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Original Article

The Tilt Test in the Assessment of Syncope and Pre-syncope. Effective and safe? Analysis of a Series of 2364 Patients over 6 Years

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ABSTRACT

The tilt table test (TT) provides relevant information about individual susceptibility to neuro-mediated hypotension and bradycardia. Its importance has been questioned. In this work, we analyze the results and safety of TT in the investigation of syncope, presyncope or postural dizziness. Cross-sectional study, with TT exams performed by specialists in cardiac arrhythmias, in the period 2016-2021, in a syncope unit. Analyzes were performed using the Mann-Whitney test, multiple logistic regression, with a significant p value <0.05. The protocols used were Westminster or Italian protocol. There were 2364 TT performed, 61.7% female, aged 51.1 (31-71) years. The positivity rate was 32.6%, 37.2% with pharmacological sensitization (p< 0.01). For the investigation of syncope, positivity was 34.2% (477) x 30.65% (285) for other symptoms (p<0.001), while evaluating syncope and presyncope together the difference was 37.55% (623) x 20.9% (139) for other symptoms (p<0.001). Positivity was higher in males (p<0.01; OR=1.40(1.16-1.69)), in sensitized tests (p<0.01;2.01(1.64-2, 38)), in patients with early orthostatic hypotension (OH) with symptoms (p <0.01; 9.68(4.13-27.44)). The complication rate was 3.29%, but without severity. The TT remains an important and safe methodology in clinical practice for the investigation of patients with suspected neurally mediated syndromes.

KEYWORDS: Primary Dysautonomias; Orthostatic Hypotension; Tilt-Table Test; Vasovagal Syncope.

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INTRODUCTION

AThe orthostatic tolerance test or tilt table test (TT) provides relevant information about individual susceptibility to neuromediated hypotension and bradycardia, being indicated for the investigation of syncope, pre-syncope and dysautonomic conditions[1]. The method has been criticized due to variability in its sensitivity and specificity, and its importance has been questioned with the advent of implantable cardiac monitors[2].

Vasovagal syncope is the most common cause of syncope in the general population, with a favorable prognosis. Some cases may, however, present with severe clinical forms, convulsive syncope and prolonged asystole documented in the TT or implantable looper[3]. Treatment may involve preventive clinical measures, various drugs, such as mineralocorticoids, alpha-adrenergic, cardiac pacemaker implants in well-selected cases or, more recently, ablation of the vagal plexuses in the right atrium[4].

Patients with diabetes mellitus, Parkinson's disease, cognitive dysfunctions such as Lewy body dementia, amyloidosis, renal failure and several other pathologies can often develop dysautonomia, with various clinical manifestations that can be evaluated during TT[5].

In this work, we analyzed the results and safety of the tilt test in investigating syncope, pre-syncope or postural dizziness. As secondary objectives, we analyzed the predictors of TT positivity.

METHODS

Cross-sectional study, with analyses of continuous TT exams carried out by 5 specialists in cardiac arrhythmia from 2016 to 2021 in a private specialized unit for the investigation of syncope (Syncope Unit), a reference in the region that has carried out these tests for 20 years. The protocols used were the Westminster or Italian protocol, with a sensitization phase of 1.25 mg of sublingual isosorbide after a 20-minute passive phase, with sensitization being used according to the doctor's assessment during the examination.

The exams were requested from several other services and professionals from different areas, such as clinicians, geriatricians, neurologists and cardiologists. The exam was considered positive in the presence of significant hemodynamic changes, especially if accompanied by symptoms. If there was the reproduction of prodromal symptoms or during positivity, the test was considered true positive, with the information made available in the report. In the presence of characteristic symptoms and relevant hemodynamic changes, the examination was immediately interrupted, and the table was returned to its normal zero-degree position or to the Trendelenburg position if there were symptoms and important hemodynamic changes[6,7].

The international classifications for the types of response during the exam were followed, being divided into vasovagal (vasodepressor, cardioinhibitory or mixed), psychogenic or postural orthostatic tachycardia type response (*SPOT* or POTS). The classification of positive responses is: mixed type, when the heart rate (HR) falls at the time of syncope but not below 40 bpm. In this context, blood pressure (BP) falls before HR. Type 2 or cardioinhibitory occurs when the HR drops below 40 bpm or asystole occurs for over three seconds. The drop in BP precedes or coincides with the drop in HR. Regarding type 3 or vasodepressor, HR does not fall by more than 10% related to the peak at the time of syncope, and blood pressure drops to < 90 mmHg or < 60 mmHg in relation to baseline. In Postural Orthostatic Tachycardia Syndrome (POTS or SPOT), there is an excessive increase in HR (i.e., greater than 130 bpm) both at the beginning and during most of the tilt, usually with a mild hypotensive response. The psychogenic response occurs in the presence of symptoms of pre-syncope or syncope without significant hemodynamic changes to justify it and is called pseudo-syncope[8,9].

The examination room had cardiac resuscitation material, cardiac defibrillator, material for venous access, intravenous hydration, and the examination was always accompanied by a specialist in cardiac arrhythmia and a nursing technician [8,10].

The decision to sensitize the test was carried out according to the doctor's request; however, with strict judgment from the person performing the test, the aim was to minimize complications. Patients with baseline hypotension (systolic

pressures less than 100 mmHg), very frail or with recent clinical comorbidities were not sensitized, as were those using phosphodiesterase inhibitors such as sildenafil or similar.

Statistical analysis

The variables were analyzed in relation to the normality test using the Kolmogorov-Smirnov method. Normal variables were described as mean and their respective standard deviation, and non-normal variables as medians with their 25-75% interquartile ranges. Categorical variables were described as percentages and their standard deviations.

When applicable, comparative analyses were performed using the t-student or Mann-Whitney tests, chi-square for categorical variables, with a p-value less than 5% considered significant.

Comparative analyses were also carried out using multiple logistic regression, with a p-value <0.05 considered significant. The explanatory variables were selected by the stepwise method, using the Akaike information criterion.

Data were analyzed using Stata/SE software version 12.1 (StataCorp LP, College Station, TX, USA).

Ethical aspects

The data described in the Declaration of Helsinki were strictly observed. The work was approved by the Ethics and Research Committee of the Federal University of Ceará/PROPESQ, with opinion number 5.542.323 and CAAE 59920822.6.0000.5054.

RESULTS

Two thousand three hundred sixty-four (2,364) tilt tests were analyzed, with 25 incomplete data, 61.7% female and 37.5% male, with a median age of 51.1 (31-71) years. The overall positivity rate was 32.6%, 37.24% with pharmacological sensitization (p < 0.01). 1619 (68.05%) patients were sensitized during the tests (Table 1).

Table 1. Results of tilt test exams and hemodynamic responses.

VARIABLES	TOTAL
Total number	2364*
Tilt Positive Test	789(32,6%)
Tilt Normal Test	1550(66,27%)
Tilt sensitized test	1619 (68,05%)**
Positive Tilt with Awareness	602(37,24%)
Negative Tilt with Awareness	1010(62,62%)
Response Types	---
Vasovagal	681(29,12%)
Vasodepressor	380(16,25%)
Mixed	275(11,76%)
Cardioinhibitory	26 (1,11%)
POTS	36(1,54%)
Psychogenic	12(0,51%)
Dysautonomic	60(2,57%)
Complications	78(3,29%)
Prodromes	478 (20,22%)

*Numerical variables expressed as mean ± standard deviation or median with interquartile ranges 25-75. Nominal variables are expressed as numbers (%). Twenty-five (25) inconclusive answers or incomplete data. **p-value <0.01 for positivity with sensitization in relation to non-sensitization.
Source: Prepared by the authors.

In patients with tests requested to investigate syncope, positivity was 34.2% (477) compared to 30.65% (285) positive for other symptoms, being statistically significant concerning the overall rate (p <0.001), while in the investigation of syncope and pre-syncope analyzed together, the positivity was 37.55% (623) x 20.9% (139) of tests requested for other indications (p<0.001).

Positivity rates were higher in males (p <0.01; OR = 1.40 (1.16-1.69)), in sensitized tests (p < 0.01; 2.01 (1.64 -2.38)), in patients with orthostatic hypotension with symptoms (p <0.01; 9.68 (4.13-27.44)) or with OH without symptoms (p < 0.01; 2.93 (2.07-4.18)) (Table 2).

Table 2. Factors associated with the highest positivity rate in the tilt test.

Factor analyzed	Value of or*
Male	OR = 1,40 (1,16-1,69)
Older age	OR = 1,01(1,009-1,02)
Sensitized tests	OR = 2,01(1,64-2,38)
Orthostatic hypotension with symptoms	OR = 9,68(4,13-27,44)
Orthostatic hypotension without symptoms	OR= 2,93(2,07-4,18)

*OR- odds ratio; In parentheses is the confidence interval.
Source: Prepared by the authors.

The previous use of drugs that cause hypotension and the previous pathologies presented did not determine significance as predictors of a positive response. The complication rate was 3.29%, being higher in severe cardioinhibitory conditions (p=0.01) but without the need for hospitalization or death.

Types of responses

The response types were: 681 (29.12%) vasovagal; 60 (2.57%) dysautonomic; 36 (1.54%) POTS; 12 (0.51%) psychogenic. Of the vasovagal responses, 16.25% were vasopressors, 11.76% were mixed, and 1.11% were cardio inhibitory (Fig. 1).

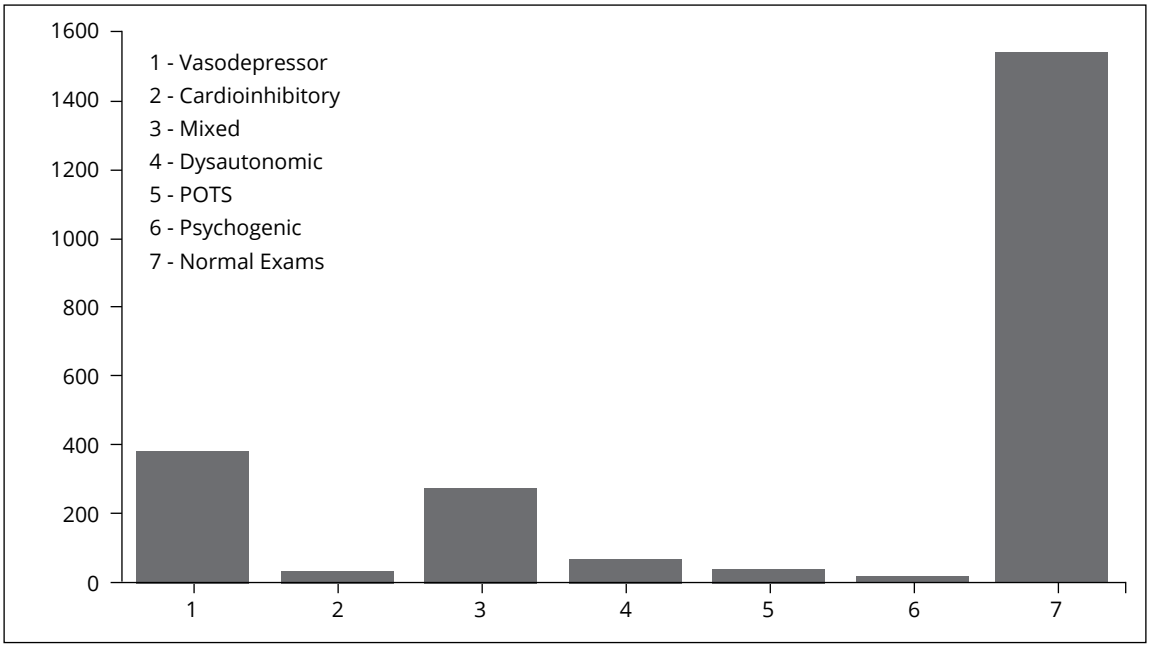


Figure 1. Types of responses during the Tilt test.
Source: Prepared by the authors.

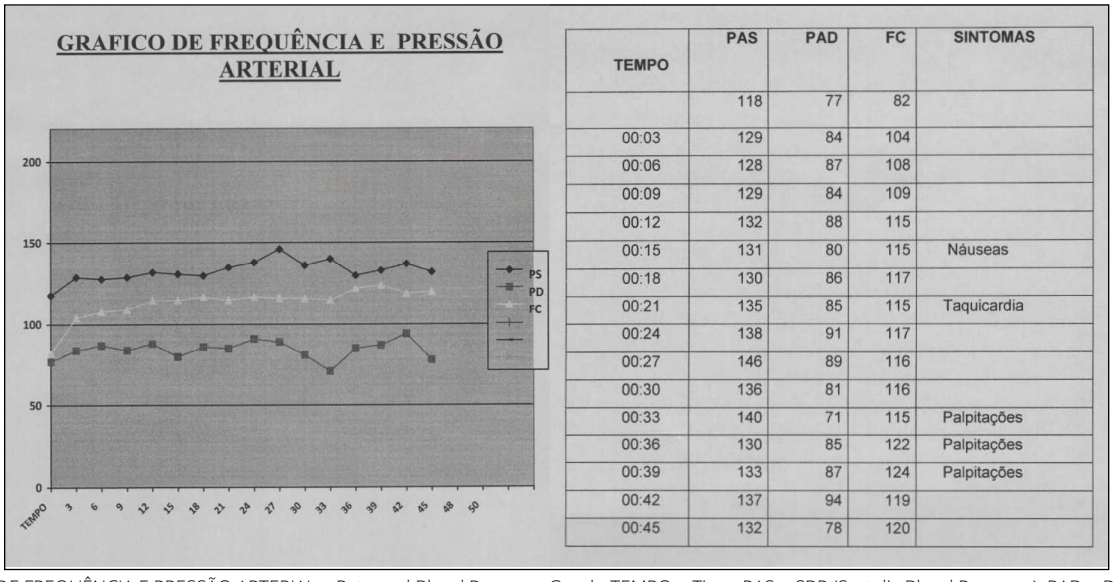
Prodromes were observed in 478 cases (20.22%), 155 (16.1%) in the elderly and 323 (23.3%) in the youngest (p<0.001).

What are the predictors of cardioinhibitory response (CIR) in TT?

Of the 26 patients with CIR, 20 underwent sensitization, and 6 were not sensitized (p=0.27). For an increase of one year of age, the odds ratio for the cardioinhibitory response was 0.98 (p = 0.017;0.96-0.99), approximately 2% lower than at the previous age. The other variables analyzed in the multiple regression did not obtain significant results. Cardioinhibitory responses were infrequent in TT exams in the general population when investigating syncope or pre-syncope, with no differences in sensitized tests, with age being a predictor of this type of response.

SPOT or POTS-type response

A total of 14 patients were previously suspected of SPOT, 42.8% (6) with positive TT, while 57.1% (8) had negative. In the group that did not have suspected SPOT, the values were 32.7% (756) and 67.2% (1554), respectively, with a p-value = 0.47. The symptom reproduction rate in patients with SPOT response was 52.7% (19) (Fig. 2).



TEMPO	PAS	PAD	FC	SINTOMAS
	118	77	82	
00:03	129	84	104	
00:06	128	87	108	
00:09	129	84	109	
00:12	132	88	115	
00:15	131	80	115	Náuseas
00:18	130	86	117	
00:21	135	85	115	Taquicardia
00:24	138	91	117	
00:27	146	89	116	
00:30	136	81	116	
00:33	140	71	115	Palpitações
00:36	130	85	122	Palpitações
00:39	133	87	124	Palpitações
00:42	137	94	119	
00:45	132	78	120	

GRAFICO DE FREQUÊNCIA E PRESSÃO ARTERIAL = Rate and Blood Pressure Graph; TEMPO = Time; PAS = SBP (Systolic Blood Pressure); PAD = DBP (Diastolic Blood Pressure); FC = HR (Heart rate); SINTOMAS = Symptoms; Náuseas = Nausea; Taquicardia = Tachycardia; Palpitações = Palpitations.

Figure 2. Postural orthostatic tachycardia (POTS) type response.
Source: Prepared by the authors.

Unusual cases

We describe some peculiar cases during the TT in our sample below.

Case 1. Female patient, 78 years old, with recurrent syncope for two (2) years, some episodes with rapid convulsive movements. He reported a stroke 23 years ago and epilepsy, without seizures for 11 years. The current situation was different from when she started anticonvulsants. She underwent cardiological examinations without significant changes. During TT, after sensitization, she presented lipothymia, followed by convulsive syncope and asystole for more than 30 seconds, with a total atrioventricular block (AVB). There was a reversal after the Trendelenburg maneuver, rapid external cardiac massage and intravenous hydration, with reproduction of the clinical picture. She underwent permanent PM implantation. During follow-up, she reported dizziness and sweating with documented hypotension, also associated with fludrocortisone. The patient has been progressing for 12 months without recurrences.

Case 2. LVR, 21 years old, with infrequent syncope for eight (8) years, occurring during body-piercing, watching horror films or seeing blood. Regular physical and laboratory examinations. In the TT without sensitization, he presented a short prodrome with dizziness, followed by convulsive syncope and asystole for 22 seconds, which quickly reversed after Trendelemburg. He opted for conservative clinical treatment with hygienic-dietary measures and general guidelines on

how to act to avoid the onset of prodromes, which progressed after five (5) years, without syncope, with some episodes of dizziness reversing after lying down quickly (Fig. 3).

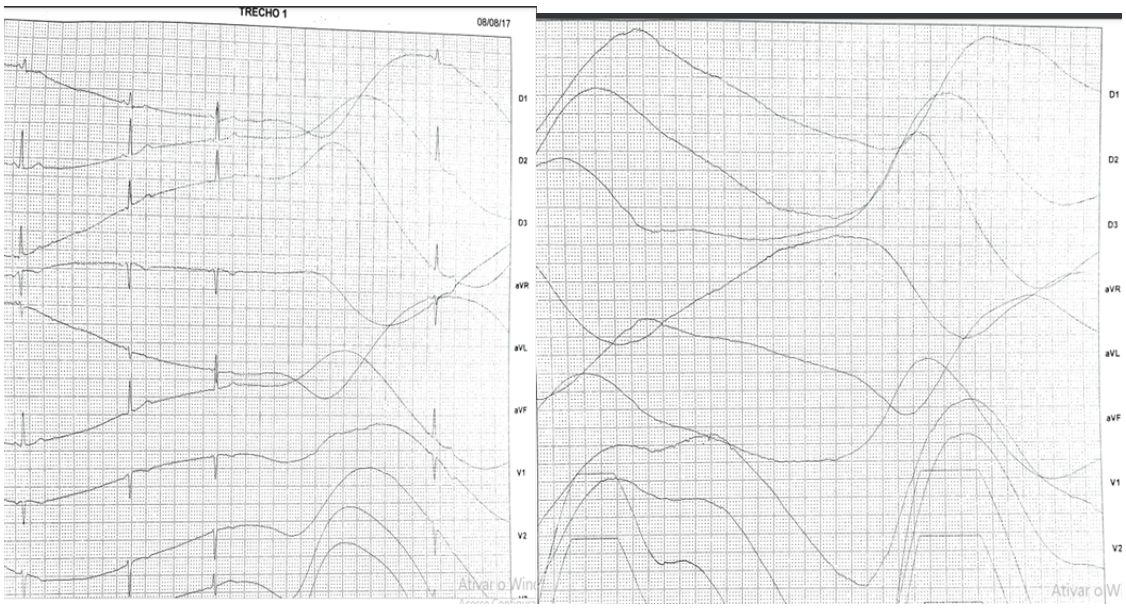


Figure 3. Patient with recurrent syncope, with prodromes, long intervals between attacks, with specific triggering factors and tilt test with a severe cardioinhibitory response.
Source: Prepared by the authors.

Caso 3. MC, female, 22 years old, with a history of more than ten years of multiple hospitalizations, with symptoms of loss of consciousness, with intensification in recent years, with trauma, with descriptions and videos showing tonic movements with upward gaze deviation, with pallor, recurrent falls, palpitations, with significant interference in their quality of life and that of their family. There was a history of sexual abuse in childhood and dependence on the use of morphine to treat fibromyalgia and herniated discs. Laboratory tests were performed with nonspecific findings. An electrocardiogram demonstrated sinus tachycardia (120 bpm), even lying down, with no changes in inclination. 24-hour Holter results were normal, with RR variability showing preserved sympathetic and parasympathetic autonomic balance. Electroencephalograms had negative results. In 2020, she underwent a TT with a report of pseudo syncope. In 2021, the picture was fully reproduced during a new TT recording without any correlation with hemodynamic changes. The diagnosis was made of Münchhausen Syndrome, according to criteria from the diagnostic manual for mental disorders (DSM-5), and the patient was referred to a psychiatrist. In the evolution, the family no longer returned for reevaluation, a situation described in the syndrome after confirmation of the diagnosis, remaining, however, with other hospitalizations and evaluations by other professionals. The case presented highlights the importance of understanding Münchhausen Syndrome due to the richness and variety of symptoms presented and the role of TT in excluding other etiologies since the diagnosis is rarely made by a psychiatrist but rather by a specialist.

DISCUSSION

The work presented demonstrates the importance and safety of using the tilt test to investigate syncope, pre-syncope, or postural dizziness in the general population, being a methodology that remains useful, particularly in developing countries[11].

Positivity rates follow the variations described in the literature, depending mainly on the characteristics of the population, the professionals who request it, the location of the test in tertiary or outpatient hospitals, the indications, and, therefore, the positive pre-test probability. Most of our cases were patients with unexplained syncope/pre-syncope symptoms, in which positivity is around 30-40%, similar to our study[12,13]. TT positivity can reach 70-90% in conditions with typically vasovagal

history, and it is crucial to reproduce the condition to initiate appropriate preventive measures and facilitate adherence to these measures by the patient[12,13].

In our study, the sensitization rate was high (68%), using a 20-minute passive phase protocol, followed by 20 minutes of sensitization with nitrate (1.25 mg of sublingual isosorbide)[14,15]. It is known that pharmacological sensitization in the test increases sensitivity but reduces specificity, potentially increasing the rate of false positives. Careful attention was paid to evaluating prodromal symptoms to determine the positivity of the test, thus defining a true positive test. In most cases, there was no need to wait for syncope to progress.

These observed positivity rates should not discourage the use of the method for diagnosing these clinical conditions, which are usually difficult to diagnose, such as in investigations of syncope unexplained pre-syncope, which may have diagnostic clarification rates of no more than 50% in the general population, being reduced with the advent of new research methods such as the implantable looper[11].

Criticisms of performing the TT due to positivity in other clinical conditions not responsible for the symptoms should be viewed with caution. The possibility of diagnosing susceptibility to neuromediated phenomena and not the actual causal determination of syncope needs to be analyzed globally, with the patient's symptoms during the test, the real reproducibility related to spontaneous events and the pre-test probability of the method. Streamlining this analysis will determine a high true positive rate. Positivity information also serves to therapeutic adjustments of hypotensive drugs or drugs that cause bradycardia, which can promote reductions in falls and fractures, and improve quality of life. Other cases with general non-syncopal symptoms but suggestive of reflex changes (neuromediated), with nausea, vomiting, pallor, cold sweating, and intolerance to orthostasis, may have a positivity rate of around 51-56%[10,16].

Detailed analysis of the result by a specialist doctor, especially in doubtful cases, together with the patient's clinical data and associated with the reproduction of the initial characteristics of the condition (no need to wait for syncope or convulsive movements in the test) and other exams already carried out will certainly help or define the patient's behavior. These precautions are necessary as it is known that 40% of patients with cardiac syncope may present a positive tilt test[17].

Implantable cardiac monitors (implantable looper) in the investigation of syncope have a higher cost, being an interventional procedure, despite very low risk, with more difficult access for some centers, depending on the experience of the operator to implant and monitor, not being, however, a strategy that competes with the tilt test, especially with suspected neuromediated conditions. In the looper, waiting for a new event to occur is also necessary before making a therapeutic decision.

Many elderly people do not present prodromes because they have difficulty perceiving them or, as in the case of patients with dysautonomia, they are used to low pressures in orthostasis, reporting symptoms mainly as fatigue, tiredness, dizziness, and sometimes they can progress to syncope and do not report prodromes. It is challenging to make differential diagnoses with cardiac syncope, which usually does not have prodromes18. Many of these cases can be diagnosed by TT, without the need for looper implantation.

The importance of TT for patients with dysautonomia is excellent, as they are patients with associated pathologies that evolve with falls, weakness, fatigue, and sometimes non-specific symptoms that precede syncope and should be diagnosed earlier to begin treatment and preventive measures. These patients have high morbidity and mortality. Groups with pathologies known to develop dysautonomia must be closely monitored by looking for symptoms and carrying out specific tests, such as the RR, Valsalva, Respiratory and 24-hour ABPM variability tests. The TT should not be the only or the most important in evaluating these cases[6,19].

Patients with SPOT were predominantly young, represented a small percentage of our tests, reproduced the symptoms in most cases and had predominantly no prior suspicion of postural orthostatic tachycardia syndrome.

Therefore, we believe that our study contributes to demonstrating that in reality, the tilt test is still a widely used and safe method, being able to diagnose a wide variety of pathologies, from vasovagal syncope to dysautonomic syndromes, in addition to psychogenic conditions, tachycardia syndrome posture and assist in the assessment of chronic fatigue. The method should definitely remain in the evaluation of syncope and pre-syncope, in addition to syndromes that evolve with

symptoms of orthostatic intolerance. Adequate interpretation and clinical correlation are fundamental for management and prognosis.

Limitations

This is a cross-sectional study, carried out in a single center, with professionals specialized in the area, in a non-hospital environment, with exams requested for different causes and by several different professionals, therefore with a lot of heterogeneity, which may not represent the data of the general population and the population treated in emergencies or in cardiology centers. The data, therefore, must be considered within the context of our study population; however, they reinforce that the method is safe and effective for the elderly.

Assessments of responses due to carotid sinus hypersensitivity during the tilt test were not considered in this work, and the positivity of the test may, therefore, be higher in the general context.

CONCLUSION

The tilt table test continues to be an essential and safe methodology in investigating patients with suspected neurally mediated syndromes in clinical practice in Brazil. Positivity was higher in patients investigated for syncope compared to pre-syncope and other symptoms. Male sex, pharmacological sensitization and orthostatic hypotension were significantly associated with positivity. The exam showed a low rate of complications.

CONFLICT OF INTEREST

Not applicable.

FUNDING

Not applicable.

DATA AVAILABILITY STATEMENT

Survey data will be provided upon request.

AUTHORS' CONTRIBUTION

Conception and drawing: Rocha EAQA, Kubrusly BS, Gurgel AAA, Rocha EA; **Data analysis and interpretation:** Pinho LGB, Rocha EA; **Article writing:** Farias AGP, Coimbra VO, Gondim PS, Rocha MCT, Rocha MEQA; C**ritical review:** Pereira FTM, Marques V, Farias RL; **Aprovação final:** Rocha EA.

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