Elderly patients with unexplained syncope: What should be considered a positive tilt test response?

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Abstract

Introduction: Syncope is a common problem and can lead to serious consequences in the elderly. Tilt test is useful to investigate recurrent syncope, but few studies have investigated the hemodynamic responses of this population to tilt test.

Objective: To describe the tilt test responses of elderly patients with recurrent syncope of unknown origin and to determine the occurrence of altered cardiovascular autonomic function in a subset of those with the diagnosis of dysautonomic pattern to the tilt test.

Methods: Elderly patients (n=165; >60 years old) who sought medical assistance because of recurrent syncope during 18 months were initially enrolled and submitted to a two-stage, nitroglycerin-potentiated tilt test. A subset of patients who presented with dysautonomic response to tilt test performed clinical autonomic tests.

Results: The most frequent cause of syncope during tilt test was the dysautonomic pattern (43%), followed by mixed type neurocardiogenic syncope (35%). Most patients who remained asymptomatic during tilt test showed clear abnormal hemodynamic response during the exam.

Conclusion: Autonomic dysfunction, which can be found during tilt test, is probably an important cause of syncope in the elderly, regardless of the occurrence of symptoms during the tilt test.

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1. Introduction

Syncope, defined as the sudden loss of consciousness and postural tone with spontaneous recovery, is a very common problem, accounting for 1% of all hospital admissions and 3–5% of casualty department visits (Kapoor et al., 1982). In elderly people syncope is even more frequent. Among elderly confined to long-term care institutions, the annual incidence may be as high as 6%, with a recurrence rate of 30% and a 10-year incidence of 23% in people older than 70 years old (Lipsitz et al., 1985).

Syncope may present as a symptom of many different diseases, from benign ones, as neurocardiogenic syncope, to malignant and fatal others, as ventricular arrhythmias.

Nevertheless, syncope is a potentially disabling problem, with a great impairment in physical and psychosocial function. In elderly patients, syncope is even more important because of the various consequences of falling to the ground, such as head trauma.

Tilt test is a useful tool to investigate recurrent syncope (Brignole et al., 2004). During tilt test it is possible to evaluate blood pressure and heart rate responses to orthostatic stress and to vasodilator stimulus (usually sublingual administration of nitroglycerin). The main objective of tilt test is to determine which pattern of hemodynamic response is responsible for the occurrence of syncope or pre-syncope. On its turn, the pattern of hemodynamic response to tilt test may be a key factor to determine the cause of syncope, with direct clinical relevance as the prognosis may be quite different.

Some patients with syncope can exhibit a dysautonomic response during tilt test (see Methods). This response, also
known as autonomic failure response, is characterized by a minimal change in heart rate despite the marked blood pressure fall, during tilt test (Mathias and Bannister, 1999). Although not generally accepted, tilt test may be used to evaluate unexplained syncope in the setting of peripheral neuropathies or autonomic dysfunction (Benditt et al., 1996). Even when tilt test reveals a dysautonomic pattern response, the diagnosis of autonomic dysfunction can only be accomplished after further investigation. Usually, cardiovascular autonomic dysfunction can be easily and non-invasively investigated by analyzing the blood pressure and heart rate responses to different stimuli, such as static and dynamic exercises, deep breathing and standing (Mathias and Bannister, 1999).

The aim of this study was to describe the tilt test responses of elderly patients with recurrent syncope of unknown origin and to determine the occurrence of altered cardiovascular autonomic function in a subset of those with the diagnosis of dysautonomic pattern to the tilt test.

2. Methods

In a prospective study (duration = 18 months), 171 elderly patients (>60 years old) who sought for medical assistance because of recurrent syncope were initially enrolled. None of these patients were institutionalized in elderly care center. The patients were submitted to clinical history and examination and a 12-lead surface electrocardiogram and a full investigation to rule out cardiac and neurological causes of syncope. After this work-out they were referred by their physicians to our laboratory for tilt test evaluation. Each patient continued using his routine medications during the tests. Patients with atrial fibrillation (n=2) or pace controlled heart rhythm (n=4) were not included in this study. The study’s protocol was submitted and approved by the Institutional Ethics Committee and all patients signed an informed consent before participating in this study.

Tilt test was performed in a quiet room with light, humidity and temperature control. During the whole exam digitally recorded 12-lead electrocardiogram (ECG 98® Heart Ware, Brazil) and continuous blood pressure by digital infrared photoplethysmography (Finometer®, Finapres, Netherlands). Tilt test protocol was as follows (Brignole et al., 2004): (1) supine pre-tilt phase of 10 min; (2) passive tilting to an angle of 70°; (3) passive phase of 20 min; (4) drug challenge (400 μg of sublingual nitroglycerin) phase duration of 20 min; (5) carotid sinus massage (10 s of massage on each carotid sinus). Tilt test was interrupted if patient developed syncope or pre-syncope. The patients were divided in two groups according to the presence or absence of symptoms (syncpe or pre-syncope).

The possible hemodynamic responses during tilt test are described below (Grubb and Olshansky, 2005):

- Neurocardiogenic: sudden drop of blood pressure and heart rate. Divided in three types: vasodepressor (heart rate falls less than 10% of peak heart rate during orthostatic position), mixed (heart rate falls more than 10% of peak heart rate during orthostatism but no less than 40 bpm and there is no asystole) and cardioinhibitory (heart rate falls below 40 bpm or there is asystole of more than 3 s).

- Dysautonomic response: gradual decline in blood pressure with chronotropic incompetence (minimal change in heart rate).
- Postural hypotension: gradual decline in blood pressure with reflex tachycardia.
- Postural Orthostatic Tachycardia Syndrome (POTS): minimal change in blood pressure and great tachycardia (heart rate increase of more than 30 bpm or heart rate ≥ 120 bpm within 10 min of head up tilt).
- Carotid sinus hypersensitivity: carotid sinus massage, during orthostatic position, elicits 3 s asystole and/or a fall in systolic blood pressure ≥ 50 mm Hg.
- Physiologic response: fall of less than 20 mm Hg on systolic blood pressure during tilt test.

Another possible response to tilt test is psychogenic syncope, characterized by syncope occurring without significant hemodynamic changes. Usually this diagnosis can only be confirmed if cerebral blood flow (accessed by transcranial Doppler or electroencephalography) can be performed during tilt test, showing that cerebral perfusion was not impaired during the “syncopal” episode.

A subset of patients who presented with a dysautonomic response to tilt test (4 who presented syncope during tilt test and 5 with no symptoms during tilt test) were further submitted to a clinical autonomic evaluation with continuously recording of 12-lead electrocardiogram (ECG 98®, Heart Ware, Brazil) and blood pressure (Finometer®, Finapres, Netherlands). All clinical autonomic tests were performed in the same day, at least 3 h after a light meal, in a quiet room with controlled light, humidity and temperature. The following tests were performed by each patient (Benditt et al., 1996; Castro et al., 1992a,b):

- Response to respiratory sinus arrhythmia: the patient is asked to breathe from maximal to minimal respiratory capacity in a respiratory frequency of 5–6 breaths/min.
- Response to Valsalva maneuver: the patient blows with an open glottis into a mouthpiece connected to a sphygmomanometer and maintains a forced expiratory pressure of 40 mm Hg for 15 s.
- Response to isometric exercise (handgrip): sustaining handgrip of 30% of peak force during 5 min.
- Response to dynamic exercise (4 s test): patients were requested to pedal very fast, for exactly 4 s, with no resistance set (unloaded cycling) on a cycle ergometer. The test was performed at maximal inspiratory apnea, beginning 4 s before and ending 4 s after the exercise (Nóbrega et al., 1990; Araújo et al., 1992).
Abnormal responses of blood pressure and heart rate during these tests are respectively considered as sympathetic and parasympathetic dysfunctions.

Qui-squared test was used to compare medicine use and chronic disease between patients who presented with syncope during tilt test and asymptomatic patients. Unpaired $t$-test was used to compare age between groups. $P<0.05$ was considered statistically significant.

3. Results

During the period, 165 patients met the inclusion criteria (age $77\pm7$ years old; 80 males). One patient had the tilt test interrupted because of angina pectoris and another due to the occurrence of paroxysmal atrial fibrillation. Data from these patients was excluded from the study.

From the remaining 163 patients, 79 presented syncope or pre-syncope during tilt test. The distribution of the hemodynamic response patterns of these patients during tilt test is shown in Fig. 1. The most frequent cause of syncope during tilt test was the dysautonomic pattern, followed by mixed type neurocardiogenic syncope.

It is interesting to note that only 5.5% ($n=9$) of all patients exhibited physiological response to tilt test. Most patients, although not complaining of any symptom and not presenting with syncope or pre-syncope, showed clear abnormal responses. Dysautonomic pattern was the most frequent hemodynamic response not only in patients who presented syncope, but also in the asymptomatic group (Fig. 2).

Patients under regular nitrate administration and those with coronary artery disease were less likely to have symptoms during tilt test than patients who did not use this class of medicine or with other diseases. Clinical characteristics of both groups can be seen in Table 1.

As dysautonomic pattern was the most frequent hemodynamic response in both groups of patients, we decided to perform clinical autonomic tests in a subgroup ($n=9$) of patients with this pattern of response (4 with syncope during tilt test and 5 who were asymptomatic during the test). The presence of autonomic dysfunction was similar in both groups (Table 2).

4. Discussion

Syncope is a common problem in elderly patients, whose proportion in the population is increasing all over the world. Although most causes of syncope are benign, in elderly
patients syncope has an additional importance because it may lead to bone fractures and associate depression that may significantly alter quality of life (Lipsitz et al., 1985).

Tilt test is a useful diagnostic tool for investigation of unexplained syncope. Although patients may present altered hemodynamic response to tilt test associated or not with symptoms, currently, guidelines only consider a positive tilt test when impaired hemodynamic function and syncope are concomitant during tilt test (Brignole et al., 2004; Mathias and Bannister, 1999).

Interestingly, in our study, patients who currently use nitrates for relief of symptoms in angina pectoris presented fewer symptoms during tilt test. This may have occurred because these patients may be used to blood pressure drops consequent to vasodilatation. As we could not find any study where this hypothesis has been tested, this finding deserves further investigation.

Although tilt test potentiated with nitroglycerin has already been proved to be a specific and useful tool in the investigation of unexplained syncope in elderly patients (Mussi et al., 2001), there are currently few studies that have investigated the most common hemodynamic responses to tilt test in this population.

To our knowledge, there is only one published study reporting the responses to nitroglycerin-potentiated tilt test in asymptomatic older adults (Kumar et al., 2000). This study did not even mention possible responses other than neurocardiogenic to orthostatic stress. Actually, the same study showed that 52% of asymptomatic elderly individuals submitted to tilt test with sublingual nitrate provocation exhibited neurocardiogenic syncope response. Our study showed that even individuals who do not present syncope during the test, despite nitrate provocation, may have an unexpected hemodynamic response pointing to a dysautonomic pattern.

Petersen et al. (2000) have described the normal response to prolonged passive head up tilting in asymptomatic subjects of different age ranges. This study showed that patients older than 70 years presented a fall in systolic (less than 20 mm Hg) and diastolic blood pressures (less than 20 mm Hg) and mild increases in heart rate during tilt test.

Laitinen et al. (2004) investigated the age dependency of cardiovascular autonomic responses to tilt test in healthy subjects. In this study, although elderly subjects maintained their blood pressure in upright posture by means of increased peripheral resistance, whereas they increased heart rate less than the young volunteers, they also exhibited physiologic responses to tilt test. Comparing our results to the ones which investigated healthy elderly people, it seems clear that abnormal tilt test results should not be underestimated, even if syncope does not occur during tilt test. Unfortunately, there is no current guideline establishing how to manage patients with abnormal hemodynamic responses to tilt test, unless patient develops syncope during the exam.

The present study investigated the tilt test responses in 165 elderly patients with unexplained syncope. Only 47.8% of our patients presented with syncope during tilt test. Most of them had syncope because of a dysautonomic hemodynamic response (43%) or a mixed type neurocardiogenic response. In contrast, most studies found that neurocardiogenic syncope is the most common cause of tilt test induced syncope in elderly patients. Marangoni et al. (1996) submitted 59 patients to a prolonged drug free tilt test and found that 31% of them presented with neurocardiogenic syncope. The most common type of neurocardiogenic syncope usually described is the vasodepressor one (Brembilla-Perrot et al., 1996; Galetta et al., 2004). This was not found in the present study, where vasodepression was the cause of syncope in only 11% of patients, being the 3rd most common cause of syncope. Our study included all elderly patients with sinus rhythm that were consecutively investigated for unexplained syncope in our laboratory. No patient was excluded because of any disease or medication use. This may be the reason why our real-world study had some different results from previous ones.

Another interesting finding of the present study was the high incidence of dysautonomic hemodynamic response during tilt test in patients who presented syncope as well as in the asymptomatic ones. As previously discussed, although this is a known possible response to orthostatic stress (Mathias and Bannister, 1999; Benditt et al., 1996), it

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Syncope during tilt test</th>
<th>Asymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>78±3</td>
<td>83±8</td>
</tr>
<tr>
<td>Autonomic Dysfunction, n (%)</td>
<td>3 (75%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Mixed dysautonomy n (%)</td>
<td>2 (50%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Parasympathetic dysautonomy</td>
<td>1 (25%)</td>
<td>2 (40%)</td>
</tr>
</tbody>
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There was no difference in the frequency of autonomic impairment between both groups (P > 0.05).
is usually not described in syncope studies, where only neurocardiogenic syncpe is considered.

Tilt test is not the gold standard for the diagnosis of autonomic dysfunction. Thus, even when a dysautonomic hemodynamic response is found in tilt test, further investigation is needed. A practical and non-invasive alternative for the investigation of autonomic dysfunction is a group of maneuvers called clinical autonomic tests. Our study used these tests to evaluate whether patients with a dysautonomic hemodynamic response during tilt test really have impaired autonomic function. In our sub-group analysis, 60–75% of patients had autonomic dysfunction confirmed after a tilt test suggesting this diagnosis.

Nevertheless, patients with known dysautonomia (multiple system atrophy and pure autonomic failure) showed dysautonomic response during tilt test as previously described (Chandler and Mathias, 2002). Our results show that in patients with no other autonomic dysfunction symptoms other than syncope, further investigation is required before the diagnosis of autonomic dysfunction is done.

4.1. Study limitations

Although the present study did not include a control group, it seems in the literature (Kumar et al., 2000; Petersen et al., 2000; Laitinen et al., 2004; Marangoni et al., 1996; Brembilla-Perrot et al., 1996) that healthy elderly patients should exhibit a physiologic response to tilt test. Thus, the different responses obtained in the studied individuals during tilt test should be taken into account, even when patients do not present syncope or other symptoms.

In conclusion, the present study showed that the hemodynamic pattern shown during tilt test is of clinical relevance, even if there is no syncope during the exam. Also, dysautonomic hemodynamic response during tilt test is currently being underestimated in clinical setting. This response can point out for the presence of sub-clinical or initial autonomic disorder, and must be further investigated in elderly patients.

References


