Tilt Test - from the Necessary to the Indispensable

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Abstract

The head-up tilt test (HUTT) is widely used for investigation of syncope and presyncope, since it allows diagnosing different types of dysautonomia. The main cause of syncope is the vasovagal syndrome, the most common diagnosis among patients with HUTT indication. The test has been used for nearly 20 years, but many doctors are unaware of the methodology. After the cardiac causes of syncope are ruled out, the appropriate indication of the test and instructions to patients are important to ensure that the test will be carried out in a safe and relaxed manner. There are controversies in the literature over the diagnostic capacity and reliability of results. Studies with various protocols may explain the variability of results. This review describes the guidelines-recommended methodology and indications, complications, limitations and perspectives of this test.

Introduction

The head-up tilt test (HUTT) is a widely used method for investigation of syncope, presyncope, dizziness, palpitations related to orthostatism and dysautonomia symptoms[1]. However, the main indication has been to investigate the vasovagal syndrome (VVS).

In 1986, Kenny et al[2] reported, for the first time, the usefulness of HUTT in the investigation of patients with syncope of probable vasovagal origin. They noted that the exposure to a 60° tilt for 60 minutes triggered the vasovagal reflex in 66% of patients with syncope of unexplained origin. Since then, protocols of shorter duration or drug-potenciated protocols have been used, so as to increase sensitivity and shorten the execution time of the test.

Lately, the test has been criticized due to a great variation in sensitivity and specificity rates in different studies. Furthermore, the result of the HUTT has well-defined therapeutic implications and the reproducibility is limited[3,4].

The European Guidelines on Diagnosis and Management of Syncope, updated in 2009, describe the recommendations of the methodology and the indications of the test and types of response that are expected[5]. In this paper, we discuss the current indications, protocols, limitations and perspectives of this test.

Keywords

Tilt test; syncope; vasovagal syndrome; guidelines.

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Indications of the tilt test

The 2006 American Heart Association Scientific Statement on The Evaluation of Syncope does not recommend HUTT for evaluation of syncope, but such document has attracted widespread criticism, which will be commented on below[6,7]. In clinical practice, the indications described by the European Guidelines of Syncope are used[5]. These guidelines state that the HUTT shall be used for diagnostic purposes in the situations below.

Class I recommendation

In young patients, without obvious or suspected heart disease, with recurrent syncope of unexplained origin, in which the history is not typical enough for the diagnosis of neurally mediated syncope.

In cases of a single episode of unexplained syncope, which occurred in situation where there is high risk of physical injury or with occupational implications; or in cases of recurrent syncope in the absence of heart disease, or yet, if in patients with heart disease, the cardiac causes of syncope are ruled out.

In cases where the demonstration of susceptibility to neurally mediated syncope is clinically relevant.

Class II recommendation

When understanding the pattern of hemodynamic response during syncope may alter the treatment planning.

In the differentiation between convulsive syncope and epilepsy.

In diagnosis to differentiate between reflex syncope and orthostatic hypotension.

For the evaluation of patients that have had unexplained recurrent falls.

When dealing with patients with presyncope or recurrent dizziness.

In the evaluation of patients with recurrent syncope and psychiatric illnesses.

The European guidelines state that, in cases in which the test is recommended and in the absence of an associated heart disease, the positive result with reproduction of the

spontaneous syncope is sufficient for defining the diagnosis of neurally mediated syncope.

The use of HUTT for controlling treatments or for monitoring the VVS in the long term has not been recommended. Even though the European guidelines on syncope do not recommend the HUTT for patients that have a typical clinical history of VVS, the tilt test is valuable in identifying the type of VVS (cardioinhibitory, vasodepressor or mixed). Some authors recommend different treatment options depending on the type of vasovagal syncope, so in this case, HUTT would serve as therapeutic guidance[5,8]. Pachon et al[8] recently published a new therapeutic alternative for patients with neurocardiogenic syncope, which would be more suitable for patients with cardioinhibitory VVS.

Protocols

In the descriptions of previous protocols, the terms "sensitivity" and "positivity" get mixed up due to the absence of a gold standard test for diagnosing VVS. When the clinical diagnosis is considered to be the gold standard, the term "HUTT sensitivity" has been used, because the patient with the disease was selected according to the clinical history. When the test is carried out in patients with unexplained syncope, the term "positivity" is generally applied. However, in this review, the term "sensitivity" was standardized for both situations, in order to simplify the description of the studies, but it is understood that in many cases, the term represents only the positivity of the test. The use of clinical diagnosis as the gold standard has been criticized because of the subjectivity inherent in medical judgment. However, to date, no other method has proved to be more accurate.

Initially, the authors recommended only the orthostatic tilt for prolonged periods, without the use of drugs, which is called the extended passive protocol. In the analysis of five studies that evaluated the result of exposure to passive orthostasis, lasting at least 40 minutes, the sensitivity rates noted were 13%, 25%, 31%, 35% and 75% (median of 31%)[9-12]. In contrast to the low sensitivity, the specificity was 100%, 100%, 95%, 92% and 89%, respectively (mean of 95%).

In an attempt to increase the diagnostic accuracy of HUTT, the administration of various sensitizing drugs was tested after a negative passive phase.

Currently, isoproterenol and nitrate are the drugs most commonly used for this purpose. In the several studies conducted, the sensitivity of the test with nitrate ranged between 57.5% and 87%, and the specificity between 70% and 100%, while the test with isoproterenol showed variations between 42% and 69% and between 70 and 90%, respectively[9,11,13-15]. Isoproterenol is being abandoned due to the lower sensitivity, inconvenience of intravenous access and side effects, especially in patients with ischemic heart disease[16] (Table 1).

Initially, nitrate was used in the form of intravenous nitroglycerin, with sensitivity of 53% and specificity of 92%, considering only the sensitized phase[17]. In a subsequent study, the same researchers evaluated the effect of sublingual nitroglycerin[10]. Initially, patients lay on a table that was tilted up to an angle of 60° for 45 minutes (passive tilt), which resulted in low sensitivity (25%) and high specificity (100%). After administration of 300 mg of sublingual nitroglycerin, a positive response was observed in more than 26% of the patients and in 6% of the control group, resulting in a specificity of 94%. Similar data were presented by other authors in subsequent years[9,15,18] (Table 1).

The European guidelines on syncope, published in 2004, reported an analysis of studies that used 20 or 45 minutes of passive phase followed by sensitization with nitrate. The conclusion reached was that the sensitivity of tests of shorter or longer duration is similar (69% versus 62%), without any decrease in specificity (94% for the protocols with 20 minutes of passive phase)[1]. Since then, it is recommended that the HUTT should consist of 20 minutes of passive phase and 20

Table 1 - Methodology and results of different studies with the sensitized tilt test

Author	s	Tilt angle	Nitrate	Passive phase [11]	Sensitized phase [11]	Sensitivity (%)	Specificity (%)	Accuracy (%)
Raviele et al 1995[10]	235	60º	NTG 300 mg	45	20	51(65)	94	56(67)
Aerts et al 1997[9]	32	70º	DNIS 5 mg	45	15	87	70	81
Del Rosso et al 1998[18]	202	60º	NTG 400 mg	20	25	70(74)	94(82)	81(83)
Ammirati et al 1998[15]	73	60º	DNIS 1,25 mg	30	15	57(71)	100	62(75)
Bartoletti et al 1999[38]	84	60º	NTG 400 mg	5	20	35	96	NA
Aerts et al 2005[28]	38	70º	NTG 400 mg	-	30	82	84	83
Oraii et al1999[11]	65	70º	GTN 400 mg ISOP 1-4 g	45	20 10-40	71 69	85 90	NA
Hermosillo et al 2000[14]	120	70º	DNIS 5 mg ISOP 4 g	30 30	12 10	83 51	88 70	84 71
Nava et al 2004[111]	128	70º	NTG 400 mg ISOP 1-3 g	15 30	15 20	60.9 42.2	NA NA	NA NA

S - sample size; NTG - nitroglycerin; ISDN - isosorbide dinitrate; GTN - glyceryl trinitrate; ISOP - isoproterenol; NA - not available

minutes of sensitized phase (nitroglycerin or isoproterenol). Thus, the classical protocol (without the use of sensitizing drugs) has been replaced by the protocol that combines the passive phase followed by the sensitized phase.

In Brazil, sublingual nitroglycerin has not been traded since 2002, so the vasodilator used is isosorbide dinitrate, at a dose of 1.25 mg (1/4 of the sublingual administration pill), as recommended by the Brazilian Guidelines for Evaluation and Treatment of Patients with Cardiac Arrhythmias, published in 2002[19]. In three studies that evaluated the use of this drug during the HUTT, the sensitivity ranged from 57 to 87%, and specificity from 70 to 100%[9,14,15]. The dose of 1.25 mg was evaluated in only one of these studies and it was the one related to the highest specificity (100%)[15].

The sensitization of the test with the use of nitrate reproduces the same types of vasovagal responses as the passive tilt: cardioinhibitory, vasodepressor and mixed[20]. However, the mechanism by which nitrate induces vasovagal syncope is still not understood, and the most studied hypotheses have been: 1. vasodilatation, 2. activation of the sympathetic nervous system, 3. direct action in the central nervous system (CNS), and 4. action in the central nervous system (CNS) via neurohormones[20-22].

Recommended methodology

HUTT must be conducted in a quiet environment, with dimmed lighting and pleasant temperature. The monitoring is carried out by doctors and nursing technicians, trained for the test, and the presence of relatives is not recommended. The room must be equipped with cardiac resuscitation materials, although the use of such materials is rarely necessary[19]. Patients must fast for at least four hours for liquids and six hours for solids and they must lie down for at least ten minutes, before the tilting[19]. Venipuncture should be avoided in this phase, but if necessary, the resting time before the test should be increased to at least 20 minutes[1]. The test table has a footrest and safety straps and it can be tilted up to 60 or 70 degrees (Figure 1). Angles that are above and below the default configuration show lower specificity and lower sensitivity of HUTT, respectively[1,23]. Throughout the examination, electrocardiogram and blood pressure (BP) readings are used to monitor the patient. Ideally, BP should be monitored in a continuous and non-invasive way. If the BP is intermittently measured, the interval between measurements should be as small as possible, especially in the phase that is close to the positive result of the test. In patients aged over 40 and with a clinical history of syncope, the carotid sinus massage is also recommended, because during tilting, the sensitivity of this technique is higher, and it is also possible to evaluate the vasodepressor component[24]. The test can be carried out at any time of day, but when the goal is to study the reproducibility of results, it is important to repeat the test at the same time it is was previously carried out[25].

Types of response to tilt testing

The Brazilian Guidelines for Evaluation and Treatment of Patients with Cardiac Arrhythmias considers the HUTT positivity criterion when there is reproduction of the

Figure 1 - Table tilted at an angle of 70 degrees, with footrest and rest for the upper limb in which the BP will be measured. The Velcro straps allow securing the patient in case of loss of postural tone. The necessary equipment is (from the right to the left): device for noninvasive monitoring of BP, beat to beat, and BP curve and ECG monitoring devices.

spontaneous symptoms associated with the hemodynamic collapse[19]. There is controversy surrounding the interruption of the test before the occurrence of syncope. Many authors consider that it is enough to stop the HUTT when the doctor believes that the loss of consciousness is imminent – phase called presyncope -, and there is no reason to subject the patient to the huge discomfort resulting from hypotension or bradycardia, which will allow defining the vasovagal response[1,26,27]. More recent studies have considered that the positivity criterion is the induction of syncope or presyncope, when associated with bradycardia or hypotension[11,13,14,18,26,28].

A modified classification of VASIS (Vasovagal Syncope International Study) is the most accepted one to define the types of response to tilt testing: type 1 or mixed; type 2A or cardioinhibitory without asystole; type 2B or cardioinhibitory with asystole; and type 3 or vasodepressor (Table 2 and Figure 2)[1].

However, the type of response to HUTT does not necessarily define the hemodynamic pattern of the patient's clinical syncope. The ISSUE-2 study showed that 36% of patients with mixed or vasodepressor response to HUTT had asystole during a spontaneous episode recorded by the loop recorder[29]. Thus, more recently, it has been considered that the most important aspect of the response to tilt testing is the differentiation between reflex syncope and other forms of orthostatic intolerance[5].

Other diagnoses obtained by means of the tilt test

Besides the vasovagal response, HUTT allows diagnosing other forms of dysautonomia and orthostatic intolerance. The carotid sinus hypersensitivity is confirmed if, during the massage, there is a ventricular pause that exceeds or is equal to three seconds or if there a drop in systolic blood pressure that is greater than or equal to 50 mmHg[1]. The massage during tilt allows diagnosing half of the patients with the disease that would not be diagnosed if the procedure was performed only in a supine position. In a retrospective study with 1,719 patients, the diagnosis of carotid sinus hypersensitivity was made in 226 cases during the procedure in the supine position and in 217 cases only after repeating the procedure at a tilted position[24]. In addition, the continuous monitoring of BP during the HUTT makes it easier to evaluate the vasodepressor component, which is important for the diagnosis because, in most cases, syncope results both from the drop in HR and the decrease in BP - mixed response.

Another frequent dysautonomia is the Postural Orthostatic Tachycardia Syndrome or Postural Tachycardia Syndrome, in which the patient complains mainly of palpitations, dizziness and presyncope related to orthostatism. HUTT is essential to confirm the diagnosis, which is considered positive when there is an increase in HR that is greater than or equal to 30 bpm, after orthostatic exposure in relation to basal HR or maintenance of HR above 120 bpm during the tilt[30]. On the other hand, there is the chronotropic incompetence, which is characterized by the failure to increase the heart rate during the tilt, i.e., an increase of less than 10% of the baseline heart rate[31]. This diagnosis can only be made when there are no effects of negative chronotropic drugs.

HUTT also allows diagnosing other forms of orthostatic intolerance, such as the dysautonomic response, characterized by slow and progressive drop in BP to below 80 mmHg, without any drop in HR, associated with symptoms of hypotension such as sudoresis, dizziness and blurred vision[31]. The patient has these symptoms for at least five minutes without the occurrence of syncope, and at such moment, the examination shall be discontinued.

The primary diseases of the autonomic nervous system (Pure Autonomic Failure, Shy-Drager Syndrome and Multiple System Atrophy) or secondary autonomic failures to systemic diseases (Parkinson's Syndrome, Diabetes mellitus and Amyloidosis) can also be evaluated by HUTT[32]. They are characterized by supine hypertension and orthostatic hypotension, which do not recover after the first few minutes of postural exposure. Depending on the intensity of the autonomic impairment, this postural hypotension may be of greater or lesser magnitude and it may be accompanied by insufficient increase in HR or not, thereby indicating more or less advanced degrees of autonomic failure.

Table 2 - Classification of positive responses to tilt testing

Type 1 or mixed	The heart rate (HR) drops at the time of the syncope, but not to less than 40 bpm. If there is a drop in HR to below 40 bpm, the drop lasts less than ten seconds. The blood pressure (BP) drops before the HR.
Type 2A or cardioinhibitory without asystole	The heart rate drops below 40 bpm for more than ten seconds. The BP drops before the HR.
Type 2B or cardioinhibitory with asystole	There is asystole that lasts more than three seconds. The decrease in BP precedes or coincides with the drop in HR.
Type 3 or vasodepressor	HR does not drop more than 10% compared to the peak at the time of syncope.
Exception 1 - Chronotropic incompetence	There is no significant increase in HR during the tilt (i.e., less than 10% of the HR before the tilt).
Exception 2 - Postural Orthostatic Tachycardia Syndrome (POTS)	Excessive increase in HR (i.e., greater than 130 bpm) both initially and throughout the tilt before the syncope.

Complications

HUTT is a safe examination if it is carried out under the conditions recommended above and if the cardiac causes for syncope are ruled out. In this sense, before requesting this test, it is important to survey the clinical history of the syncope episode. If there is the suspicion of cardiac or neurological cause, the specific investigation must be conducted[33]. Leman et al[16]. reported the occurrence of ventricular fibrillation during a tilt test with the use of isoproterenol at a dose of 5 ug/kg/min, in an 80-year-old patient, with history of previous myocardial infarction and who was being tested for syncope, but who had not undergone an echocardiogram or had not been tested for myocardial ischemia prior to the HUTT. After successful defibrillation, the patient underwent coronary angiography, which revealed 99% obstruction of the circumflex artery.

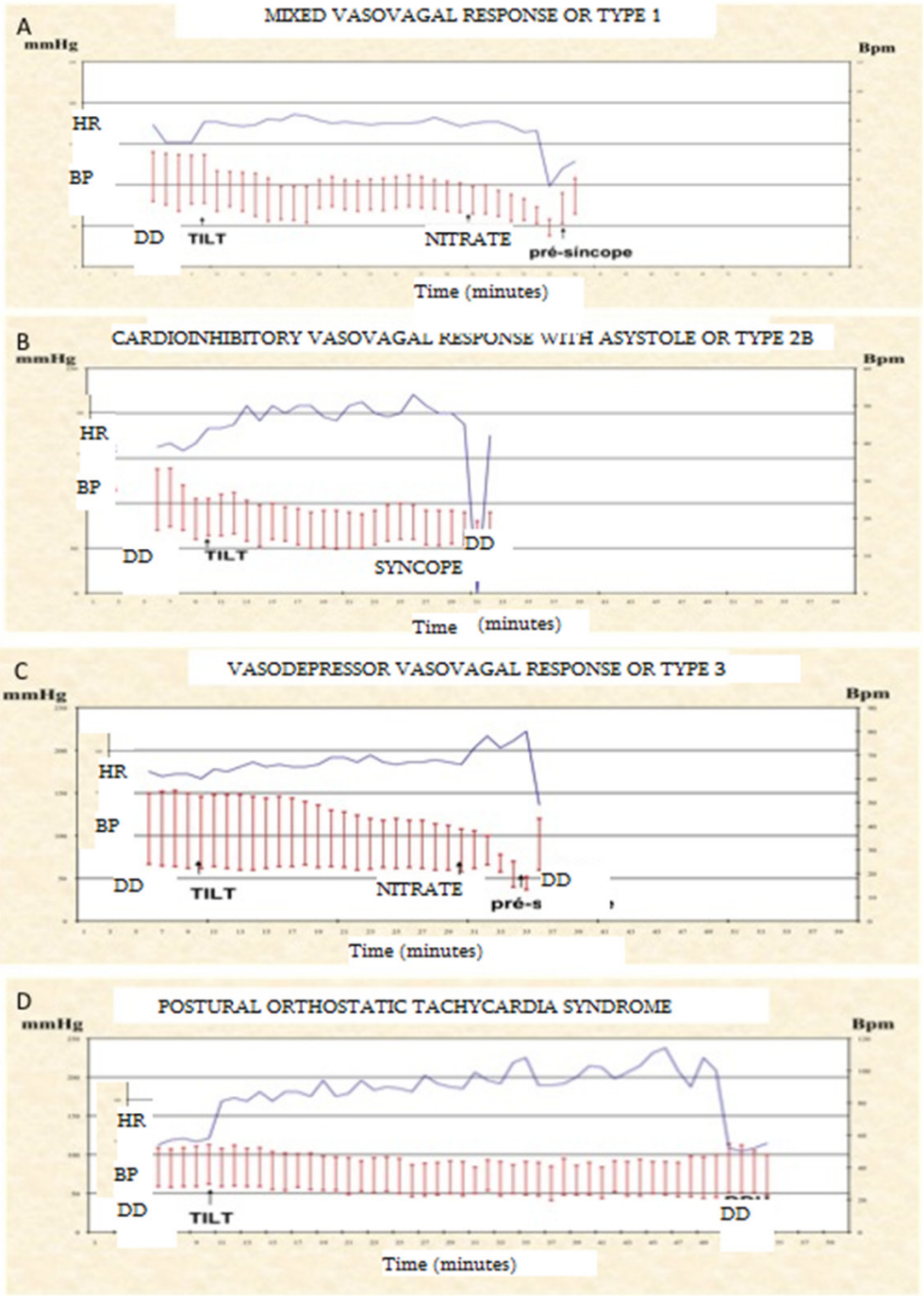

Figure 2 - Charts showing the behavior of BP and HR during different vasovagal responses and SPOT. A - mixed vasovagal response or type 1; B - cardioinhibitory vasovagal response with asystole or type 2B; C - vasodepressor vasovagal response or type 3; D - postural orthostatic tachycardia syndrome. Acronyms: DD - dorsal decubitus; TILT - orthostatic tilt; BP - blood pressure; HR - heart rate; N - nitrate.

In contrast, an English study attested to the safety of this test. The study included 1,969 elderly people aged over 60, 44% of whom were over 75 years old. The tilt test consisted of a passive phase followed by a sensitized phase with using the passive protocol or the protocol sensitized by glyceryl trinitrate[34]. Only a 74-year-old patient had atrial fibrillation at the 26th minute of the passive tilt, which was the only cardiovascular event observed during the tests, and there was no neurological event. Another study conducted in Spain showed no complications during the examination of 1,219

individuals, including young and old people, in which the methodology with only the passive phase was used or the passive phase together with isoproterenol sensitization[35].

The occurrence of prolonged asystole, as a result of vasovagal reflex induced by HUTT, is not rare, but in most cases, it is not necessary to initiate resuscitation, because the quick return to the supine position or Trendelenburg position is enough for regaining of consciousness. There have been reports of asystole of 73 seconds, which was reversed with resuscitation and atropine, without any sequelae after the examination[36]. The pauses usually last less than 30 seconds, but longer pauses are not considered major complications. Such pauses are considered exacerbated responses[1].

Clinical use and limitations

Due to its capacity to reproduce the patient's symptoms in a laboratory, together with the corroboration of hemodynamic changes, the tilt test has been used to confirm the diagnosis of VVS for over 20 years. Specific guidelines recommend the use for diagnosis of syncope of unexplained origin, presyncope, dizziness, falls and seizures.

In 2006, the American Heart Association Scientific Statement suggested that HUTT contributed little to the diagnostic investigation[6]. The criticism was about the sensitivity, specificity, accuracy and reproducibility, and only four references were provided to justify the disqualification of the test - while the European Guidelines on syncope were not cited. On the other hand, the Ad Hoc Syncope Consortium argued that such document was incomplete, showed only a partial view of the disease context and failed to mention current and important evidence, such as the European Guidelines on syncope[7].

Other authors have also questioned the validity of HUTT[3,4]. With regard to sensitivity and specificity, some people consider that the results are very different, depending on the method used, specially the degree of tilt, duration of the passive phase, the use or non-use of sensitizing drugs and the type of population studied. The variation in results is justified exactly by the evaluation of studies that use very different methodologies, which is one of the reasons that led to the standardization of the test in the European Guidelines. Petkar e Fitzpatrick[3] criticize the low sensitivity of the test with only the passive phase and the decrease in specificity when sensitizing drugs are used. The authors illustrate the low specificity by mentioning a study that found 55% false positives in a test sensitized with isoproterenol[3,37]. However, in this study, the tilt test was carried out with a tilt of 80 degrees, which is known to reduce the specificity and it is not recommended[1]. Likewise, when one analyzes more recent studies, it is possible to notice a significant decrease in specificity when, in sensitized protocols, the duration of the passive phase is equal to or more than 30 minutes. Protocols with shorter passive phases, or even without a passive phase, followed by sensitization with nitrate or isoproterenol, are linked with specificities that range from 84 to 97%[18,28,38], whereas, in studies that used a more prolonged passive phase, there was a decrease in specificities (48 to 70%)[9,11,15]. Therefore, limiting the total duration of the examination seems to guarantee good specificity.

The sensitivity of the passive phase alone is highly variable, but most studies have found low rates of positivity. When this phase lasted between 40 and 45 minutes, the sensitivities found were 13%, 25%, 31% and 35%[9-11,26]. It was only when the duration was 60 minutes that the positivity increased to 75% yet the specificity decreased to 89%[12] . As for the tests sensitized with nitrate, for example, the sensitivity varies between 53 and 87%[9,11,13-15,17,26].

Considering that the combination with drugs significantly increases the sensitivity of HUTT and that the decrease in specificity may be acceptable, the combined protocol is most suitable for clinical use in the diagnostic investigation of syncope.

Tilt test in the prognostic evaluation

Some studies have been conducted to evaluate the ability of the HUTT result to predict the clinical evolution[4]. Hachul et al[39] reported that, after the institution of the treatment for Vasovagal Syndrome, the HUTT with negative result was associated with the lower recurrence of symptoms in relation to the positive result (4.9 *versus* 52.4%, in 12 months, $p<0.0001$). Bastos et al[40] analyzed the capacity of the test to predict the recurrence of symptoms after discontinuation of medication and they found that 84% of patients with positive HUTT, under this condition, developed the symptoms again after being monitored for 12 months. Moreover, the average time for the first relapse was significantly shorter in patients with positive test compared to those with a negative test. However, some authors found different results. Grim et al[41] monitored 80 patients with whom the HUTT test had been carried out, with at least one prior episode of syncope. Only 14 patients of such patients had a positive result. After monitoring the patients for 23 months, on average, the authors concluded that the result of the HUTT was not useful to predict the clinical course of patients, but the presence of two or more previous episodes of syncope was. Sheldon et al[42] demonstrated that the risk of syncope in two years was similar among patients with positive and negative HUTT. The test method used was a single phase sensitized with isoproterenol, at a tilt of 80º and maximum duration of ten minutes, which is quite different from what is used today.

The ISSUE study is also used by some authors to justify the low prognostic value of HUTT[3,4,43]. One hundred and eleven patients were included, and only 29 of them (26%) had a positive HUTT. A device to monitor electrocardiographic events (loop recorder) was implanted in all patients, and it was possible to notice that there was a relationship between the HUTT positivity and the bradycardias recorded in the event monitoring device. However, the etiologic diagnosis of syncope was possible in only 20 (18%) patients (16 due to asystole lasting longer than three seconds, three due to severe bradycardia and one due to paroxysmal supraventricular tachycardia), despite the use of an implantable device that could monitor events for up to 15 months. The small number of patients with positive outcome in each one of the tests makes it difficult to reach a more reliable conclusion on the data.

In a recent study, 276 patients diagnosed with VVS were monitored for two years. The HUTT, which was carried out

as recommended by European guidelines, was positive in 37% of patients. The positive predictive factors for syncope recurrence were the number of prior syncope events, female gender and bronchial asthma, but not the HUTT[44]. Therefore, before the emergence of new studies, the result of HUTT does not seem to be useful in the prognostic evaluation of syncope.

Tilt test in evaluation of the therapeutic response

With respect to the repetition of HUTT to assess the therapeutic response, two variables should be discussed. A possible limitation of this analysis is the poor reproducibility of HUTT when the first result is positive, which ranges from 31 to 92%[1]. On the other hand, the reproducibility of the negative test is better - 85 to 94%[1] . Another variable is the very failure to define which medication is really effective in treating the disease. There have been attempts to explain the failure of the therapy with metoprolol, by attributing the cause of such failure to the selection of patients with positive result in the HUTT sensitized with isoproterenol[4,45]. However, a randomized and controlled study with atenolol also showed no reduction in symptoms, although the selection of patients was based on the clinical characterization of vasovagal syndrome, regardless of the outcome of HUTT[46]. The failure of the therapy with the use of a pacemaker has also been attributed to the selection of patients with bradycardia during the HUTT[3,4]. However, further studies are needed to define the efficacy of artificial cardiac stimulation and, this way, justify the negative results of previous studies by a selection bias.

When is the tilt test most important?

Even though the prognosis of patients with syncope and without heart disease is excellent, many of them are tormented by the absence of a definitive diagnosis, and the subsequent anxiety may result in more frequent episodes of vasovagal syncope. Another good example of the importance of the tilt test is the investigation of patients with a history of sudden syncope and with negative cardiac evaluation. The HUTT can reproduce the syncope without prodromes, which occur either because the patient does not notice the drop in blood pressure or heart rate, or because the hemodynamic collapse develops very quickly.

The VVS is responsible for 31 to 34% of the syncope cases in the elderly[47,48] In this population, it is especially important to perform the HUTT after the cardiac causes are ruled out, because the correct diagnosis and appropriate treatment can prevent falls and complications resulting from the syncope, such as fractures and subdural hematoma. In addition, the HUTT increases the chance of identifying carotid sinus hypersensitivity, which is linked with up to 20% of syncopes in the elderly[49]. The test is also very useful in the differentiation with epileptic symptoms, and the identification of the dysautonomia syndrome in these patients avoids the social limitations imposed by the diagnosis of epilepsy and side-effects resulting from the anticonvulsant medication[50].

In addition, it is possible to characterize the psychogenic syncope during the HUTT, when the patient simulates the syncope episode, without any sign of related hemodynamic change[51]. Other diagnoses associated with syncope, such as orthostatic intolerance and Postural Orthostatic Tachycardia Syndrome, also may be revealed or confirmed by HUTT.

Perspectives

In an attempt to improve the specificity of the test and patients, shorter HUTT protocols have been tested. In this sense, the methods under study have evaluated the reduction in time or the exclusion of the passive phase, and the results so far are conflicting.

In patients with unexplained syncope, Bartoletti et al[38] compared the results of passive tilt for 45 minutes *versus* tilt with nitrate preceded by a passive phase lasting only five minutes. In this study, the positivity rate was significantly higher with the classic 45-minute-long method (51% versus 35%, p=0.04), suggesting that a longer passive phase would be necessary before administering the nitrate. However, this conclusion differs from other studies. Aerts et al[52] assessed the HUTT with nitrate preceded by three passive tilt protocols: 45 minutes, 30 minutes and without passive phase. The authors found sensitivities of 87%, 77% and 76%, respectively, and almost unchanged specificity of 83%, 83% and 82%, respectively. There was little difference in accuracy, although not statistically significant, of 78%, 80% and 71%, respectively. In addition, in this study, the sensitivity found was greater than in the study of Bartoletti et al[38]. This is a probable consequence of the selection of patients with typical clinical history of vasovagal syncope.

More recently, Aerts and Dendale[28] analyzed the accuracy of HUTT without passive phase. The tilt test was carried out with thirty-eight patients and thirty healthy subjects after administration of 400 ug of sublingual nitroglycerin, for a maximum period of 30 minutes. The noted sensitivity was of 82%, the specificity was of 84% and the accuracy of 83%. The authors also reported that, when the results achieved at 15 minutes were analyzed, there was no significant decrease in sensitivity, which suggested that the test could be shorter. Furthermore, compared with previous studies, high sensitivity was found, which the authors attributed to the selection of patients that were strongly suspected of having vasovagal syncope.

The rate of false negatives in the HUTT during the investigation of vasovagal syncope is still significant - up to 30% when the nitrate is used[14]. Thus, new sensitizing drugs must be tested to reduce this rate. Examinations with false positives are less common, but studies show that, on average, 15% of patients with no history of syncope have a positive result. Undoubtedly, the elucidation of the mechanisms involved and the limits between the physiological response and pathological response will make it easier to interpret the test.

Other studies are also needed to define the usefulness of HUTT in the prognostic evaluation and treatment planning. On the other hand, the use for monitoring the VVS treatment depends primarily on the confirmation of the treatment effectiveness. Randomized and controlled studies have shown that some medications very used until some time ago and the use of implantable devices are not effective in reducing syncope events[45,46,53].

Conclusions

The head-up tilt test (HUTT) is a helpful tool in the investigation of unexplained syncope. The indiscriminate use, without well-demonstrated methodological criteria, may compromise the credibility and importance of HUTT.

The test plays an important role in the differential diagnosis and it has been essential to help understand the hemodynamic changes related to dysautonomia. Perhaps, with the evolution of knowledge about the physiopathology and the treatment of these diseases, the results of HUTT can also be used in therapeutic guidance.

The HUTT methodology has been improved over time. Thus, the proposed protocols should be evaluated considering possible false positives and false negatives, and future studies should be aimed at the development of methods that are more accurate without loss of specificity.

In conclusion, HUTT is an important noninvasive test in the diagnostic evaluation of unexplained syncope, but it has limitations and sometimes it is not capable of defining the diagnosis. However, these imperfections do not justify abandoning the test. Instead, they justify trying to improve the technique. In clinical practice, HUTT is widely recognized, but the indication must be careful and the protocols shall be in accordance with what was proposed in international standards, so as to enable the correct interpretation of results.

Potential Conflict of Interest

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