

## Neurally Mediated Syndromes

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A syncope is a transient loss of consciousness because of reduced brain blood flow with loss of postural tonus followed by fast and spontaneous recovery. It is a common medical condition that accounts for up to 6% of hospitalizations, 3% of emergency consultancy episodes and high recurrence rate (34%)<sup>1</sup>. The medical term “syncope” comes from the Greek “syncopa”, meaning “to cut short” or “faint” in English and just “faint” in Portuguese. Hippocrates, one thousand years before Christ, reported that patients who suffered frequent faints usually died, whereas Engel reports that the single difference between syncope and sudden death is the fact that the patient wakes up in the first case<sup>2</sup>.

At the initial syncope evaluation, the physician should try to distinguish potentially fatal causes, such as hypertrophic cardiomyopathy; aortic stenosis; severe coronary insufficiency; total or advanced atrioventricular blockage; and sustained ventricular tachycardia from autonomic dysfunctions/disorders. It is known that syncopes in cardiac patients are related to a high mortality rate, whereas vasovagal syncopes point to increased morbidity<sup>1,3,4</sup>.

The study of syncopes has undergone a great deal of progress; for example, in the last decades, the understanding of the pathophysiological mechanisms of neurocardiogenic syncope and the possibility of diagnosis using the tilt table test. High resolution imaging testing, hemodynamic and electrophysiological studies have contributed to the large variety of complementary research methods, which can make the study highly expensive. In the past, syncopes of undetermined origin accounted for up to 50% of diagnoses. Today this rate has fallen to 20% to 30% at most<sup>5</sup>.

Clinical history and physical examination have been considered highly valuable for reaching diagnosis or for guiding adequate management. Many times these elements are considered enough, especially when combined with conventional electrocardiogram, providing diagnosis in 25% to 35% of cases and offering invaluable help in 30% to 75%

Blood pressure reduction following orthostasis over 20/10 mmHg in the first three to five minutes is called

orthostatic hypotension. Reductions below this level in the presence of clinical symptoms are called orthostatic intolerance.

Several disorders of the autonomic control have been associated with orthostatic intolerance: reflex syncopes (vasovagal or neurocardiogenic); Postural Orthostatic Tachycardia Syndrome; pure autonomic failure (acute and chronic, primary and secondary); and the multiple system atrophy (Shy-Drager Syndrome)<sup>4</sup>.

These conditions present specific characteristics and treatments very often differentiated. Orthostatic intolerance affects patients with intact autonomic nervous system in reflex syncopes, with the presence of transient disorders for exacerbated responses in susceptible patients. Autonomic failures have been identified in dysautonomia when the body has difficulties to compensate for the reduced venous return caused by orthostasis.

Changes in others organs and systems as well as signs and symptoms compatible with Parkinson's disease or cerebellar disorder (Shy-Drager syndrome) can be also observed in the presence of these autonomic nervous system disorders.

In the last two decades, with the introduction and routine use of the tilt test for studying these autonomic disorders, these conditions started to receive more attention from cardiologists and neurologists and the understanding about their mechanisms has improved. Tilt test determines the likelihood that a patient is susceptible to syncope or pre-syncope episodes due to changes in the autonomic system control.

Several terms have been used in the literature<sup>4</sup> to describe patients with orthostatic intolerance such as: irritable heart; neurocirculatory asthenia; hyperadrenergic orthostatic hypotension; vasoregulatory asthenia; idiopathic hypovolemia; orthostatic postural tachycardia syndrome; soldier's heart; partial dysautonomia; mitral valve prolapse dysautonomia. Many of these syndromes' manifestations and therapies are similar; however, it is very important to customize patient's follow-up and treatment. Symptoms of some patients are mild fatigue, discomfort or dizziness, whereas some others may present severe debilitating clinical conditions with higher morbidity.

### KEY WORDS

Syncope, vasovagal, dysautonomia.

The objective of this paper is to present a review of dysautonomic syndromes with their different clinical entities, pathophysiological mechanisms and treatment.

## **PATHOPHYSIOLOGY**

The evolution of the species and the adoption of orthostasis has triggered several implications for the neurocirculatory system. In the orthostatic position gravity displaces approximately 500-800ml of blood to the abdomen and lower limbs, reducing venous return and ventricular filling, which can reduce the cardiac output by 40%. In normal individuals, blood pressure balance is achieved in less than one minute. This initial pressure reduction activates the high pressure receptors in the aortic and carotid sinuses as well as pulmonary and cardiac low pressure receptors. Therefore, these receptors receive less stimuli and less afferent signs are sent to the spinal chord, where information is also sent to the nucleus of the vagus nerve (solitary tract) and the sympathetic nucleus (medially and laterally in the spinal chord). As a consequence, there is an increase in the sympathetic tonus, blood pressure and heart rate.

The heart takes part in this reflex arc due to the presence of mechanoreceptors, nonmyelinated C fibers, found mainly in the atrium, in the infero-posterior region of the left ventricle and in the pulmonary artery, and via the nucleus of the vagus nerve. Following orthostasis, stimuli on these receptors are reduced, which first triggers a sympathetic response, and eventually leading to increased cardiac rate<sup>10-15</sup>, pulse, diastolic arterial pressure (10 mmHg) and mild decrease or maintenance of the systolic arterial pressure. These reflexes are also activated by neurohumoral regulation, such as that from the renin-angiotensin system, serotonin (already recognized as a neurotransmitter that takes part in the blood pressure regulation)<sup>6</sup>, endogenous opioids and adenosine<sup>7</sup>.

In patients with predisposition to vasovagal syncope (likely to present excessive fluid retention in the lower limbs) the sustained adrenergic overstimulation activates the cardiac mechanoreceptors resulting in vigorous and fast ventricle contraction, with reduced internal volume. This eventually triggers a reflex response with parasympathetic hyper-activation and cessation of the sympathetic activity, resulting in a sudden decrease in blood pressure and cardiac rate.

It is known that the activation of the limbic system triggered by emotions or by strong stimuli, such as the sight of blood, can also trigger vasovagal responses<sup>8</sup>, suggesting that there are other central mechanisms involved in this reflex. This has already been demonstrated with the use of the transcranial Doppler ultrasound that shows reduced brain blood flow as a primary effect of the reflex, with paradoxical cerebral vasoconstriction<sup>9,10</sup>.

Kochiadakis et al.<sup>11</sup> have shown that neurohumoral changes occur at the beginning of the tilt test and are observed in normal individuals, with increased sympathetic and decreased parasympathetic activity. Patients with positive tilt test do not show those changes immediately after the table is tilted; a slow and parallel decrease in

both sympathetic and parasympathetic activities, followed by increased sympathetic activity before the patient faints and sudden decrease afterwards<sup>11</sup>.

Many patients with partial dysautonomia or vasovagal syncope present with decreased tonus of the vessels of the lower limbs, some denervation of the lower limbs and hypersensitivity to alpha 1 and beta 1 adrenergic receptors, in addition to reduced plasma renin activity<sup>7</sup>.

Failures of the early mechanisms described affect patients with dysautonomia, partial or not, differently from vasovagal syncopes. The failures can be aggravated by the patient's blood volume, position during long orthostasis and use of drugs such as vasodilators, antihypertensives, anti-Parkinson drugs, tricyclic antidepressants and alpha-blockers. Several common diseases also impair the integrity of the autonomic nervous system, such as diabetes mellitus, chronic kidney diseases, neoplasia, and neurological diseases such as Parkinson's, multiple sclerosis and Alzheimer disease –these are called secondary dysautonomias<sup>12</sup>.

Circulation is different during the passive tilt that takes place during the test and active orthostasis. The latter involves contractions of the muscles of the legs and abdomen, increasing peripheral vascular resistance (PVR) and the pressure in the right atrium, activating the heart's low pressure receptors. This determines a subsequent reduction in the PVR, up to 40%, and more than 20mmHg decrease in the blood pressure within seconds. The compensation mechanisms that take place are the same activated during the tilt test<sup>13</sup> (Tab. 1).

## **CLINICAL SYNDROMES**

### **Vasovagal syncopes**

Vasovagal, neurocardiogenic or reflex syncopes are responsible for the highest incidence of syncope in the non-selected global population, accounting for 50 to 80% of the episodes in some studies<sup>5</sup>. They affect patients from several age groups, although it is more common in young individuals, with no underlying heart disease. Several recognized factors can trigger them, such as excessive heat, prolonged orthostasis, fasting, hypovolemia, alcohol intake, sight of blood, fear and strong smell. Response to these factors is individual. It can be a single, self-limiting syncope, for example, in patients with acute diarrhea or debilitating acute infections.

Some patients have reflex or situational syncope with the involvement of the autonomic nervous system in the following situations: repeated cough episodes; micturition; defecation; swallowing; and after meals. The syncopes probably occur due to sudden changes in the autonomic tonus, intravascular volume and intracranial pressure.

Prognosis is good, with no mortality increase; however, patients with a high recurrence rate usually experience poor quality of life. These patients, along with those with episodes without the presence of prodromes or with syncope with trauma, usually require pharmacological therapy in order to reduce the number and type of

**Table 1 – Autonomic Disorders**

<b>Primary or Idiopathic Dysautonomia</b>	
1.0	Acute Pandysautonomia
2.0	Reflex Syncope
2.1	Vasovagal Syncope
2.2	Carotid Sinus Hypersensitivity
2.3	Situational
3.0	Pure Autonomic Failure Acute – Chronic
4.0	Multiple System Atrophy – cerebellar, parkinsonian or mixed forms (Shy-Drager Syndrome)
5.0	Postural Orthostatic Tachycardia Syndrome (POTS)
<b>Secondary Dysautonomia</b>	
1.0	Central
1.1	Brain Cancer
1.2	Age
1.3	Brain Tumors
1.4	Multiple Sclerosis
2.0	Peripheral
2.1	Afferent
2.1.1	Tabes Dorsalis
2.1.2	Guillain-Barré
2.2	Efferent
2.2.1	Diabetes Mellitus
2.2.2	Enzyme Deficiencies
2.3	Medullar
2.3.1	Mielite transversa
2.3.2	Siringomielia
2.4	Renal
2.5	Paraneoplastic
2.6	Collagen Diseases
2.7	AIDS
2.8	Amyloidosis
2.9	Alcoholism

episodes. Patients with vasovagal syncope present with several characteristics that distinguish them from dysautonomic patients; therefore, they should not be labeled as such. Total cardiovascular mortality in this group is not affected, but up to one third of patients may experience recurrence, especially the group with more than five episodes<sup>14</sup>.

Some signs and symptoms might suggest the diagnosis of vasovagal episodes such as clear triggering factor, malaise, visual darkening, dizziness (not vertigo), nausea or epigastric pain followed by pale skin, intense sudoresis, “cold sweat”, feeling of “be running out of blood”, vomiting and quick recovery. Presence of tonic-clonic movements does not rule out this diagnosis, especially if it takes place after the syncope and not parallel to it<sup>15</sup>.

### Carotid sinus hypersensitivity

Carotid sinus hypersensitivity may affect mainly the elderly, who experience dizziness, visual darkening, pre-

syncope and syncope when the carotid sinus region is compressed or manipulated, e.g. when they shave, wear shirts with tight collars or ties, for example. During the tilt test, a mild and fast (five seconds) compression is performed in the carotid region, one side at a time. This can be repeated after fifteen seconds with slight increase in the exertion and result is considered positive when the symptoms mentioned are present and correlated with pauses longer than three seconds and/or associated hypotension. The procedure should be avoided in patients with carotid murmurs and significant carotid artery atherosclerotic disease. Some authors have recommended that the maneuver is performed when the table is already tilted in order to enhance the result<sup>16</sup>.

The most common responses are sinus pauses or atrioventricular block during the massage, when the symptoms are triggered, which could indicate, in some cases, the need to implant a permanent pacemaker because the cardio-inhibitory component is extremely relevant in this syndrome. Patients with pacemakers may present more than 10% recurrence because of the vasodepressor component.

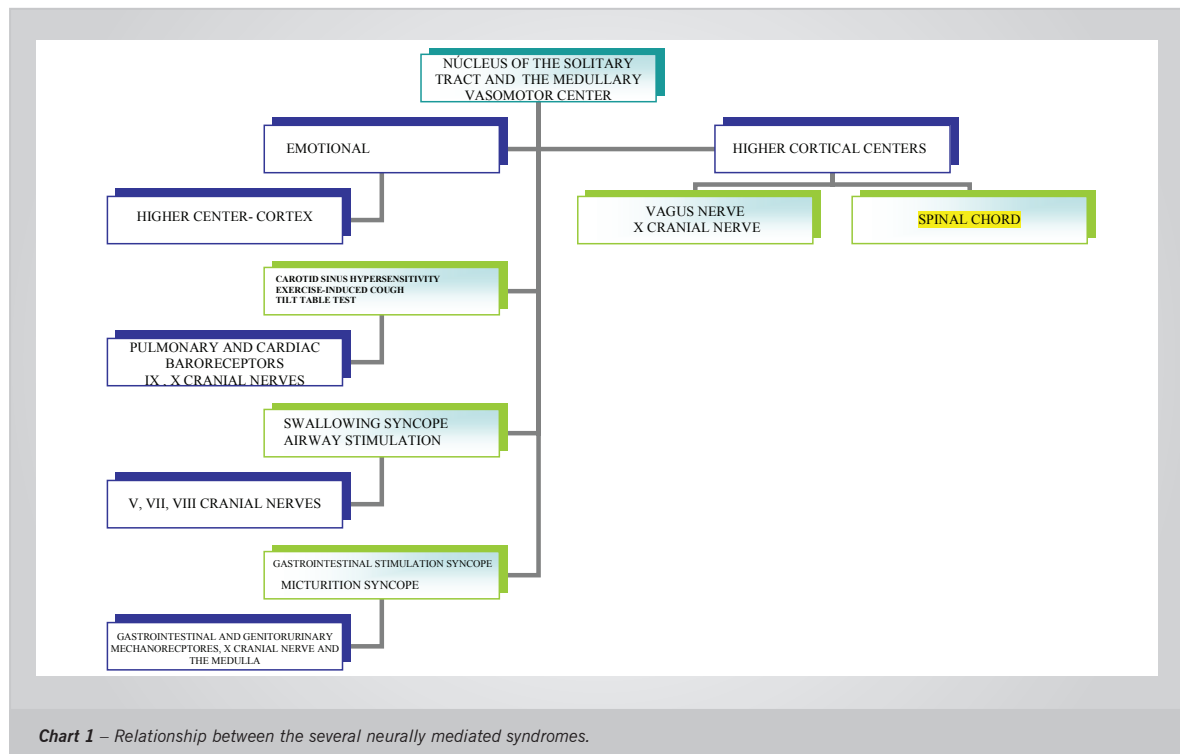
Some patients may respond positively during the compression test of the carotid sinus without any history of syncope or pre-syncope. Previous cervical surgery, cancer or radiotherapy in this region should be investigated. Because they are sudden, the pauses can be mistaken as Stokes-Adams syndrome.

The vasodepressor component should be gauged continuously by pressoric measuring methods and decreases above 50 mmHg combined with symptoms should be carefully studied.

### Dysautonomic syncope

Transient failures in the mechanisms involved in the arc-reflex occur in these syndromes. Their origin might be central or peripheral, secondary to failure in the afferent or efferent loops of the baroreflex, or a minor response of the organ to neurotransmitters. Several of these patients present a dysautonomic pattern of response when submitted to tilt test, with slow and gradual decline in their blood pressure, no significant changes in their heart rate, and symptoms of orthostatic intolerance triggered. (chart 1)

Patients with dysautonomia are more likely to present recurrent events, and differently from those with vasovagal syncope, show signs of impairment in other organs, such as urinary and fecal incontinence, changes in the gastrointestinal motility, anhidrosis or hypohidrosis, impotence and changes in the pupillary reflexes. Many patients in advanced stages present permanent and persistent symptoms of orthostatic intolerance, with pre-syncope, syncope and inability to deambulate<sup>17</sup>. Prognosis of these patients is usually reserved/poor, depending mainly on the etiology and stage of the disease<sup>18</sup>.



The multiple systemic atrophy or Shy-Drager Syndrome<sup>19,20</sup> is a progressive, degenerative disease, with gliosis and neuronal loss in several regions of the nervous system and clinical manifestations such as dizziness, lipothymia or syncope, postural hypotension, impairment of the cerebellar (olivopontocerebellar atrophy) or parkinsonian functions (striatonigral degeneration), with symptoms of rigidity and bradykinesia and less trembling compared to patients with Parkinson's disease. These patients do not respond well to levodopa. It is possible that many patients diagnosed as having Parkinson actually present this syndrome.

Pure autonomic failure, a less common condition with better prognosis, also impair the sympathetic and parasympathetic systems with the involvement of peripheral post-ganglionic neurons rather than promoting central changes. Levels of basal noradrenaline are reduced in this condition, differently from the Shy-Drager; however, both have mild increase of noradrenaline during the tilt test.

Acute dysautonomias are rarer, and the clinical picture is usually more severe because it affects younger individuals and its etiology can be self-immune. Damaged digestive and urinary systems, deambulation impairment, nausea, vomiting, abdominal pain and permanent bradycardia with chronotropic incompetence are also present. We observed this clinical picture in a 16-year old boy with history of severe acute dysautonomia events which required hospitalization. This patient presented decompensation related to recent infections, and further studies revealed that it was an autonomic failure with

exclusive involvement of the circulatory system.

Therefore, in spite of presenting syncope of cardiovascular origin as their main etiology, patients with congestive heart failure may have hypotensive and dysautonomic syncopes due to the insufficient cardiac output to compensate prolonged orthostasis, in addition to the use of diuretics, vasodilators, betablockers, cardiac consumptive conditions and neurohumoral changes<sup>21</sup>.

Patients with hypertension and autonomic dysfunctions represent a therapeutic challenge because it is hard to clinically and pharmacologically manage them. Patients with no history of hypertension, but after having developed some of the mentioned clinical syndromes, usually present hypersensitivity to vasodepressors<sup>22</sup> or even large variations in their blood pressure when this is verified by the ABPM - Ambulatory Blood Pressure Monitoring. Thus, ABPM is a useful complementary test for following up these patients. Low plasma levels of noradrenaline found in patients with supine hypertension and orthostatic hypotension suggest the involvement of other blood pressure control mechanisms, not related to the sympathetic nervous system<sup>22</sup>.

When managing patients with recurrent clinical pictures of syncope/pre-syncope, mainly the elderly, the common causes of these autonomic dysfunctions should be investigated, such as drugs currently used or underlying diseases with dementia (Alzheimer), neurological diseases such as Parkinson's, cerebellar disorder, multiple sclerosis, acute or chronic infections, severe diabetes mellitus with neuropathy, chronic renal failure, AIDS, adrenal gland or multiple gland insufficiency, alcoholism and cancer.

Many elderly patients can present sudden syncope

without the prodromes, contrary to what is expected in these situations, simulating Stoke-Adams Syndrome. This is usually confirmed during the tilt test, in which, in spite of the sustained hemodynamic changes patients do not show any symptoms until the syncope is suddenly triggered.

### Chronic fatigue syndrome

The manifestations of the chronic fatigue syndrome are chronic fatigue and tiredness (for more than six months)<sup>23,24</sup>, changes in the cognitive functions, myalgia, excessive discomfort, mainly following physical activity. It affects patients with no previous symptoms, when etiologies such as hypothyroidism, depression, adrenal gland insufficiency and other debilitating clinical conditions are ruled out.

Patients usually present extreme difficulty for doing their routine activities. Many individuals can tell the day symptoms started, and several patients have reported previous viral infections. It may be associated with neurally mediated hypotension<sup>23</sup>, with therapeutic response to this condition, although most individuals chronically sustain some symptoms.

No specific treatment or precise complementary tests for diagnosis are available; however, the tilt test has been widely used in order to obtain hemodynamic and clinical findings – present in more than 80% of this type of patient – that provide diagnostic confirmation.

### Postural orthostatic tachycardia syndrome (POTS)

POTS may represent a partial, mild form of dysautonomia, non-progressive in most cases. Patients with POTS present with fatigue, discomfort, dizziness, tachycardia and palpitations, mainly postural, and symptoms are reproduced during orthostasis or during the tilt test, when relevant increases in the sinus rate are observed in the first minutes of the test, with slight blood pressure decrease<sup>25</sup>.

This condition emerges when the peripheral resistance increase fails in the attempt to compensate the blood volume loss that takes place because of orthostasis, followed by a compensatory increase of the heart rate. Many patients are misdiagnosed as having panic attacks or inappropriate sinus tachycardia and are referred for further electrophysiological studies. POTS may manifest following viral infections<sup>26</sup>.

There is evidence that shows sympathetic denervation of the lower limbs, whereas some other patients present beta-adrenergic hypersensitivity.

Treatment with exclusive use of betablockers might not be a good choice because of the already mentioned pathophysiological mechanisms involved, and mineralocorticoids may be more effective.

### Tilt table test

The tilt table test is the method used to evaluate the causes of syncopes and lipothymia whose origin is related to autonomic nervous system dysfunctions. It was first described by Kenny et al.<sup>27</sup> in 1986, and it reveals up to 50% of the undetermined origin syncopes. This test can significantly reduce the number of tests patients with syncope of possible autonomic cause have to undergo<sup>28</sup>.

The sensitivity of this method ranges from 53% to 70%, attaining up to 80 to 85% with the use of isoproterenol<sup>29,30</sup>. Individual susceptibility to hypotension and/or bradycardia is determined based on autonomic nervous system reflexes<sup>31</sup> (Bezold-Jarisch reflex). Vasovagal responses for the tilt test might be vasodepressor (predominant sudden decrease of the blood pressure, without any changes in the heart rate), cardioinhibitory (blood pressure decrease following or concurrent to significant bradycardia or prolonged pauses) or mixed (blood pressure and heart rate changes). Other types of responses described are dysautonomic pattern, such as the POTS and the psychogenic response<sup>4,5</sup>.

Slow and progressive blood pressure decline, until symptoms are triggered, is observed during the test when there is dysautonomic response. Heart rate increase in the first ten minutes above 30 heart beats or above 120 beats per minute with triggering of symptoms of orthostatic intolerance is observed in the Postural Orthostatic Tachycardia Syndrome (POTS) response. Some patients are reported as presenting cerebral or psychogenic syncope because they present multiple symptoms, including syncope, with no correlation to blood pressure changes. As it has already been mentioned, some individuals might present symptoms of orthostatic intolerance, with changes in their brain blood perfusion which is not gauged in the regular protocol of this test whereas some others have the symptoms only due to their psychosomatic condition. The standard response during the tilt test can provide significant information for the management of these patients<sup>32</sup>.

The test is performed under adequate conditions, with the presence of a doctor and a practical nurse, under appropriate temperature conditions and continuous electrocardiographic and blood pressure monitoring. A special table designed to allow 60 to 80° tilting (70° is most commonly used) is used and the test involves 20-minute rest in the supine position and 45-minute head up posture at the tilted table. Isoproterenol<sup>30</sup> (1 to 2 µg/min), sublingual nitrate (1.25 mg) or spray (400 µg) can be used for pharmacological sensitivity enhancement in order to increase the heart rate by 30%. Higher dosages can affect the test specificity, ranging from 70% to 92%, with 62% to 77% reproducibility rate in seven days at most<sup>28,31</sup>. The risks involved for undergoing the test is extremely low. The use of the tilt table test to evaluate the therapeutic efficacy has been controversial as observed in different series<sup>31,32</sup>.

Several other methods have been described and are being evaluated, such as the use of sensitization agents in the first phase or shorter tests (twenty minutes) followed by pharmacological sensitization<sup>28,33</sup>.

The orthostatic stress induced during the tilt test is different from that present during spontaneous manifestations. The ISSUE study compared the syncope episodes induced during the tilt test with the spontaneous episodes registered by a implantable loop recorder of the cardiac rate, and its findings revealed that more severe bradycardia is present during spontaneous events<sup>34</sup>. (Chart 2).

## SAMPLES

A study<sup>17</sup> evaluated 152 patients with suspicion of primary or secondary dysautonomia. Fourteen patients presented with dysautonomic responses in the tilt table test, mean age of 73 years, 44% with concurrent visceral impairment, 35% with Shy-Drager Syndrome (primary pandysautonomia with neurological signs of Parkinson's or cerebellar disorders) and 23% with pure autonomic failure (component of exclusive orthostatic hypotension). Some patients had undergone chemotherapy and some presented severe conditions, such as stroke, multiple sclerosis, diabetes mellitus, alcoholism, AIDS and adrenal gland insufficiency, therefore with secondary dysautonomia. All patients presented favorable initial clinical response; however, recurrence, morbidity and mortality rates were high. We found that the severe initial clinical picture predicted therapeutic failure.

We carried out another study<sup>15</sup>, in which 117

patients were evaluated in a cardiology tertiary care hospital. They had presented 285 syncope episodes, and the cardiac causes were the most common (43.5%) – sustained ventricular tachycardia (17%), advanced atrioventricular blockage (11.9%), sinus node disease (6.8%), undetermined etiology (23%) and only 11.9% related to dysautonomia. The lowest incidence of the latter, contrary to what is described in the literature<sup>3,7</sup>, was a consequence of possible pre-selection of patients because the study was conducted with patients that had sought a cardiology hospital. As expected, this group presented higher mortality rate than the groups of patients with vasovagal syncope or with dysautonomia<sup>36,37</sup>.

High mortality rate was also observed in patients with syncope of established cardiac etiologies, as the congenital long QT syndrome<sup>33</sup> and the primary polymorphic ventricular tachycardia<sup>37</sup>.

In another study, we evaluated patients carrying the latest hi-tech cardiac pacemakers and we found that these devices can help diagnosing patients with symptoms of palpitations, pre-syncope or syncope due to the registration of endocavitary electrogram – EGM (electrocardiograms stored with information provided by implanted electrodes and recovered by telemetry by the programmers). As patients can activate the EGM with the use of a magnet, diagnoses of these symptoms due to arrhythmic causes can be clarified or ruled out.

## THERAPEUTIC ASPECTS

Customized treatment should be provided, taking into consideration the morbidity, recurrence of episodes and

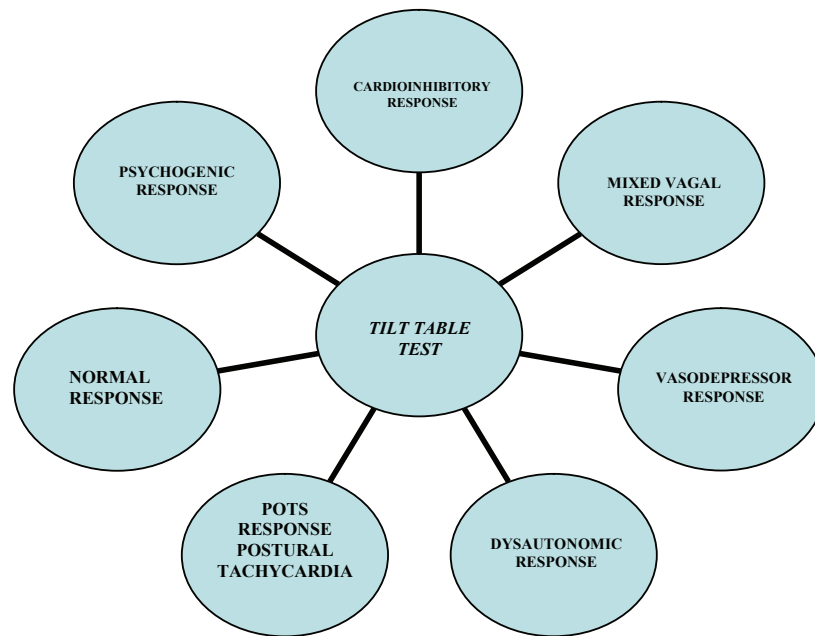


Chart 2 – Tilt Test Responses

interference in life quality, in addition to increased concern of family members, mainly of those who have witnessed the syncope. Therapy approach should be based on clinical history, age, diagnostic of the syndrome involved, presence of prodromes, trauma and other concurrent diseases such as hypertension. There is little evidence suggesting drug therapy in the presence of syncope and positive tilt test<sup>9</sup>, although most large treatment centers use it when the episodes are recurrent.

Adequate hygiene and nutrition recommendations<sup>4,9</sup> play an important therapeutic role because they help to calm down the patient, reassuring that most of these conditions (vasovagal) are benign or that it is possible to achieve clinical improvement (dysautonomia). Liquid and salt intake and the use of compression socks have been proven to be effective treatment measures, as well as the discontinuation of drug agents or the avoidance of potentially triggering situations.

Krediet et al.<sup>39</sup> have described effective maneuvers for reducing syncope episodes, such as the *handgrip* and the *crossing legs* that can be applied at the beginning of vasovagal symptoms. These isometric contraction movements increase the systemic blood pressure.

Recently, the TILT training method<sup>40,41</sup> has been used in order to reduce the recurrence of vasovagal episodes. It can be done at home following the first five sessions at a hospital, with 10 to 50-minute duration, once a day for five days, with an increase of the test duration of 10 minutes per day, followed by twice a day, in which the scapular region of the patient should be supported and his/her feet should be 15 cm away from the wall. The method can be also applied during the sleep. In that situation, the head rest of the bed should be at a higher position (30 to 45°) than the foot rest region<sup>42</sup> (Fig. 1).

Several drugs have been used; however, most of them show no significant scientific evidence in randomized trials that studied their efficacy or even when compared to control groups, which is extremely important in these conditions<sup>35</sup>. Atenolol, midodrine (alpha 1 adrenergic agonist of direct action) and paroxetine have shown to

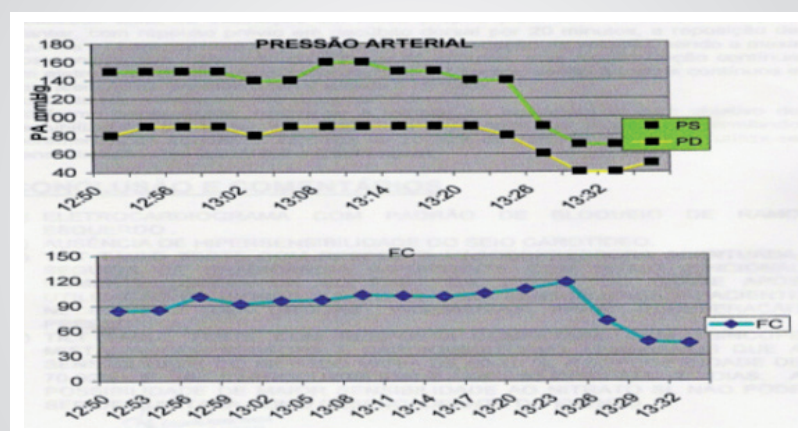
be effective at least in one prospective, randomized and placebo-controlled study<sup>9</sup>. Recently, at a congress of the American Society of Arrhythmia, a study with that profile was presented, and it questioned the effect of betablockers for controlling vasovagal conditions in which a group of patients younger than 42 years presented the poorest results, contrary to what had been shown earlier<sup>43</sup>. Mineralocorticoids, commonly used by patients with dysautonomia, have been very effective in some series, ours included; however, no large controlled study has been conducted (Tab. 2).

Pacemakers are being less used for this condition, restricted only to selected and non-respondent patients. The devices used have specific functions for vasovagal syncope, such as the rate drop response function. The non-randomized VPS I, VASIS and SYDIT studies have demonstrated the pacemaker efficacy in reducing the number of syncope episodes, but two randomized, double-blind studies (VPS II e SYNPACE) did not show any significant differences<sup>44,45</sup>. Nevertheless, some studies reveal evidence of reduction of number of syncope and increase in the prodromic time. The use of pacemakers should be limited for patients with marked cardioinhibitory components or for patients with syncope of the carotid sinus hypersensitivity.

Recently, the idea of establishing syncope research units have improved the management of these patients, reduced the number of unnecessary tests that a patient has to undergo and reduced the costs of diagnostic studies<sup>46</sup>.

## CONCLUSIONS

The clinical picture of patients with syncope is usually a consequence of changes originated in the autonomic nervous system, and it is important that cardiac etiology is ruled out as its cause due to poorer prognosis of this condition. The tilt test is very relevant for studying patients with autonomic dysfunctions, and its sensitivity, specificity and reproducibility rates are good. It can demonstrate significant hemodynamic changes and provides diagnosis



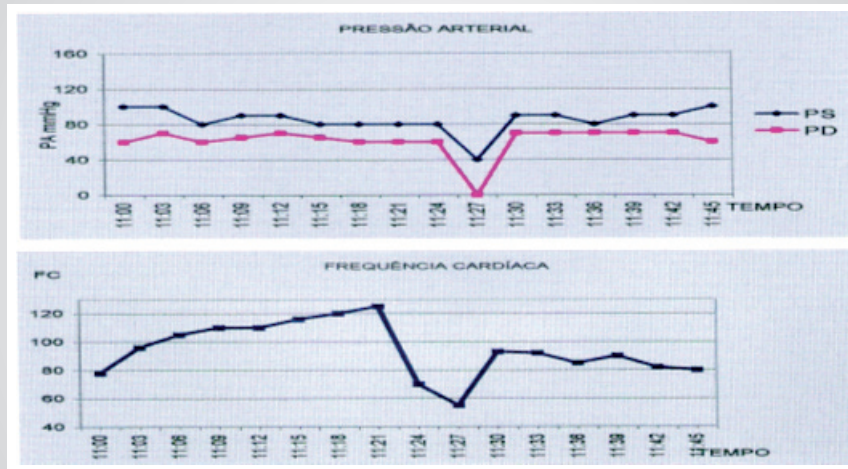
**Fig. 1** – Tilt test with positive and mixed pattern response. Heart rate increase before the test is positive may suggest benefit with the use of betablockers. However, some patients with bradycardia during the TILT have their conditions worsened with these agents (pro-syncope). Pressão Arterial - Blood Pressure

**Table 2 – Treatment of the neurally mediated syndromes**

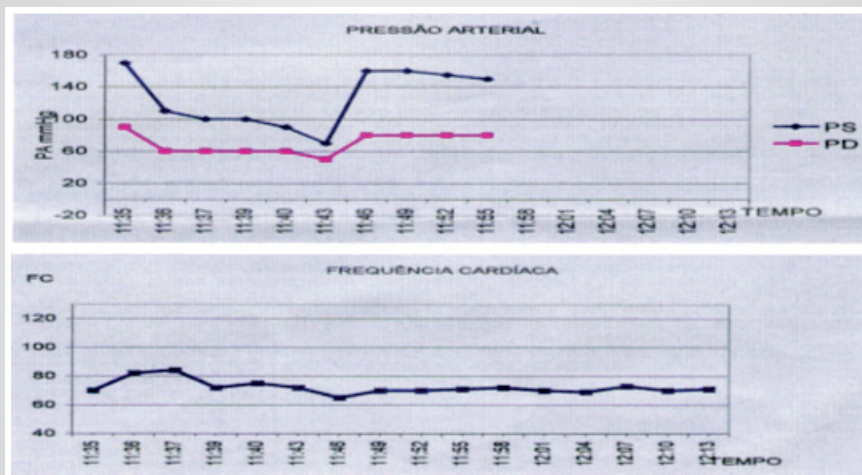
TREATMENT	USAGE/DOSING	ADVERSE EFFECTS
Salt and fluid intake Diet	> 3 L /day and 150-250 mEq of Na or ↑ 3 g of additional salt	Low compliance, edema, Systemic Hypertension or Congestive Heart Failure Decompensation
“Handgrip” and “crossing legs”	Symptom onset	Patient should avoid lying down immediately afterwards. Valuable at symptom onset
200 ml fluid intake before getting up or during a meal <sup>47</sup>	Acute BP increase in patients with dysautonomia	
Compression socks	30-40 mmHg to the waist, if possible	Warm, difficult to put them on
“Tilt training”	Once-twice /day	Low compliance, trauma
Bed inclination	30-45°	Fall off the bed
Light aerobic exercise	Improved venous return	It worsens if intense of in the absence of hydration
Betablockers – atenolol*, propranolol, metoprolol*		Hypotension, bradycardia, pro-sincope. Not effective in young individuals
Fludrocortisone	0.1 – 0.2 mg / máx. 0.4 mg. Very useful in orthostatic hypotension	Hypokalemia, hypomagnesemia, edema, headache, worsened CHF
Fluoxetine, paroxetine*, sertraline	20m / 50 mg /day	Nausea, anorexia, insomnia
Venlafaxine	75 mg XR	Nausea, anorexia, hypertension
Pyridostigmine	60 mg , twice a day	Nausea, diarrhea
Psychological therapy <sup>48</sup>		Improved self-esteem, confidence
Midodrine*	5-10 mg Q 4 hours	Hypertension, high cost (imported)
Erythropoietin	4,000 SC twice a week	High cost, injectable, ↑ hemotocrit
Disopiramide	150 mg twice a day	Low effectiveness, anticholinergic effects, pro- arrhythmia. No longer being used
Theophylline	100 -200 mg, twice a day	Trembling, nausea, arrhythmia
Double-chamber pacemaker with rate drop sense function	Automatically activated with heart rate reduction.	Invasive, permanent, expensive, not complication- free. It does not prevent the vasodepressor component
* Assessed by randomized studies.		

of the neurally mediated syndrome involved, and it also helps to determine the therapeutic approach. Not every patient with vasovagal syncope require pharmacological treatment – only those individuals without prodromes and with history of recurrent trauma and syncope. The therapy can start with the adoption of hygiene and nutrition measures and the use of drugs (mineralocorticoids, betablockers, serotonin reuptake inhibitors, peripheral vasoconstrictors, either alone or associated with other drugs). Cardiac pacemakers are used only for treating highly refractory cases, such as patients with cardio-

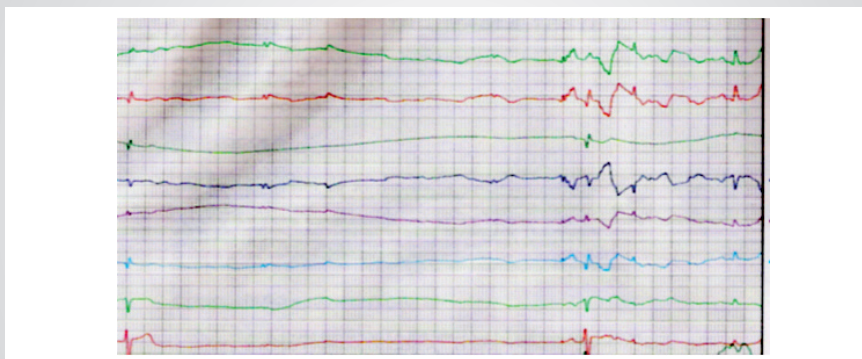
inhibitory syncope or carotid sinus hypersensitivity. The distinction between patients with vasovagal syncope and primary or secondary dysautonomia is crucial because this affects both treatment and prognosis, with increased morbidity for the second condition as well as increased mortality depending on the underlying etiology. Some patients present with Postural Orthostatic Tachycardia Syndrome (POTS) or the Chronic Fatigue Syndrome, conditions related to the neurally mediated syncope, and require specific therapeutic approach because of the major impact on their quality of life. (Figs. 2, 3 and 4).



**Fig. 2** –22-year old athlete patient, with history of recurrent syncope. The patient was admitted to a hospital with transient hemiparesis and disorientation. Neurological, hematological and immunological studies showed normal results. TILT test was clearly positive. Holter heart monitoring revealed inappropriate sinus tachycardia with mean heart rate of 103 and periods of increased sinus rhythm during orthostasis (compensatory). Major orthostatic intolerance with difficulty to ambulate. Therapeutic response to mineralocorticoid and betablocker. Control TILT test: normal. No recurrence in two-year follow-up. Pressão Arterial - Blood Pressure; Frequência Cardíaca - Cardiac Frequency; Tempo - Time



**Fig. 3** –Elderly patient, with lipothymia and syncope with positive TILT test with dysautonomic response pattern. Supine hypertension is observed in patient previously normotense, with slow decline of blood pressure after tilting up to symptoms onset. The patient was diagnosed as having Shy-Drager Syndrome. Pressão Arterial - Blood Pressure; Frequência Cardíaca - Cardiac Frequency; Tempo - Time



**Fig. 4** –33-year old patient, a teacher with recent history of seizures. Refractory to neurological treatment. TILT test (three times) showed severe cardio-inhibitory response with prolonged asystole during the 15-minute duration of the test, with seizures. The patient did not accept the implant of a permanent pacemaker. He is currently being treated with mineralocorticoids and serotonin reuptake inhibitor. Without any recurrence for a year. Pressão Arterial - Blood Pressure; Frequência Cardíaca - Cardiac Frequency; Tempo - Time

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