ELMER PRESS

Original Article

Cardiol Res. 2024;15(6):453-459

Yield of Tilt Table Test in Diagnosing Syncope in Patients With Suspected Neurally Mediated Syncope

Bandar Saeed Al-Ghamdi[a, b, g], Nagy Fagir[a, c], Fahmi Alnahdi[a, d], Ahmad Alhamami[a], Mawadah Baali[e], Sara Alghamdi[f], Nadiah Alruwaili[a], Edward De Vol[e]

Abstract

Background: Syncope is a common medical condition. The reflex or neurally mediated syncope (NMS) is the most frequent type. The tilt table test (TTT) helps distinguish syncope from other common causes of complete loss of consciousness, such as epilepsy, define syncope subtypes and guide management. This study aimed to assess the TTT yield in patients with suspected NMS and to compare the nitroglycerin (NTG) and isoproterenol (Isuprel) provocative protocols.

Methods: This study was a retrospective analysis of the data of 426 consecutive patients who underwent TTT at the Heart Center at King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia, between January 1, 2006, and March 31, 2017.

Results: The age at referral for TTT ranged from 7 to 84 years (mean 38.4 ± 15.75 years), and 212 (49.8%) were males. The main clinical manifestations were recurrent syncope in 259 patients (60.8%), a single syncopal episode in 60 (14.1%), and pre-syncope or dizzy spells without loss of consciousness in 171(25.1%). The test was positive in 295 patients (69.2%), with type 1 (mixed response) seen in 151 patients (51.19%), type 2a (cardioinhibitory without pause) in 16 (5.4%), type 2b (cardioinhibitory with pause) in 10 patients (3.39%), and type 3 (vasodepressor) in 118 patients (40%). A false positive test was seen in 11 patients (2.6%) and a false negative in 27 patients (6.3%). The overall test sensitivity was 91%, specificity was 89%, positive predictive value (PPV) was 96%, and negative predictive value (NPV) was 79%.

Conclusions: The TTT is beneficial in diagnosing syncope in males and females and patients of young and old ages. A provocative test utilizing NTG provides a shorter, more straightforward test with the same diagnostic accuracy as the isoproterenol test. Lifestyle modification is effective and remains the primary intervention in managing patients with NMS.

Keywords: Syncope; Tilt table; Vasovagal; Lifestyle; Pacemaker

Manuscript submitted July 16, 2024, accepted November 6, 2024
Published online November 18, 2024

[a]Heart Centre Department, King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia
[b]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[c]Heart Center, King Saud Medical City (KSMC), Riyadh, Saudi Arabia
[d]Dr. Sulaiman Al Habib Hospital, Riyadh, Saudi Arabia
[e]Biostatistics, Epidemiology, and Scientific Computing Department, King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia
[f]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[g]Corresponding Author: Bandar Saeed Al-Ghamdi, Heart Centre Department, King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia. Email: bandar2001sa@yahoo.com

doi: https://doi.org/10.14740/cr1701

Introduction

Syncope is a common medical condition with a lifetime incidence of 35% in the general population [1]. The reflex or neurally mediated syncope (NMS) is the most frequent type of syncope. NMS includes vasovagal syncope (VVS), carotid sinus syndrome (CSS), and situational syncope [2]. Tilt table test (TTT) is a diagnostic test used to replicate reflex syncope in the lab under controlled situations. TTT helps in distinguishing syncope from other common causes of complete loss of consciousness (LOC), such as epilepsy, defining syncope subtypes, and guiding management [3, 4].

Several protocols have been reported since the debut of TTT in 1986, with differences in the initial stabilization phase, length, tilt angle, type of support, and pharmacological provocation [3-5].

This study is significant as it aims to assess the TTT yield in patients with suspected NMS and compare the nitroglycerin (NTG) and isoproterenol (Isuprel) provocative protocols. It seeks to contribute to the understanding and management of syncope, a common and often challenging medical condition. Furthermore, data about syncope and its management are limited in the Middle East, a region with a hot climate. So, this study aims to cover this gap.

Patients and Methods

This study was a retrospective analysis of the data of 426 consecutive patients who underwent TTT at the Heart Centre at King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia, between January 1, 2006, and March 31, 2017. The patients' demographic, TTT, and follow-up data were meticulously collected from clinical and electronic notes and TTT sheets, ensuring the thorough-

Table 1. Different Types of Response to Tilt-Testing

Positive test	Changes in blood pressure and/or heart rate meeting the modified VASIS criteria with syncope, pre-syncope, orthostatic hypotension, or POTS and symptoms identical to clinical symptoms.
Negative test	Syncope, pre-syncope, orthostatic hypotension, or POTS are not provoked.
False-positive	Syncope, orthostatic hypotension, or POTS are provoked with symptoms different from clinical symptoms.
False-negative	Syncope, orthostatic hypotension, or POTS are not provoked in patients with solid clinical suspicion of neurally mediated syncope.

POTS: postural orthostatic tachycardia syndrome; VASIS: Vasovagal Syncope International Study.

ness and reliability of the study.

Inclusion criteria

This study included all patients who completed TTT and had regular clinic follow-ups at KFSH&RC.

Exclusion criteria

The following patients were excluded: 1) Patients were unable to complete the test; 2) Patients with incomplete TTT data; 3) Patients with cerebrovascular diseases (e.g., chronic cerebrovascular disease, cerebrovascular malformations, cerebral tumor or bleeding of any date, migraine, and Parkinson's disease or dementia); 4) Patients with previously confirmed psychogenic or mental disorders; 5) Patients with no regular follow-up.

Definitions

Syncope is a complete LOC due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and complete spontaneous recovery [6]. The complete LOC is a state of the actual or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and short duration [6].

Presyncope, reflex syncope or NMS, CSS, situational syncope, orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), and psychogenic pseudosyncope are defined as in the published guidelines [6-9].

TTT

The patients were dressed in a hospital gown without restrictive binding around the abdomen or legs. An intravenous catheter was inserted in the right or left arm. The test was conducted in a quiet room equipped with a resuscitation trolley. Patients were strapped with precautionary straps to avoid falls while being tested on a tilting table with a footboard (e.g., Akron Streamline, Arjo Huntleigh Ltd., Gloucester, UK). Before starting the test, the patients rested in a supine position for 5 - 20 min. The Task Force 3040i Monitor (CN systems, Graz, Austria) was used to record baseline and continuous blood pressure readings, heart rate, oxygen saturation, and rhythm. The table rapidly moved to an upright position (60 - 80°) for approximately 20 min. If there were no significant changes and syncope was not produced by tilting alone, the provocation was performed using isoproterenol (Isuprel) infusion or sublingual NTG. In the isoproterenol protocol, the table was tilted back to a supine position after the initial negative phase. Isoproterenol was administered by intravenous infusion at progressive doses from 1 to 5 mg/min to achieve at least a 10% increase in the heart rate and then tilting the table to 60 - 80° for 10 - 20 min. In the NTG provocative group, a sublingual NTG 0.4 mg tablet was given with a table still at 60 - 80° based on the clinician's discretion with the continuation of the test for an additional 10 - 20 min. The endpoints were either induction of syncope and systolic blood pressure that fell below 70 mm Hg or completion of the planned test. After the test compilation, the patients were placed in supine or reverse Trendelenburg positions if blood pressure did not normalize. A 250 mL bolus of 0.9% NaCl was administered for hypotension. The patients were monitored until their blood pressure and heart rate returned to baseline.

Classification of responses to TTT

The classification of response to the TTT is shown in Table 1.

The positive test is classified based on the modified Vasovagal Syncope International Study (VASIS) classification into mixed (type 1), cardioinhibitory without asystole (type 2a), cardioinhibitory with asystole (type 2b), and vasodepressor response (type 3) [10].

Statistical analysis

Data analysis was conducted using the SAS/JMP version 15.0 statistical software package. Data were summarized with descriptive statistics (means and standard deviations for continuously scaled variables and counts and percentages for categorically scaled variables). Estimation of the diagnostic parameters included calculating 95% confidence intervals. The evaluation of the relative magnitudes of the diagnostic parameters was conducted using logistic regression techniques and accompanied by the calculation of odds ratios.

Ethical considerations

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki (2013), the ICH Harmo-

Table 2. The Patients' Demographic Characteristics

	The patient's total number (426), N (%)
Age, mean ± SD	38.40 ± 15.75 years
Gender	
Male	212 (49.8.0%)
Female	214 (50.2%)
Clinical presentation	
First episode of syncope	60 (14.1%)
Recurrent syncope	259 (60.8%)
Presyncope/dizziness	171 (25.1%)
CV risk factors/diseases	
Diabetes mellitus	44 (10.3%)
Hypertension	76 (17.8%)
Dyslipidemia	38 (8.9%)
Ischemic heart disease	29 (6.8%)
Valve heart disease	40 (9.4%)
Heart failure	18 (4.2%)
Atrial fibrillation	15 (3.5%)
Ventricular tachycardia	4 (0.9%)
Congenital heart disease	36 (8.5%)

SD: standard deviation; CV: cardiovascular.

nized Tripartite Good Clinical Practice Guidelines, the policies and guidelines of the KFSH&RC Hospital, and the laws of Saudi Arabia. As this study was retrospective, the Research Ethics Committee (REC) approved a waiver of informed consent.

Results

Four hundred twenty-six consecutive patients who underwent TTT during the study period were enrolled after four patients were excluded (two due to incomplete tests and two due to a lack of TTT information). Table 2 depicts the patients' demographic characteristics.

In summary, the age at referral for TTT ranged from 7 to 84 years (mean 38.4 ± 15.75 years), and 212 (49.8%) were males. The main clinical manifestations were recurrent syncope in 259 patients (60.8%), a single syncopal episode in 60 (14.1%), and pre-syncope or dizzy spells without LOC in 171 (25.1%) (Table 2).

Cardiac comorbidities included diabetes mellitus (DM) in 44 patients (10.3%), hypertension in 76 (17.8%), and dyslipidemia in 38 (8.9%). Fifteen patients (3.5%) had atrial fibrillation, and four (0.9%) had a history of ventricular tachycardia.

The underlying cardiac diseases in TTT patients included ischemic heart disease in 29 patients (6.8%), valvular heart disease in 40 patients (9.4%), heart failure in 18 patients (4.2%), and congenital heart disease in 36 patients (8.5 %).

The diagnostic workup included an electrocardiogram (ECG) and an echocardiogram in all patients. Holter monitors and implantable loop recorders (ILR) were performed in selected patients.

Some patients had neurology work, with 94 patients (22.1%) having an electroencephalogram (EEG), which was abnormal in 40 (9.4%), mostly with nonspecific changes. Brain computed tomography (CT) and/or magnetic resonance imaging (MRI) were done in 108 (25.4%) patients, of which 43 patients showed abnormal results (10.1%); however, the changes did not explain LOC.

TTT characteristics and results

Of the 426 patients, 333 (78.2%) were tilted at 70°, 70 patients (16.4%) at 80°, and 23 patients (5.4%) at 60° (Table 3).

The test was positive in 295 patients (69.2%), with type 1 (mixed response) seen in 151 patients (51.19%), type 2a (cardioinhibitory without pause) in 16 (5.4%), type 2b (cardioinhibitory with pause) in 10 patients (3.39%), and type 3 (vasodepressor) in 118 patients (40%). A false positive test was seen in 11 patients (2.6%) and a false negative in 27 patients (6.3%).

Besides, the TTT carotid sinus massage was performed in three patients (0.7%) with a history suggestive of carotid hypersensitivity (CH), and it was positive in two of them (0.47% of total patients). Two patients had situational syncope, one cough-related and one micturition-related syncope. Both had positive TTT with vasodepressor response. Eight patients (1.9%) were labeled to have psychogenic syncope, and 10 (2.3%) had results compatible with POTS. An ILR was inserted in 11 patients (2.6%) post-test.

The comparison of clinical and TTT parameters between NTG and isoproterenol provocative test is shown in Table 4.

There was no difference in the patient's baseline characteristics except the younger age in the isoproterenol group. TTT utilizing NTG had a shorter total test time of 27.7 ± 6.5 min vs. 46.9 ± 12.4 min in isoproterenol. It also had a higher positive test and fewer false negatives but higher false-positive results.

Table 5 presents the test sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV).

The overall test sensitivity was 91%, specificity was 89%, PPV was 96%, and NPV was 79%. Regarding the provocative test, the NTG group had a higher sensitivity of 94% but a lower specificity of 78%, and the isoproterenol group had a higher specificity of 100% and a lower sensitivity of 68%.

No significant gender or age differences are noted in these parameters.

Management

During the follow-up period of 1.8 - 14 years (mean 5.71 ± 3.67 years), vasovagal precautions are the primary treatment in 385 patients (90.4%). Beta-blockers were used in 104 patients (23.9%), mainly to treat accompanying palpitations or for other cardiovascular indications; fludrocortisone was used in 30 patients (7%), midodrine long-term used in 22 patients (5.2%),

Table 3. Tilt Table Test (TTT) Characteristics and Results

TTT	N/%
Degree of tilting	
60	23 (5.4%)
70	333 (78.2%)
80	70 (16.4%)
Total test duration, mean ± SD	29.0 ± 15.397
Provocative test	
Nitroglycerin (NTG)	181 (42.5%)
Isoproterenol	95 (22.3%)
None	150 (35.2%)
TTT results	
Positive	295 (69.2%)
Negative	131 (30.8%)
False-negative	27 (6.3%)
False positive	11 (2.6%)
Neurally mediated syncope (NMS) type	
Vasovagal	295 (69.2%)
Carotid sinus syndrome	2 (0.47%)
Situational syncope	2 (0.47%)
Psychogenic	8 (1.9%)
Postural orthostatic tachycardia syndrome (POTS)	10 (2.3%)

SD: standard deviation.

and combined treatment in five patients (1.2%). Permanent pacemaker implantation was required in four patients (1.3%). During the follow-up period, 341 patients (80%) reported improvement in their symptoms in terms of less frequency in 250 patients (58.7%) and duration of syncope episodes in 91 patients (21%).

Table 4. Comparison Between Nitroglycerin and Isoproterenol Protocols

	Nitroglycerin (n = 181, 42.5%)	Isoproterenol (n = 95, 22.3%)	P value
Age, mean ± SD	35.7 ± 16.5	30.1 ± 18.4	0.0001
Gender			
Male	94 (51.9%)	52 (54.7%)	0.1939
Female	87 (48.1%)	43 (45.3%)	
Syncope			
First episode	29 (16.0%)	16 (16.8%)	0.1850
Recurrent	113 (62.4%)	48 (50.5%)	0.0600
Presyncope/dizziness	112 (61.9%)	66 (69.5%)	0.3670
Tilt table test			
Total test time duration, mean ± SD	27.7 ± 6.5	46.9 ± 12.4	0.0001
Tilt table test result			
Positive	140 (77.4%)	30 (31.6%)	0.0001
Negative	41 (22.7%)	65 (68.4%)	0.0001
False-negative	8 (4.4%)	14 (14.7%)	0.0020
False-positive	9 (4.97%)	0 (0.0%)	0.0230

SD: standard deviation.

Table 5. Tilt Table Test Sensitivity, Specificity, Positive and Negative Predictive Values, and Accuracy After Adjusting for Age Group and Gender

	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	91% (0.88, 0.94)	89% (0.84, 0.95)	96% (0.93, 0.98)	79% (0.72, 0.86)	91% (0.88, 0.93)
Provocative test					
Isoproterenol	68% (0.54, 0.81)	100% (1, 1)	100% (1, 1)	78% (0.68, 0.88)	85% (-0.016, 0.050)
Nitroglycerin	94% (0.90, 0.98)	78% (0.66, 0.90)	94% (0.89, 0.97)	80% (0.68, 0.92)	91% (0.88, 0.93)
None	96% (0.92, 0.99)	87% (0.73, 1.01)	98% (0.94, 1.00)	80% (0.64, 0.95)	95% (-0.011, 0.033)
Age group					
Age ≥18 years (adult patients)	92% (0.88, 0.95)	85% (0.77, 0.92)	94% (0.91, 0.97)	79% (0.70, 0.87)	90% (-0.014, 0.044)
Age < 18 years (pediatric patients)	95% (0.89, 0.99)	83% (0.72, 0.93)	90% (0.83, 0.96)	91% (0.82, 0.99)	91% (0.88, 0.93)
Gender					
Male	92% (0.88, 0.96)	82% (0.72, 0.91)	92% (0.87, 0.96)	83% (0.73, 0.92)	89% (-0.014, 0.044)
Female	93% (0.88, 0.96)	87% (0.79, 0.95)	95% (0.90, 0.98)	83% (0.74, 0.92)	91% (0.88, 0.93)

NPV: negative predictive values; PPV positive predictive values.

Discussion

Syncope may occur in all age groups. However, the initial syncopal episode follows a distribution characterized by a bimodal curve. It exhibits a primary peak during early adulthood (between 10 and 30 years) and a secondary peak in individuals beyond 65 years [11, 12].

Syncope is usually related to VVS in the first group and to a broader range of causes, including cardiac arrhythmias, structural heart disease, and orthostatic hypotension in the second group [11, 12]. VVS is still a common cause of syncope in the second group. TTT yields a good diagnosis of VVS in both groups. Our patients' ages ranged from 7 to 84, covering these two peaks of presentation.

Previous studies showed a female predominance in VVS [1, 13]. However, the incidence is similar between genders, as observed in our study and others [9].

Positive TTT responses in patients with VVS are 61-69%, and the specificity is 92%-94% [9]. However, in a recently published study that included 4,873 patients, the overall TTT-positive response was 48.1% [14]. The TTT is positive in about 70% of our patients. This study has a higher sensitivity and specificity, likely due to the inclusion of patients with a high pre-test suspicion of VVS who were referred from the cardiology clinics after full evaluation. Furthermore, about one-third of our patients were less than 18 years old, with a higher likelihood of having VVS.

The different protocols used in TTT, including the angle of tilt, the duration of the test, and the use of pharmacologic agents, can affect the test yield. The most used protocol includes tilting to 70° for a passive unmedicated phase of 20 min, application of sublingual NTG at the 20th min, and an additional 20 min of standing [3, 15, 16]. Isoproterenol infusion during the second tilt is another commonly accepted protocol [3, 15, 16].

These agents blunt the adaptive response of the autonomic nervous system and further unmask abnormal reflexes. Both reported similar sensitivity (61-69%) and specificity (92-94%) [15, 17].

A systematic literature review shows that the TTT is positive in 66% of patients with syncope for the NTG protocol and 61% for the isoproterenol protocol [16]. In a previous study comparing the two protocols, the tilt test with NTG was shorter, more straightforward, painless, and had the same diagnostic accuracy as the test with isoproterenol [17]. In another study, NTG- and isoproterenol-augmented tilt tests were associated with equal sensitivity in diagnosing neurocardiogenic syncope in children and adolescents. However, more false-positive tests were noted with NTG, producing more prolonged vasovagal symptoms [18].

In our study, the isoproterenol test has higher specificity, and the NTG test has higher sensitivity. However, the TTT sensitivity, specificity, positive and negative predictive values, and accuracy are good and not significantly different regarding gender and age (pediatric vs. adult patients).

TTT is a time-consuming procedure, which is one of the limiting factors for test utilization in clinical practice. In patients with suspected VVS, the diagnostic value of the fast Italian TTT protocol (10 min passive phase plus a 10 min 0.3 mg NTG if the passive phase was negative) is similar to that of the traditional protocol (20 min passive phase plus a 15 min 0.3 mg NTG if the passive phase was negative), which includes a 5-min supine pre-tilt phase. There is no significant difference in the distribution of hemodynamic responses. In this study, the TTT duration was reduced from 40 to 25 min. This warrants further studies to confirm this finding and make it a clinically attractive approach [19].

In a recent study, a mixed-type response was most frequently observed in positive TTT patients, followed by the vasodepressor type [14]. A previous study also showed that a mixed type was the most common, but the cardioinhibitory type was the second most frequently observed [20].

The predominant positive response in this study is the mixed type (type 1), followed by a vasodepressor (type 3) response and then a cardioinhibitory response (type 2). A possible explanation is the younger age in this study compared to

those seen in studies with the cardioinhibitory response, as the cardioinhibitory response decreased with age [20, 21].

The management of VVS depends mainly on education and reassurance of the disease's benign nature, which significantly reduces syncope recurrence in most patients [22]. Early identification of prodromes and avoiding triggers is essential to prevent syncope/presyncope episodes. Increasing water and salt intake is strongly recommended. All patients should be advised to lie down quickly with the onset of presyncope when feasible [22]. Counter-pressure maneuvers, leg-crossing, limb/abdominal contractions, and squatting might be beneficial. These maneuvers are not recommended in older subjects because of evidence of ineffectiveness [22]. Patient education and lifestyle modification were adequate for most of our patients.

Pharmacologic therapy might be needed as 15-20% of patients may have recurrent VVS refractory to nonpharmacological measures [6]. Although fludrocortisone or midodrine are considered first-line therapy (class IIb) in patients with recurrent VVS and hypotension phenotype by the European Society of Cardiology (ESC) guideline [6], midodrine is regarded as first-line therapy (class IIa) and fludrocortisone as second-line therapy (class IIb) by the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm Society (HRS) guideline [7]. Beta-blockers in patients older than 42 years and selective serotonin reuptake inhibitors are recommended as second-line therapy (class IIb) by the ACC/AHA/ HRS guideline for recurrent VVS [7]. However, neither is recommended in the ESC guidelines [6]. About 12% of our patients were on pharmacologic therapy. Beta-blockers were mainly used to treat accompanying palpitations or for other cardiovascular indications. Midodrine and fludrocortisone were the two commonly used medications for VVS.

Indications for cardiac pacing in selected patients with VVS remain controversial. An ACC/AHA/HRS class IIb recommendation is provided for dual chamber pacing in a select population of patients 40 or older with recurrent VVS and prolonged spontaneous pauses [7]. In contrast, the ESC guideline provides a class IIa recommendation for patients with recurrent reflex syncope with spontaneous asystolic pauses due to "extrinsic (functional) causes (i.e., vagally mediated or adenosine-sensitive)" syncope [6]. Only 1.3% of our patients required permanent pacemaker implantation.

Ganglionic plexus ablation (cardioneuroablation or cardio-neuromodulation) is a promising therapy for patients with refractory VVS [23, 24]. However, due to insufficient data, recommendations about this management option have not yet been included in the current syncope guidelines. We do not have any patients who have had this ablation procedure [7, 8].

Limitations

This is an observational and not randomized study. It covers syncope related to VVS only and does not cover other types of syncope, which limits the generalizability of the findings. It is a single-center study, so our data were collected chronologically, and the methods were primarily based on our experience.

Conclusions

The TTT is beneficial in diagnosing syncope in males and females and patients of young and old ages. A provocative test utilizing NTG provides a shorter, more straightforward test with the same diagnostic accuracy as the isoproterenol test. Lifestyle modification is effective in managing patients with NMS. Pacemaker implantation is rarely needed.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

This work was presented in part or in whole as an oral abstract at the HC Research Day 2022.

Informed Consent

Informed consent was waived by the Institutional Review Board (IRB) due to the retrospective nature of the study.

Author Contributions

All authors contributed to this manuscript. Bandar Saeed Al-Ghamdi conceived and designed the study and wrote the manuscript. Nagy Fagir:data collection and review of the manuscript. Fahmi Alnahdi: data collection. Ahmad Alhamami: data collection. Mawadah Baali: statistical analysis. Sara Alghamdi: data collection. Nadiah Alruwaili: data analysis. Edward De Vol: statistical analysis.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. J Cardiovasc Electrophysiol. 2006;17(11):1172-1176. doi pubmed
2. da Silva RM. Syncope: epidemiology, etiology, and prog-

nosis. Front Physiol. 2014;5:471. doi pubmed
3. Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, Maloney JD, et al. Tilt table testing for assessing syncope. American College of Cardiology. J Am Coll Cardiol. 1996;28(1):263-275. doi pubmed
4. Iana Simova. Role of tilt-table testing in syncope diagnosis and management. e-Journal of Cardiology Practice. 2015;13(35).
5. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. Lancet. 1986;1(8494):1352-1355. doi pubmed
6. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39(21):1883-1948. doi pubmed
7. Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, Grubb BP, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017;136(5):e60-e122. doi pubmed
8. Sheldon RS, Grubb BP, 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, Raj SR, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015;12(6):e41-63. doi pubmed
9. Task Force for the Diagnosis Management of Syncope European Society of Cardiology, European Heart Rhythm Association, Heart Failure Association, Heart Rhythm Society, Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631-2671. doi pubmed
10. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, et al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. Europace. 2000;2(1):66-76. doi pubmed
11. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. Am J Cardiol. 2003;91(8):1006-1008. doi pubmed
12. Duncan GW, Tan MP, Newton JL, Reeve P, Parry SW. Vasovagal syncope in the older person: differences in presentation between older and younger patients. Age Ageing. 2010;39(4):465-470. doi pubmed
13. Sandhu KS, Khan P, Panting J, Nadar S. Tilt-table test: its role in modern practice. Clin Med (Lond). 2013;13(3):227-232. doi pubmed
14. Xu L, Cao X, Wang R, Duan Y, Yang Y, Hou J, Wang J, et al. Clinical features of patients undergoing the head-up tilt test and its safety and efficacy in diagnosing vasovagal syncope in 4,873 patients. Front Cardiovasc Med. 2021;8:781157. doi pubmed
15. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, Menozzi C, et al. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace. 2000;2(4):339-342. doi pubmed
16. Forleo C, Guida P, Iacoviello M, Resta M, Monitillo F, Sorrentino S, Favale S. Head-up tilt testing for diagnosing vasovagal syncope: a meta-analysis. Int J Cardiol. 2013;168(1):27-35. doi pubmed
17. Morillo CA, Klein GJ, Zandri S, Yee R. Diagnostic accuracy of a low-dose isoproterenol head-up tilt protocol. Am Heart J. 1995;129(5):901-906. doi pubmed
18. Vlahos AP, Tzoufi M, Katsouras CS, Barka T, Sionti I, Michalis LK, Siamopoulou A, et al. Provocation of neurocardiogenic syncope during head-up tilt testing in children: comparison between isoproterenol and nitroglycerin. Pediatrics. 2007;119(2):e419-425. doi pubmed
19. Russo V, Parente E, Tomaino M, Comune A, Sabatini A, Laezza N, Carretta D, et al. Short-duration head-up tilt test potentiated with sublingual nitroglycerin in suspected vasovagal syncope: the fast Italian protocol. Eur Heart J. 2023;44(27):2473-2479. doi pubmed
20. Oraii S, Maleki M, Minooii M, Kafaii P. Comparing two different protocols for tilt table testing: sublingual glyceryl trinitrate versus isoprenaline infusion. Heart. 1999;81(6):603-605. doi pubmed
21. Noormand R, Shafiee A, Davoodi G, Tavakoli F, Gheini A, Yaminisharif A, Jalali A, et al. Age and the head-up tilt test outcome in syncope patients. Res Cardiovasc Med. 2015;4(4):e27871. doi pubmed
22. Primary Writing Committee, Sandhu RK, Raj SR, Thiruganasambandamoorthy V, Kaul P, Morillo CA, Krahn AD, et al. Canadian cardiovascular society clinical practice update on the assessment and management of syncope. Can J Cardiol. 2020;36(8):1167-1177. doi pubmed
23. Pachon JC, Pachon EI, Pachon JC, Lobo TJ, Pachon MZ, Vargas RN, Jatene AD. "Cardioneuroablation"—new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005;7(1):1-13. doi pubmed
24. Vandenberk B, Lei LY, Ballantyne B, Vickers D, Liang Z, Sheldon RS, Chew DS, et al. Cardioneuroablation for vasovagal syncope: A systematic review and meta-analysis. Heart Rhythm. 2022;19(11):1804-1812. doi pubmed