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MINIREVIEWS

Tilt table test today - state of the art

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Abstract

A tilt table test (TTT) is an inexpensive, noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance and has good diagnostic yield. The autonomic system malfunction which underlines the reflex syncope is manifested as either hypotension or bradycardia, while an orthostatic challenge is applied. The timing of the response to the orthostatic challenge, as well as the predominant component of the response help to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions (*e.g.*, pseudosyncope). Medications, such as isoproterenol and nitrates, may increase TTT sensitivity. Sublingual nitrates are easiest to administer without the need of venous access. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. TTT is not useful to access the response to treatment. Recently, implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope, because pacemakers are beneficial in many of these patients, especially those over 45 years of age. The stepwise use of both TTT and ILR is a promising approach in these patients. Recently, TTT has been used for indications other than syncope, such as assessment of autonomic function in Parkinson's disease and its differentiation from multiple system atrophy.

Key words: Syncope; Orthostatic intolerance; Tilt table test; Hypotension; Bradycardia

Core tip: A tilt table test (TTT) is a noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance. The way of the response to the orthostatic challenge helps to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. Implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope. The stepwise use of both TTT and ILR is a promising approach. TTT has been used to assessment of autonomic function in Parkinson's disease.

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INTRODUCTION

The tilt table test (TTT) was initially described by Kenny *et al*[1] in 1986 as a tool to diagnose syncope of unknown origin. Since then various protocols have been developed. The cornerstone of the test is an orthostatic challenge which is done with the upright tilt. Apart from its main use in the syncope workup, use of the test was described in the evaluation of the presence of autonomic neuropathy in a variety of conditions[2,3]. The main idea behind the test is that reflex syncope is due to the abnormal cardiac autonomic reflexes, which lead to inappropriate vasodilatation (vaso-depressive reflex syncope), inappropriate bradycardia (cardio-inhibitory reflex syncope) or a mixed response[4-6]. A prolonged upright position is a known trigger of reflex syncope, where, after an initial normal adaptation to standing, inappropriate vasodilatation or bradycardia appears, leading to symptoms. This is different from the orthostatic hypotension, where the initial response to standing is abnormal.

DEFINITION OF DIFFERENT TYPES OF ORTHOSTATIC INTOLERANCE

European Society of Cardiology guidelines on diagnosis and management of syncope describe 6 major types of syndromes of orthostatic intolerance, which may cause syncope[7] and the tilt test is useful for making a correct diagnosis. Four of them are different types of orthostatic hypotension. The initial orthostatic hypotension (up to 30 s since postural challenge) is caused by the mismatch between cardiac output and systemic vascular resistance. It usually happens either in young, thin patients or in elderly patients treated with medications or with carotid sinus hypersensitivity and is usually manifested by the fall in blood pressure associated with dizziness in rare syncopal episodes. Classic orthostatic hypotension takes from 30 s to 3 min, is caused by autonomic failure to increase the systemic vascular resistance while standing, with the resultant pooling of blood in lower extremities and subsequent fall in blood pressure. Sometimes, significant volume depletion may cause this type of orthostatic intolerance, even when autonomic reflexes function normally. This form of orthostatic hypotension usually occurs in elderly patients, or in association with vasodilator or volume depleting medications, with orthostatic dizziness as a main manifestation and infrequent syncope. Delayed orthostatic hypotension occurs between 3 and 30 min, is caused by a progressive fall in venous return, low cardiac output and diminished reflex vasoconstriction; however, there is no decrease in heart rate. This type is present in elderly patients with autonomic failure, vasoactive medications and comorbidities. It is manifested by a prolonged prodrome of dizziness, weakness, visual disturbances, chest, neck and back pain, followed by rapid syncope. Reflex (vasovagal) syncope takes 3 to 45 min of postural challenge to develop. It is characterized by an initially normal adaptation reflex, followed by a rapid vasovagal reaction with reflex vasodilation and bradycardia. It is manifested by prodrome, which includes dizziness, nausea and sweating (some symptoms are caused by autonomic activation), always followed by syncope and mostly occurring in young female patients. Post exercise syncope, which happens in the first minute after cessation of intense physical activity, is now understood to be a form of reflex syncope[8,9]. When investigating the exercise related syncope, the initial effort should concentrate on excluding cardiac causes of syncope such as hypertrophic cardiomyopathy, valvular disease, or channelopathies.

Elderly patients with comorbidities may have a combination of delayed orthostatic hypotension with reflex syncope. Postural orthostatic tachycardia syndrome (POTS) is manifested by a significant increase in heart rate (an increase of more than 30 bpm or a heart rate of 120 bpm or more) during postural challenge without a fall in blood pressure (it can be quite variable). The mechanism of POTS is incompletely understood and is associated with physical deconditioning, and it usually happens in young females.

THE DIAGNOSTIC VALUE OF TTT

The etiology of reflex syncope can be divided into its common form (vasovagal - where postural challenge or emotion causes the abnormal reflex) and to the situational syncope (where this reaction is caused by a specific trigger). The autonomic malfunction causing reflex syncope is either a vasodepressive response (loss of sympathetic vasoconstrictive tone with resultant hypotension), cardioinhibitory response (active para-sympathetic stimulation with resultant bradycardia or asystole) or a mixed response. Carotid sinus hyper-sensitivity is a special form of reflex syncope.

Young patients are more prone to cardioinhibitory syncope, whereas older individuals are more likely to have a hypotensive response[10-12]. Moreover, an individual patient may demonstrate different types of responses on different occasions.

Normal individuals may have syncope during the tilt test (false positive result). However, comparing normal people who have a positive tilt test with people who have a history of reflex syncope[13] demonstrated that patients with a history of syncope had less time to syncope, a more rapid and persistent fall in blood pressure and higher peak serum epinephrine levels. False negative results have been reported with a rate of up to 30%, so a negative result does not exclude reflex syncope. Prolonged electrocardiographic monitoring may later diagnose cardioinhibitory syncope in tilt test negative patients[10,14]. There is no good gold standard for

evaluation of vasodepressive syncope.

The test is relatively simple and requires a special tilt table (a bed which rapidly moves the patient from a supine to an upright position, while the patient is secured to it with a foot board and restraints). Before the test, orthostatic hypotension is usually excluded. Electrocardiogram and blood pressure are continuously monitored (mostly by noninvasive measurements). Various protocols have been published with the differences mainly in the degree of tilt (60 to 90 degrees), its duration and use of pharmacological enhancement.

After monitoring of the patient in the supine position for 5 to 20 min (a longer duration is required if the intravenous cannula is used)[7], the patient is moved to the upright position and kept there for 20 to 45 min. If symptoms develop in association with bradycardia or hypotension, the test is considered positive. Obviously, the patient is rapidly returned to the supine position. If hypotension or bradycardia develops without symptoms, the test is suggestive of reflex syncope. Additionally, orthostatic hypotension may be documented.

If the test is negative, isoproterenol infusion (the dose is titrated to increase the average heart rate by 25%) or sublingual nitrates are used[15,16] during a second tilt. These are used to blunt the adaptive response of the autonomic nervous system and further unmask abnormal reflexes. Both were reported to have similar sensitivity (61%-69%) and specificity (92%-94%)[15,16]. Sublingual nitrates are easier to administer because venous access is unnecessary. However, one study demonstrated that in the pediatric population, administration of nitrates *vs* isoproterenol was associated with lower sensitivity (24% *vs* 56%) and more severe cardioinhibitory response[17]. A recent study which compared 2 protocols of sublingual nitrate administration (with and without a 5 min rest period in the supine position before nitroglycerin administration) found no differences with positive test in 61% *vs* 60% and specificity of 92% *vs* 90%, respectively[18]. This may eliminate the use of the rest period and shorten the test. Another study demonstrated that the use of the nitroglycerin tablet *vs* the sublingual spray is more specific, the latter form of usage was associated with higher rate of false positive response in both syncope patients and control patients[19]. Efremov *et al*[20] evaluated heart rate variability in patients with previous syncope who underwent a head up tilt test. Changes in the heart rate variability parameters between the first and last 5 min of the passive tilt test predicted syncope after nitroglycerine administration. Thus, evaluation of the heart rate variability during a tilt test may obviate the need for nitrate administration and shorten the test with decrease of side effects; however, this will require additional data processing.

Other triggers described during the tilt table testing are carotid sinus massage and clomipramine administration. Carotid massage in an upright position may demonstrate hypersensitivity, which may not be present in the supine position. Clomipramine is an serotonin selective reuptake inhibitor, which causes increased stimulation of serotonin receptors and, subsequently, diminishes sympathetic tone. One study[21] demonstrated an increased rate of positive response in patients (80% *vs* 53%) without increase in false positive responses.

Indications for the tilt table testing include recurrent unexplained syncope in patients without structural heart disease[7], or in patients with structural heart disease when cardiac causes have been excluded. Patients with a single episode of syncope do not usually need a tilt table test, unless there are specific circumstances associated with high risk (lifestyle or occupational hazard, *etc.*). Patients who are diagnosed with reflex syncope on the initial assessment are usually not candidates for the tilt test. The test may be useful to differentiate syncope with jerking movements from epilepsy[22,23]. Reflex syncope and epilepsy may actually coexist, so in some cases electroencephalogram recording during TTT may be of value[23]. Tilt test is also useful to differentiate reflex syncope from orthostatic hypotension[24], to evaluate a patient with recurrent falls[25] and to diagnose patients with psychogenic syncope[26]. In this scenario, syncope during the TTT will not be preceded by hypotension and/or bradycardia. The TTT is not used to evaluate the response to treatment. It is also not useful to evaluate patients with specific triggers which cause syncope.

One study[27] assessed neuro-autonomic evaluation in elderly patients with syncope which was determined to be likely to be neurally mediated after baseline initial evaluation. A diagnosis was made in 64% of cases with a diagnostic tilt test in 50%, carotid sinus massage (CSM) in 12% and orthostatic hypotension in 20%. The study demonstrated that neuro-autonomic evaluation is useful in elderly patients with syncope and that a tilt test was the most important contributor to this evaluation.

Another study[28] evaluated the diagnostic yield of tests in syncope according to the ICD-10 discharge diagnosis. The final diagnosis was reflex syncope in 21%, cardiac in 18%, orthostatic hypotension in 10%, others in 4% and unexplained in 48%. While the overall diagnostic yield of tests was low, the tilt test had a diagnostic yield of 47% during the initial admission and 61% during the work up.

A tilt test can be used to evaluate postural tachycardia syndrome. However, its performance is similar to the active standing test. One recent study[29] comparing TTT to active standing (blood pressure and heart rate at the 3rd and 9th minute) demonstrated no difference in the presence of orthostatic intolerance (P = 0.786). Syncope or presyncope was induced in 35% of patients in both groups. The only difference was a slight fall in blood pressure after 9 min of the tilt test but not in the active standing test. Another study[30] which compared the active standing test and the tilt test using heart rate measurements after 10 and 30 min found that an increase in 30 bpm in the upright position had good sensitivity with either method, but was less specific with the tilt test (40% *vs* 67% at 10 min and 20% *vs* 53% at 30 min, respectively). Thus, clinical features of orthostatic intolerance together with positive active standing are

Table 1 Comparison of relative merits of tilt table test and implantable loop recorders

	TTT	ILR
Advantages	Noninvasive, nonexpensive Differentiates between reflex syncope, orthostatic hypotension, carotid sinus hypersensitivity and pseudosyncope Assesses function of autonomic system	Reliable diagnosis of arrhythmias causing presyncope or syncope
Disadvantages	Significant false negative response (up to 30%) Pharmacological chellenge may be required	Invasive Cannot assess nonarrhythmic causes of syncope

TTT: Tilt table test; ILR: Implantable loop recorder.

probably sufficient for the diagnosis, while a tilt test is not going to be contributory in this situation.

COMPARISON WITH AN IMPLANTABLE LOOP RECORDER

Implantable loop recorder (ILR) provides continuous rhythm monitoring and can capture spontaneous episodes of cardioinhibitory syncope. ILR may more precisely determine a cause-effect relationship between bradyarrhythmia and syncope and exclude the tachyarrhythmic cause of syncope[31-33]. In case of cardioinhibitory syncope, TTT is more likely to demonstrate hypotension and bradycardia and less asystole, whereas ILR recordings during spontaneous episodes usually demonstrate asystole[10]. Thus, an implantable loop recorder may be used for the diagnosis of the suspected cardioinhibitory syncope instead of the tilt test. The drawback of this approach will be high proportion of implanted pacemakers in patients with documented spontaneous asystolic events, whereas patients with a positive tilt test will be mostly reassured about the benign nature of their disease. ISSUE 3 trial, reported in 2012[34] demonstrated high efficacy of dual chamber pacing with a rate drop response programing in patients who are 40 years and older with at least 3 previous syncopal episodes with ILR documented cardioinhibitory syncope (asystole for more than 3 s) or asystole for more than 6 s without syncope. In this randomized placebo-controlled (sensing only pacemaker) trial pacing caused 32% absolute and 57% relative reduction of syncopal episodes. According to this data, it seems prudent to proceed with ILR without a TTT in individuals with recurrent syncopal episodes of an unexplained nature, or with a suggested cardioinhibitory response. Of note, later analysis of this cohort of patients demonstrated that the benefit pacing in this group of patients was much greater in patients with negative TTT, than with positive one (the type of positive response was not significant)[35]. Another recent study[36] used an algorithm with carotid sinus massage, followed by a tilt test, and, if it is not diagnostic, ILR implantation. Asystolic response in any of the tests led to pacemaker implantation. The recurrence rate in the pacemaker-implanted patients (about half of the total group) was 9% in 1 year and 15% in 2 years (with no difference between CSM, TTT or ILR positive patients) and was significantly lower than in patients with nondiagnostic ILR (22% in 1 year and 37% in 2 years). The significance of prolonged asystole (> 30 s) was evaluated in one study[37]. A total of 2263 patients underwent TTT, 6.5% had an asystole, 11 patients (0.5%) had asystole between 30 and 63 s. Avoidance of triggers and physical counterpressure maneuvers were recommended in all patients, no one received a pacemaker. Although no patient died, 4 patients (36%) had recurrent syncopal episodes after a median follow-up of 42 mo. The summary of relative merits of TT *vs* ILR is shown in Table 1.

BEYOND SYNCOPE: THE USE OF TTT TO ASSESS AUTONOMIC NERVOUS SYSTEM IN DIFFERENT DISEASES

Besides its main use for differential diagnosis of syncope, TTT has been utilized in a variety of different disorders. Recent studies[38,39] used TTT in Parkinson disease. One study[37] demonstrated that in Parkinson's disease patients orthostatic hypotension is associated with a combination of decreased peripheral vascular resistance and inability to increase stroke volume, which means that autonomic dysfunction, involves both vasoregulatory dysfunction and cardiac denervation. Patients with preserved cardiac autonomic response (increase in stroke volume while in upright position) did not have orthostatic hypotension during TTT, despite reduction in peripheral vascular resistance. Orthostatic hypotension was very infrequent (1 in 46 patients) in patients who elevated peripheral vascular resistance during TTT. Another study[39] demonstrated that TTT is useful in making a differential diagnosis between multiple system atrophy (MSA) with predominant Parkinsonism and Parkinson's disease. Autonomic dysfunction was much more prevalent in MSA; combination of TTT and Valsalva maneuver having 91% sensitivity and 92% specificity. TTT also documented abnormal autonomic responses in patients with persistent post-concussion syndrome[40], restless leg syndrome[41] and anorexia nervosa[42].

CONCLUSION

TTT is a time proven test with good diagnostic yield for the diagnosis of syncope. Because of its relatively low cost and noninvasive nature, TTT can be widely used.

Combined with an implantable loop recorder, TTT will provide valuable information for the physician caring for patients with syncope. Apart from syncope, TTT demonstrated efficiency in evaluation of autonomic nervous system in noncardiac disorders.

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