynamic parameters in patients investigated with Italian tilt-test protocol for unexplained syncope stratified according to test result.

	Tilt-positive (n=3129)
Systolic blood pressure, mmHg	127.2 ± 17.9
Diastolic blood pressure, mmHg	76.2 ± 11.5
Heart rate, bpm	68.0 ± 11.5
Values are presented as mean (SD). Statistical significance according to ANOVA test.	Values are presented as mean (SD).

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Figure 1. Resting systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) among tilt-positive (TT+) and tilt-negative (TT-) patients stratified by gender who were investigated using Italian tilt-test protocol for suspected syncope. Males, tilt-positive, n=1428, tilt-negative, n=923; females, tilt-positive, n=3129, tilt-negative, n=2107.

Comparison between subgroups

In univariate analysis (**Table 2**), TT positivity was higher among younger syncope patients <30 years, in patients with lower SBP defined as baseline SBP below the mean value of 128 mmHg, in patients with lower HR defined as baseline HR value below the mean value of 69 bpm, and in patients without history of hypertension. In multivariable-adjusted logistic regression model (**Table 2**), younger age, lower blood pressure and heart rate, and absence of hypertension remained the independent predictors of test positivity. In particular, in the quantitative analysis, positive response to TT was predicted by younger age (Odds ratio [per 10 years], OR: 1.04; 95% confidence interval (CI), 1.01-1.07, p=0.007), lower SBP (OR [per 10 mmHg]: 1.05, 95%CI, 1.01-1.08; p=0.006), and lower heart rate (OR [per 10 bpm]: 1.17; 95%CI, 1.11-1.22, p<0.001). Absence of hypertension diagnosis increased the probability of positive TT by over 50% (OR: 1.58; 95%CI, 1.38-1.81, p<0.001). Exclusion of one database did not substantially affect the overall results

except for the impact of low SBP on TT positivity, which was attenuated after exclusion of Lavagna data in the multivariable-adjusted (but not in univariate) logistic regression model (p=0.083).

Table 2 . Univariable and multivariable analysis of factors predicting tilt test positivity in patients investigated for unexplained syncope using the Italian tilt test protocol.

Variables	Total syncope population (n=5236) n (%)	Tilt-positive patients (n=3129) n (%)	Univariable analysis p value	Multivariable analysis p value
Age subgroups	Age subgroups	Age subgroups	Age subgroups	Age subgroups
10-29 years	748	493 (66)	0.006	0.016
30-59 years	1415	848 (60)		
[?]60 years	3072	1788 (58)		
Gender	Gender	Gender	Gender	Gender
Males	2351	1428 (61)	0.20	0.10
Females	2885	1701 (59)		
Baseline SBP at the time of tilt testing	Baseline SBP at the time of tilt testing	Baseline SBP at the time of tilt testing	Baseline SBP at the time of tilt testing	Baseline SBP at the time of tilt testing
>128 mmHg	2443	1358 (56)	0.0001	0.0001
[?]128 mmHg	2793	1771 (63)		
Baseline HR at the time of tilt testing	Baseline HR at the time of tilt testing	Baseline HR at the time of tilt testing	Baseline HR at the time of tilt testing	Baseline HR at the time of tilt testing
>69 bmp	2088	1176 (56)	0.0001	0.0001
[?]69 bpm	2324	1490 (64)		
Hypertension*	Hypertension*	Hypertension*	Hypertension*	Hypertension*
Yes	1655	864 (52)	0.0001	0.0001
No	3581	2265 (63)		

SBP, systolic blood pressure; HR, heart rate. * Adjusted for age, gender and heart rate.

Discussion

In this multi-center analysis of syncope patients with high pre-test probability of reflex mechanism, we found a characteristic hemodynamic pattern among those who were tilt-test positive. Tilt-positive patients had lower systolic and diastolic blood pressure and heart rate compared with tilt-negative patients. These differences were present among both males and females, although clinically small were highly statistically significant.

We sought a pathophysiological background for hypotensive susceptibility shown by a positive tilt test. It must be emphasized that we were not attempting to predict individual TT results. From our observations, we propose that patients prone to reflex syncope during orthostatic provocation differ hemodynamically from tilt-negative syncope patients. Tilt-test positive patients have narrower hemodynamic margins in the face of orthostatic stress and more compromised cardiac output, expressed by lower initial SBP, rendering their potential for less optimal compensation, also, contributing were lower heart rate and DBP. Consequently, we infer that there are two different hemodynamic patterns corresponding to two levels of hypotensive susceptibility, i.e. patients who may be susceptible to reflex syncope but are resistant to orthostatic stress thanks to well-functioning compensatory mechanisms, and those with a more pronounced hypotensive susceptibility who are prone to develop reflex syncope during TT. The latter with lower BP may compensate less efficiently than the tilt-negative syncope population. Thus, patients with higher BP and HR who are TT-negative may only sustain reflex syncope under clinically more adverse conditions than the more hypotensive susceptible

TT-positive patients.

Mechanistic explanation of test positivity

Recent studies have indicated that TT positivity is associated with neuroendocrine activation characterized by excess epinephrine and vasopressin release[21,22], whereas adrenomedullin seems to play a protective role, probably acting against intravascular volume escape.[21] Further, older age and higher resting SBP have been suggested to be predictors of hemodynamic stability on TT.[11,21] These findings were corroborated by Lindenberger et al. who also found upregulation of vasopressin release, reduced cardiac filling and cardiac output in women prone to reflex syncope.[23] Despite these studies, there remains a tenable possibility that the documented endocrine changes are precipitated by the developing adverse hemodynamic picture.

Lower circulating blood volume and tendency to blood pooling in the capacitance vessels during orthostatic challenge may have a critical impact in abruptly reducing stroke volume during TT and compensatory HR increase, as confirmed by Buszko et al.[12] The higher resting HR and DBP may signal better neuroendocrine preconditioning against orthostatic challenge, engaging the entire sympathetic system. In contrast, those with a more pronounced epinephrine and vasopressin release during tilt testing appear to be in greater need of circulatory compensation as their resting SBP and DBP are lower. This may provoke a protective response from the central nervous system, leading to reflex syncope in extreme situations.[24,25] Typically, this response occurs when cerebral tissue oxygenation is strongly compromised.[26]

Interestingly, only younger age but not gender was independently predictive of TT positivity. The protective factors against TT intolerance were resting SBP above 128 mmHg, heart rate above 69 bpm and presence of hypertension, even while on antihypertensive treatment. These findings emphasize the crucial role of global hemodynamic reserve for reflex triggering. Higher HR might indicate more efficient chronotropic compensatory mechanisms. Higher SBP suggests greater intravascular volume, well-functioning preload- and afterload-preserving mechanisms, whereas hypertension implies chronic sympathetic activation with increased total peripheral resistance and elevated arterial tone in the precapillary vascular bed. Arterial hypertension, as a variant of cardiovascular dysautonomia, is detrimental for long-term cardiovascular integrity and promotes end-organ damage.[27] On the other hand, patients with syncope affected by hypertension seem to be more resistant to orthostatic stress, either due to altered hemodynamic reserve, increased circulating blood volume, chronic neuroendocrine activation and arterial vasoconstriction or by baroreceptor resetting.

Conclusions

Tilt-positive patients who develop reflex syncope have statistically highly significantly lower systolic and diastolic blood pressure and heart rate, albeit small in clinical terms, compared with tilt-negative patients. Advanced age and hypertension, independent of therapy, are two important factors diminishing hypotensive susceptibility to tilt-induced reflex syncope. These hemodynamic differences in reflex syncope susceptibility may be considered as contributing to the understanding of hypotensive susceptibility within the phenomenon of vasovagal syncope.

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