

# Consensus statement for the diagnosis and management of syncope. Argentine Society of Cardiology

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## 1. INTRODUCTION

Guidelines and Expert Consensus are documents that have as objective to present at the scientific community all relevant evidences available on a particular subject. The objective of its preparation is to help physicians to assess the benefits and risks of diagnostic and therapeutic procedures with respect to a particular pathology. Thus, these documents, although do not intend to replace the own criterion of each physician, they should be useful for daily clinical decision making. Syncope is a common medical problem affecting a high rate of the population at some point in life. While it may have a benign evolution, may also be the cause of serious injuries or may be related with fatal cardiac events.

The population with syncope is heterogeneous, so the prognosis varies significantly depending on its cause and with dependence of associated comorbidities. Thus, the assessment of syncope and respective risk stratification associated with it is so important and challenging.

Although international guidelines have been published for the management of syncope, as well as subsequent revisions, this is the first Consensus for Diagnosis and Treatment of Syncope produced by the Argentine Society of Cardiology which is published in the local environment.

Based on the available evidence and the needs and possibilities of the environment, a group of experts in the field developed the following guidelines in order to unify criteria and behaviours, rationalize diagnostic and therapeutic resources and establish guidelines for the clinical monitoring of syncope.

The level of evidence and strength of recommendation for each diagnostic or therapeutic option in particular is determined according to predefined scales, as shown in Tables 1 and 2.

## 2. DEFINITION

Syncope is defined to transient loss of consciousness and postural tone due to transient global cerebral hypoperfusion (TGCH), fast start, short duration and complete and spontaneous recovery. According to this definition, are excluded from the diagnosis of syncope those pathologies in which loss of consciousness does not involve a TGCH (epileptic attacks, psychogenic disorder). The concept of spontaneous recovery differentiates syncope from sudden death. (1, 2)

### 2.1. Classification and pathophysiology

Although the pathophysiological mechanisms that may lead to syncope are diverse, they all share as a common final via the fall in blood pressure leading to a TGCH able to cause unconsciousness within a few seconds. The fall in blood pressure is the result of transient disruption of the balance between cardiac function, peripheral vascular resistance and venous capacitance vessels, interacting with all these with delicate mechanisms of cerebral autoregulation.

#### *Reflex or neurologically mediated syncope*

This term includes a number of situations characterized by the transient failure of autonomic cardiovascular control mechanisms. Typically, autonomic function is normal when it is assessed outside the syncopal event. The pathophysiology of reflex syncope is usually synthesized as an activation of the Bezold-Jarisch reflex with consequent vasodilatation and / or bradycardia leading to the TGCH. When the fall in blood pressure dominates, it is classified as vasomotor, when bradycardia predominates, it is called cardioinhibitory and it will be mixed when both mechanisms participate simultaneously. (3)

The reflex syncope is also classified according to

Grades of recommendation. Definition	
<b>Class I</b>	Evidence and/or global agreement that a given diagnostic/treatment procedure is beneficial, useful and effective
<b>Class II</b>	Confictive evidence and/or a divergence of opinion about the usefulness/efficacy of treatment.
<b>Class IIa</b>	The weight of evidence/opinion is in favour of the usefulness /efficacy
<b>Class IIb</b>	The usefulness/efficacy is less established by evidence / opinion
<b>Class III</b>	Evidence or global agreement that treatment is not useful/effective and in some cases may be harmful.

Table 1. Grades of recommendation

Grades of recommendation. Definition	
<b>Level of evidence A</b>	Data from multiple randomized clinical trials with randomized distribution or meta-analysis
<b>Level of evidence B</b>	Data from a single clinical trial with randomized distribution or large studies without randomized distribution
<b>Level of evidence C</b>	Opinion consensus of experts and/or small studies, usual practice

Table 2. Levels of evidence

the trigger, which has clinical implications in the diagnosis and treatment:

- Vasovagal syncope: This occurs as a result of an emotion or orthostatic stress in susceptible persons. It usually has prodromal symptoms of autonomic activation (sweating, feeling of being hot or cold, nausea, pallor). (2)
- Situational Syncope: is that one that occurs in specific situations that gives it the own name, such as: post-micturition, defecation, and cough-producing syncope, in all those it is involved the activation of local mechanoreceptors as afferent via of reflex action.
- Carotid sinus syncope: is that which occurs by manipulation of the carotid sinuses. It is rarely in its spontaneous way, but in its provoked way becomes important as a cause of syncope in the elderly.
- Syncope induced by the tilt test: refers to those cases in which there is no trigger situation that may be identified and reproduce syncope in the tilt table. This diagnosis is based on the exclusion of other identifiable causes of syncope.

### ***Orthostatic syncope and orthostatic intolerance syndromes***

Unlike what happens in reflex syncope, orthostatic hypotension is the disturbance of the autonomic nervous system leading to poor arterial vasoconstriction. However, it also may result from states of hypovolemia or secondary to the use of drugs that interfere with the normal mechanisms of vasoconstriction. The symptoms of orthostatic hypotension are varied and range from dizziness and lack of concentration to syncope. The classic orthostatic hypotension is defined as the decrease in systolic blood pressure greater than 20 mmHg and / or diastolic greater than 10 mmHg within 3 minutes of active or passive orthostasis (tilt test). Sometimes the blood pressure drop occurs after 3 minutes and is called delayed or late orthostatic hypotension. In this case, the autonomic alteration is usually minor and it is often observed in older people who take drugs that block the vasoconstrictor response or diuretics.

There are other less common forms of orthostatic hypotension, as the so-called initial orthostatic hypotension, defined as a decrease greater than 40 mmHg systolic blood pressure in the first seconds after an active orthostasis. Unlike other clinic situations, blood pressure will recover after the first 30 seconds. It is exaggerated manifestation of a normal phenomenon and is often related to physical deconditioning. (4)

Finally, it remains to mention the postural orthostatic tachycardia syndrome, typically defined as a minor dysautonomia, in which the predominant symptom is physical tiredness and the cardinal sign is an exaggerated increase in heart rate compared to orthostasis. It is more common in young women. (5) It is frequently associated with chronic fatigue syndrome.

### ***Cardiac syncope***

- Arrhythmic syncope: is the most common form of cardiac syncope. Although the primary arrhythmia is often the cause, in the mechanism of syncope there are other factors, such as ventricular function, heart rate and activation of the Bezold-Jarisch reflex. It may occur as well as in bradyarrhythmias and ventricular tachyarrhythmias or, less commonly, supraventricular ones. A special chapter is constituted by polymorphic ventricular tachycardia, which may occur as a result of primary electrical syndromes (long or short QT, J wave syndrome, Brugada, catecholaminergic, and so on) or as a result of myocardial ischemia or proarrhythmic side effect of some drugs. (6, 7)
- Syncope of structural heart disease: in this case, syncope occurs when circulatory demand exceeds the limited capacity of the heart to increase cardiac output (aortic stenosis, hypertrophic obstructive cardiomyopathy, myxoma, and so on). But they also tend to be classified within this group syncopes occurring in the context of certain cardiomyopathies of different etiologies that ultimately predispose to arrhythmic syncope.

As shown, the classification of syncope is often difficult, given the multiple mechanisms that interact in the same patient to determine a TGCH and subsequent syncope (Figure 1).

## **2.2. Epidemiology**

Syncope is a common clinical manifestation of frequent observation throughout life. While reflex syncope predominates widely among the other forms in all ages, it is extremely common in youth, with a predominance of women who often have their first episode between 10 and 30 years. According to the Framingham study, there is a sharp increase in the incidence of syncope after 70 years, from 5.7 episodios/1,000 person-year in males aged 60-69 years to 11.1 / 1,000 in those aged 70-79 years. (8)

In a survey conducted in Argentina was estimated prevalence of syncope in the general population of 18.5%, however, only 55% of patients consulted a physician after a syncopal episode. (9)

## **2.3. Prognosis and impact on quality of life**

The reflex syncope usually has an excellent prognosis. At the other extreme, structural heart disease and primary electrical disease are main risk factors for sudden cardiac death and total mortality in patients with syncope. Consequently, syncope is not in itself a risk factor, but the prognosis will be given by the underlying disease. (10-12)

Reflex syncope recurrence has important effects on the quality of life. Its incidence is about 30% at 3 years and the rate increases depending on the number of previous episodes. (13)

Syncope represents a high cost in health. 1% of the

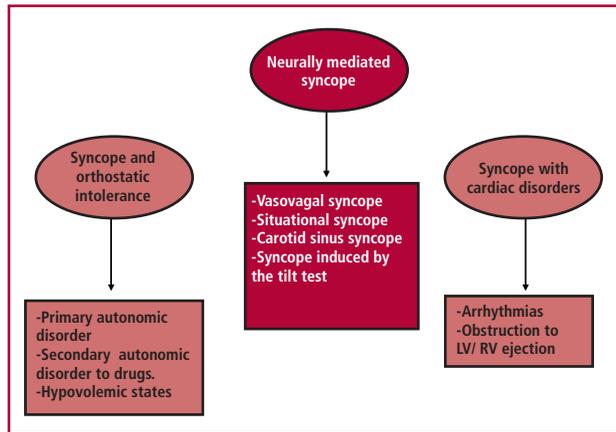


Fig. 1. Pathophysiology and classification of syncope.

consultations at guard services occur for syncope and of these 40% is hospitalized, with a mean permanence of 5.5 days. (14)

The use of diagnostic algorithms has proved to be a useful tool to increase the yield of diagnosis and allow a rational use of resources. (15)

### 3. DIAGNOSTIC METHODOLOGY

#### 3.1. Introduction

The diagnostic process in front of a patient with transient loss of consciousness and postural tone has two levels:

*First level:* establish if it is an episode related to transient global cerebral hypoperfusion (strictly syncope) or loss of consciousness from other causes.

*Second level:* establish the etiological diagnosis of syncope. Here should be appreciated the detection of pathological substrate, as well as the intervening mechanism.

For a syncopal episode happens it is necessary a concurrence of factors. Sometimes there is an underlying disease whose role may be a decisive factor or just a predisposing factor. On it acts a trigger that causes loss of consciousness and postural tone. Thus, in certain underlying heart disease, syncope may occur by different mechanisms and, likewise, the same mechanism may act on different structural alterations.

Ideally, it is to carry out the diagnosis of both components. However, sometimes the underlying disease is of sufficient significance to consider it the causal reason of syncope and require specific and early treatment and although its mechanism has not been clarified. Such is the case, for example, of an acute coronary event accompanied by syncope. By contrast, in other cases only the pathophysiological mechanism is detected without finding a pathological substrate, as, for example, isolated vasovagal syncope.

The diagnosis of underlying disease is usually easier because it is accessible. However, the mechanisms may be evident only during an episode or inferred from questioning and different findings.

The retrospective nature of diagnosis obligates to present one of the following strategies:

- To wait and monitor the spontaneous emergence of a new episode.
- To provoke an episode in the laboratory.
- To detect serious abnormalities that could explain the syncopal episode.

Some studies have detected a potential cause of syncope in 80% of evaluated patients. However, further diagnostic examination, about 20% had more than one possible cause. (16)

#### 3.2. Initial Assessment

In a patient with transient loss of consciousness and postural tone, the first diagnostic phase is the realization of: questioning, physical examination, ECG, laboratory.

The result of this initial assessment will allow us to:

- Establish the first diagnostic level: is syncope?
- Stratify risk.
- Establish the underlying disease and / or the mechanism of syncope with a high degree of certainty.
- Guide subsequent studies if the suspicion is not conclusive.

#### Is syncope?

The main differential diagnosis of syncope occurs with epilepsy and falls in the elderly. Table 3 shows the data of the questioning that guide to epilepsy or syncope, respectively. Sometimes the initial questioning is not categoric in order to separate the two entities. In that case, the neurological assessment will begin in parallel with syncope.

Other neurological causes, as subclavian steal syndrome and transient ischemic attack in the field carotid or vertebrobasilar, they usually exhibit signs of focus.

Psychiatric causes, in general, are not set in the first diagnostic phase because, previously, runs the search for causes involving potentially more life risk. The psychogenic pseudosyncope is suspected before very long episodes that occur very frequently (several times a day) without an obvious trigger. The eyes usually remain closed. The diagnosis is confirmed if the monitoring during the episode shows blood pressure, heart rate and normal EEG. (17)

#### Questioning

Even though, its importance is recognized in the diagnostic process, it has some limitations:

- Often provides little detail in the elderly patients.
- Given the frequent inability to verify effectively the mechanism acting during the syncopal episode, the etiology of some episodes has been defined by the same questioning (for example, situational syncope).
- In many cases, the description of the episodes is not characteristic of a particular etiology.

**Table 1.** Differential diagnosis with epilepsy. Oriented data \*

Epilepsy	Syncope
<b>Prodromes</b>	- Aura - Autonomic or of cerebral hypoxia symptoms
<b>Description of a witness</b>	- Prolonged tonic-clonic movements - They are started simultaneously with the loss of consciousness - Hemilateral, clonic, automatic movements. - Tongue-biting - Facial cyanosis - Brief tonic-clonic movements - They are started after the loss of consciousness - Involuntary, nonspecific movements - Stiffness - Pallor, sweating
<b>Recovery</b>	- Prolonged, with confusion. Muscle pain - Fast. Autonomic symptoms

Less common findings for the diagnosis of epilepsy: a family history of epilepsy, nocturnal episode, prodromal paresthesias, sphincter relaxation, cephalaea or post-episode somnolence

\* Modified from Moya A, et al. (1)

Some studies analyzed the diagnostic value of the questioning. The ‘Calgary Syncope Symptom Score’, for example, proposes a score for diagnosing vasovagal syncope based on a history and description of the episode. (18) The gold standard for defining vasovagal syncope in this study was positive tilt test. The authors report 89% sensitivity and 91% specificity for vasovagal syncope using the selected variables. Another more recent study has achieved to validate these results, since in its population of Calgary score has 89% sensitivity but only 32% specificity for vasovagal syncope. (19)

Despite the mentioned caveats, a thorough questioning provides a good initial orientation.

The data to be collected during the questioning are:

- Demographic data, place of origin.
- Personal history.
- History of heart failure, coronary heart disease, palpitations preceding syncope.
- Medication.
- Family history.
- Characteristics of syncopal episode:
- Circumstances
- Prodromes
- Presence of convulsions
- Relaxation of sphincters, trauma
- Recovery mode
- Description of a witness (appearance, convulsions, pale or cyanotic colour)

Table 4 shows the clinical characteristics that guide to different causes.

**Physical examination**

Clinical, cardiological and neurological tests must be complete. The physical examination includes the completion of the active orthostatic maneuver for 3 minutes to detect orthostatic hypotension. The maneuver is positive when systolic blood pressure drops  $\geq 20$  mmHg or less than 90 mmHg, or diastolic blood pressure drops  $\geq 10$  mm Hg in presence of symptoms (Class I, level of evidence C). The same hemodynamic behaviour in the absence of symptoms has less diagnostic value (Class IIa, level of evidence

C). (20)

**Laboratory**

The data that have relevance, are hematocrit and hemoglobin, white blood cell count, plasma electrolytes and blood glucose. They will detect severe anemia, infections, electrolyte disturbances and hypoglycaemia. Other specific tests (CPK, troponin, D-dimer) are requested on the basis of previous findings.

**Electrocardiographic records**

Electrocardiographic manifestations of Holter registers and monitoring consider diagnostic and suggestive (those that require continuing with assessment) of cardiovascular and / or arrhythmic syncope include:

Diagnostic findings on the electrocardiogram, Holter registers, monitoring:

- Sinus pause greater than 3 seconds.
  - Extreme sinus bradycardia.
  - Second-degree Mobitz II AV block or complete AV.
  - Bilateral bundle branch block.
  - Sustained ventricular tachycardia.
  - Symptomatic supraventricular tachycardia
- Suggestive findings in the electrocardiogram, Holter registers, monitoring
- Signs of ischemia-injury.
  - Changes in size and thickness of cavities.
  - Other changes in ventricular repolarization.
  - Second-degree Mobitz I AV block.
  - QRS greater than 0.12 seconds.
  - Long or short QT interval.
  - Ventricular preexcitation.
  - Sinus bradycardia below 40 bpm (in the absence of drugs that depress the chronotropism and intensive physical training)
  - Sinus pauses below 3 seconds.
  - Type 1 Brugada pattern.
  - Negative T waves in right precordial leads and epsilon waves.
  - Frequent ventricular extrasystoles.
  - Repetitive ventricular extrasystoles, couplets,

**Table 4.** Clinical guided characteristics of the questioning

	Cardiovascular		Situational reflex and hypersensitivity of carotid sinus	Vasovagal	Orthostatic hypotension	
	Substratum	Arrhythmic mechanism			Autonomic-homeostatic deficit	Hypovolemia
<b>Demography</b>	Older than 50 years Origin of the endemic area for Chagas disease			Young people and elderly people	Older than 50 years Young people (POTS)	Young people Elderly people
<b>Personal history</b>	Structural heart disease Coronary risk factors	Known arrhythmia	COPD Pathology of the digestive system Surgery or radiation of the neck	None	Peripheral neuropathies Parkinson's disease Pure autonomic failure, multi-systemic atrophy	
<b>Medication</b>					Beta adrenergic blockers Calcic blockers Antidepressants Diuretics	Diuretics
<b>Family history</b>	Syncope Sudden death			Vasovagal syncope		
<b>Other symptoms</b>	Dyspnea, angina, asthenia, palpitations			Pre-syncope	Difficulty in micturition Constipation Sexual impotence	Dizziness Instability Asthenia
<b>Characteristics of syncope</b>						
<b>Circumstances</b>	Exercise Prolonged immobility (pulmonary embolism)	Exercise, rest, excitement, auditive stimulus	Urination, defecation, coughing, swallowing, postprandial, laughter Compression of the neck	Excitement, fear, pain, prolonged orthostasis, blood-letting, postexercise, hot environment	Immediate orthostatic Postprandial	Fever, intense postexercise, diarrhea, prolonged fasting, bleeding, postsurgery
<b>Prodromes</b>	Angina, dyspnea	Palpitations None	None	Autonomic and of cerebral hypoxia symptoms	None Dizziness, confusion	
<b>Recovery</b>	Immediate Confusion			Autonomic symptoms Pronounced asthenia		

triplets, and non-sustained ventricular tachycardia.

- Early Repolarization and J wave in inferior and lateral face.

### **Echocardiogram**

It is indicated in patients of any age with data suggesting cardiovascular or arrhythmic syncope (Class I, level of evidence B). It is suggested in the first diagnostic phase in patients older than 60 years to have a high prevalence of heart disease.

### **3.3. Conclusion of initial assessment.**

#### **1. Risk Stratification**

Combining the different elements of the initial assessment, different scores have been developed particularly useful in emergency rooms.

Table 5 details the proposed scores. The history of heart disease and detection of an abnormal ECG are listed as risk factors in all of them. (21-24)

#### **2. Diagnosis with high degree of accuracy**

It summarizes some of the possible diagnostic findings with a high degree of accuracy obtained during the initial assessment:

**Questioning** - Physical examination: situational, vasovagal, drug, hypovolemic fever.

**Laboratory:** hypoglycemia, anemia.

**ECG:** acute ischemic event, arrhythmias.

**Echocardiogram:** severe valvular stenosis, hypertrophic obstructive cardiomyopathy, left atrial myxoma, obstructive thrombus, cardiac tamponade, aortic dissection, congenital anomalies of the coronary arteries.

#### **3. Suspicion of other causes of syncope**

It is required to continue with the diagnostic sequence.

### **4. LATER ASSESSMENT**

#### **4.1. Diagnosis of structural heart disease**

Several diagnostic methods are being required in a guided way by the initial findings. Thus, specific laboratory tests, cardiac Doppler, functional tests

and diagnostic imaging methods will allow the detection of coronary events, cardiomyopathies and/or pericardiopathies, valvular disease, pulmonary embolism, aortic aneurysm, congenital malformations.

#### 4.2. Diagnosis of arrhythmogenic syndromes

In syndromes of long QT, short QT, Brugada, right ventricular dysplasia and hypertrophic cardiomyopathy, the occurrence of syncope is a warning sign even if not always clarified the relationship between the mechanism of syncope and underlying pathology. In selected cases it is useful to have the genetic test that may confirm the diagnosis (in the case of relatives of known carriers). In some cases, genetic typing contributes to risk stratification.

#### 4.3. Diagnosis of based neurological disease

In the presence of orthostatic hypotension, neurological assessment will allow us to identify the primary autonomic failure, pure autonomic failure such as, multiple systemic atrophy or Parkinson's disease, or those secondary to polyneuropathy.

The situations that usually justify a neurological consultation include:

- History of diseases causing dysautonomia, balance disorders, migraine headaches, tremors, stiffness, stroke or transient ischemic attacks.
- Family history of epilepsy.
- Doubtful questioning between syncope or epilepsy.
- Appearance of focal signs before, during or after the episode.
- Orthostatic hypotension.

#### 4.4. Diagnosis of arrhythmic syncope mechanism

There are two types of diagnostic methods:

- By monitoring.
- Descriptive and provocation of arrhythmias.

The former ones allow us to carry out the diagnosis with greater certainty when assessing the correlation between rhythm disorder and symptoms.

Although descriptive and provocative methods have more limited value related to their sensitivity, specificity and predictive value, they are often used in first instance to detect potentially dangerous causes avoiding a spontaneous recurrence.

##### Heart Rate Monitoring

The classically heart rate monitoring is indicated in patients with suspected arrhythmic risk by initial assessment. However, cardiac arrhythmias, especially bradyarrhythmias are common in patients older than 50 years, even in the absence of evidence of risk in the initial assessment. (25)

##### Intrahospital monitoring

It is indicated in elderly patients and younger patients whose risk has justified the hospitalization.

##### Holter ECG register

It is included in the first diagnostic phase in patients with suspected arrhythmic risk.

It allows us to detect specifically but with low frequency correlation between symptoms and rhythm disturbances. The presence of symptoms in the absence of rhythm disturbances (15%) puts off arrhythmic mechanism. Its diagnostic value is increased if the episodes are very frequent. Findings during Holter register may be diagnostic or only suggestive following the criteria specified in Table 4. (26)

##### Detectors of events

There are two types, external and implantable. Both increase the diagnostic possibilities to extend the monitoring period. However, neither of these methods is a common practice in our environment. The first is not usually tolerated by the patient rather than a few weeks.

The implantable event detector has a battery life of up to 36 months. Stored in its memory records for the activation of the equipment by the patient (or control) during an episode or does it automatically during episodes of arrhythmia detection as scheduled. Furthermore, the information obtained may be sent by telephone. (27)

The indication of the detectors of events was expanded in recent years. Its use has allowed us not only to identify arrhythmic causes of syncope in patients with sporadic episodes, but also to assess the diagnostic value of other provocative methods. However, although this resource is not accessible to most of patients, in some cases, increasing the diagnostic possibilities, cost-diagnosis achieved is superior to conventional testing. (28, 29)

The detector of events is indicated in patients with recurrent syncope when an arrhythmic mechanism is suspected but the conventional diagnostic assessment (including electrophysiological studies in selected cases) is not conclusive. (30)

#### Methods of functional and provocation assessment

##### Ergometric test

In a patient with syncope, ergometric test may:

- a) Detect myocardial ischemia as the substrate of the episode.
- b) Diagnose arrhythmias.

It is indicated in patients whose syncope occurs during exercise or immediately after it is made.

Possible positive findings during the test are:

- Development of a second-degree Mobitz II AV block or third degree.
- Chronotropic incompetence.
- Symptomatic and sustained ventricular tachyarrhythmias, sensitive to catecholamines present in patients without demonstrable structural heart disease.
- Abnormal behaviour of the QT interval in patients with suspected long QT interval.

**Table 5.** Risk stratification in syncope \*

Study	Selected variables	Score	Endpoint criteria	Results
San Francisco's rule n = 684 patients Validation: 791 patients	- Abnormal ECG - Congestive heart failure - Dyspnoea - Hematocrit <30% - Systolic blood pressure <90 mmHg	No risk, no variable With risk, ≤ 1 variable	Large event within the week	Sensitivity 98% Specificity 56%
Martin, et al n = 252 patients Validation: 374 patients	- Abnormal ECG - History of ventricular arrhythmias - Congestive heart failure - Age > 45 years	0 to 4 (1 point for each variable)	Arrhythmic event or arrhythmic death a year	Score: 0%, 0 point 5%, 1 point 16%, 2 points 27%, 3 or 4 points
Score OESIL n = 270 patients Validation: 328 patients	- Abnormal ECG - History of heart disease - Absence of prodromes - Age > 65 years	0 to 4 (1 point for each variable)	Total mortality a year	Score 0%, 0 points 0.6%, 1 points 14%, 2 points 29%, 3 points 53%, 4 points
Score EGSYS n = 516 patients Validation: 260 patients	- Palpitations as prodrome (+4) - Abnormal ECG and/or heart disease (+3) - Syncope of effort (+3) - Syncope in supine position (+2) - Autonomic prodromes (-1) - Typical triggers for vasovagal syncope (-1)	Algebraic addition of scores	Total mortality at 2 years Cardiac syncope	2%, < 3 points 21%, ≥ 3 points 2%, < 3 points 13%, 3 points 33%, 4 points 77%, > 4 points

\* Modified from Moya A, et al. (1)

- Assessment of anterograde refractory period of accessory pathway.
- c) Diagnosis post-effort or intra-effort hypotension.
- May be detected hypotension of non-arrhythmic causes during the test or to conclude it.

#### **Ajmaline test**

The intravenous administration of ajmaline to highlight ECG pattern of type 1 Brugada syndrome is discussed. It has indication in patients with: a) a known history of sudden death of relatives or diagnosis of Brugada disease b) suggestive ECG but not conclusive for type 1 Brugada pattern.

In the paroxysmal AV block suspected in patients with bundle branch block or bifascicular blocks during electrophysiological test.

#### **Atropine test**

It allows us to discern whether a deficit in heart rate has a structural substrate or due to excessive vagal modulation.

#### **Adenosine test**

Some patients have increased sensitivity of purinergic receptors. This is evidenced by the appearance of prolonged AV block before administration of adenosine triphosphate (ATP). They have been proposed as diagnostic criteria the duration of asystole greater than 6 seconds or AV block greater than 10 seconds for syncope of unknown origin.

The value of positive adenosine test to predict a similar result during spontaneous episode was studied in a small number of patients by implanting a detector of events without finding a good correlation between both test. (31)

Some studies have compared the responses to tilt test and adenosine test in patients with syncope of unknown cause. In general, agreement between both results is low, suggesting that both methods would identify different mechanisms. (32)

In small uncontrolled series have shown that syncopal recurrences are lower in patients with positive adenosine test who receive a pacemaker implant than those in whom only periodic checks are made.

#### **Electrophysiological study**

It allows us to detect changes in the conduction system and, as a method of provocation, detecting the induction of tachyarrhythmias.

When the suspicion arrhythmic cause persists because of initial findings or the presence of structural heart disease but was not confirmed by other methods an electrophysiological study is carried out. The diagnostic value is increased if the study is carried out in selected patients with underlying heart disease, particularly ischemic heart disease or in those with suspicious findings on ECG or continuous monitoring of bifascicular block with prolonged PR interval, sinus

node disease, preexcitation ventricular syndrome, sustained supraventricular or non-sustained ventricular tachycardia. (33)

The factors considered as predictors of positive electrophysiology study are: heart disease, male gender, sinus bradycardia, bundle branch block, first degree atrioventricular block, ventricular extrasystoles, non-sustained ventricular tachycardia on Holter and trauma during syncope.

The full electrophysiological study includes the study of sinus function, assessment of atrioventricular nodal function and the His-Purkinje system and the induction of supraventricular and ventricular tachyarrhythmias.

In recent years, an indication of electrophysiological study in patients with syncope has decreased due to:

- The advance of prolonged monitoring methods have greater specificity for the diagnosis of pathophysiological mechanisms.
- The early indication of a cardioverter defibrillator (ICD) in patients with syncope and ventricular function severely impaired. (34)

### **Recommendations for conducting an electrophysiology study**

#### **Class I Level of evidence B**

- Patients with ischemic heart disease, suspected arrhythmic cause for initial assessment and preserved ventricular function.

#### **Class IIa. Level of evidence B**

- Patients in whom no other cause was detected with syncope and bundle branch block.
- Patients in whom no other cause of syncope is detected and this is preceded by palpitations.

#### **Class IIb. Level of evidence C**

- Patients with Brugada syndrome, arrhythmogenic right ventricular dysplasia or hypertrophic cardiomyopathy.
- Patients with high-risk occupations where it is necessary to demonstrate conclusively the absence of an arrhythmic cause.
- Patients with evidence of sinus node disease and suspected pauses which were not detected by methods of monitoring as a cause of syncope.

#### **Class III**

- Patients without underlying heart disease or evidence of an arrhythmic cause for initial assessment.

Some results have sufficient importance to be considered as the cause of syncope. However, there is a wide range in which the specificity of the findings is not yet properly clarified.

### **Diagnostic criteria in the electrophysiological study**

#### **Class I Level of evidence B**

- Time of corrected sinus node recovery > 525 msec.
- Spontaneous HV interval  $\geq$  100 msec
- HV interval  $\geq$  100 msec or induced second or third degree block.
- Induction of sustained monomorphic ventricular tachycardia in patients with previous myocardial infarction. Induction of fast supraventricular tachycardia that reproduces spontaneous symptoms.

#### **Class IIb. Level of evidence B**

- HV interval range between 70 and 100 msec.

### **4.5. Diagnosis of reflex mechanism**

#### **Situational syncope**

Diagnosis is made primarily by questioning to identify a specific trigger.

#### **Carotid sinus syndrome**

Classic triggers related to compression of the neck, sudden appearance and immediate recovery without asthenia will guide its diagnosis.

#### **Carotid sinus massage**

Massage is abnormal when produces a pause longer than 3 seconds and/or a decrease in systolic blood pressure greater than 50 mmHg. This behaviour has value when is accompanied by symptoms, as only hypersensitivity to carotid sinus massage is very common in the elderly population with hypertension and vascular changes, even without a history of syncope. (35) The test may be sensitized, carrying out the massage in orthostatic position.

It is contraindicated in the 3 months after stroke or transient ischemic attack and in the presence of murmurs in the carotid arteries.

As it happens with adenosine test, recurrence of syncopal episodes is lower in patients with abnormal response to carotid sinus massage in which a pacemaker is implanted, than in those who are only controlled. (36)

In some diagnostic algorithms are precociously described in patients older than 40 years. However, due to its low specificity, we suggest to consider its implementation after ruling out other causes.

#### **Vasovagal syncope: tilt test**

The prolonged passive orthostatic test, tilt test, was expanded as a diagnostic method for reflex or neurally mediated syncope. Since its initial use, some concepts were evolving.

- The sensitivity and specificity of the test are assessed in the absence of a gold standard for vasovagal syncope.
- In small studies it was observed little correlation between the type of positive response to tilt test (mixed, cardioinhibitory or vasodepressor) and the hemodynamic behaviour during a spontaneous episode.

- The clinical therapeutic effectiveness of treatment is not predictable by the response to tilt test under treatment.

On the other hand:

- Noting hemodynamic patterns during the early phases of the study, other entities have been defined such as postural orthostatic tachycardia and different variants of orthostatic hypotension.

The test is carried out on a bascule couch actuated automatically or manually. We recommend a prior rest period, in supine position, from 5 minutes which may extend to 20 minutes if a venous via has been placed. The pitch period is 45 minutes (or until the onset of symptoms) with an angle of 60 to 80 degrees. During the test, blood pressure and heart rate are monitored periodically or continuously. The monitoring equipment noninvasive beat to beat blood pressure are optimal for characterizing the hemodynamic changes during the test, but not essential to assess the final result.

The study may be sensitized by infusion of isoproterenol or, more commonly, by nitroglycerin. In our environment using the sublingual administration of 1.25 to 2.5 mg of isosorbide dinitrate after 20 minutes of passive orthostasis.

#### ***Accepted or suggested indications and current contraindications for the tilt test realization***

##### **Class I. Level of evidence B**

- Assessment of syncope that causes trauma or transit accident or occurs in patients with a risky activity in which it is assumed but may not be assured the cause is vasovagal in: 1) patients with no other clinical cardiovascular disease and compatible with vasovagal syncope., 2) patients with other cardiovascular disease, but whose questioning suggests vasovagal syncope and other causes have been ruled out.

##### **Class I Level of evidence C**

- Patients with other apparent cause of syncope but in whom demonstration of a vasovagal mechanism modifies the therapeutic behaviour.
- Assessment of patients with post-exercise syncope.

##### **Class II. Level of evidence C**

- Differential diagnosis of syncope with epilepsy. Orthostatic hypotension, other causes of recurrent falls, pseudosyncope by psychiatric causes.
- Detection mechanism: 1) recurrent dizziness or presyncope 2) syncope in the presence of peripheral neuropathy or dysautonomia.
- Single or repeated episode of syncope without trauma or risk, with a clear indicative questioning of vasovagal syncope.

##### **Class III. Level of evidence B**

- Syncope in which another cause has been established and in which the demonstration of a

vasovagal mechanism does not modify the therapeutic behaviour.

- Assessment of the effectiveness of treatment.

##### **Class III. Level of evidence C**

- Sensitization of isoproterenol in patients with ischemic heart disease.

Diagnostic criteria are presented as:

- In the absence of heart disease 1) induction of reflex bradycardia-hypotension or orthostatic hypotension with reproduction of symptoms is highly suspicious of vasovagal syncope or orthostatic hypotension, 2) induction of reflex bradycardia-hypotension without reproduction of symptoms is suspected vasovagal syncope.
- In the presence of heart disease or arrhythmias should exclude other causes of syncope before considering a positive tilt test diagnosis.

Relative contraindications to carry out the study, are the important obstruction of the outflow tract of the left ventricle, mitral stenosis and severe coronary lesions or severe stroke.

#### **4.6. Diagnosis of the mechanism of orthostatic hypotension**

Orthostatic hypotension is usually detected at an early phase during a physical examination by active orthostatic maneuver. However, it is not always evident in the medical interview.

To complete its investigation are carried out:

##### ***Tilt test***

Allows us to detect the following variations:

- Classic orthostatic hypotension (within the first 3 minutes).
- Initial orthostatic hypotension (first 30 seconds with later recovery).
- Delayed or late orthostatic hypotension (between 3 and 7 minutes).
- Dysautonomic pattern (slow and progressive decrease in blood pressure).
- The detection of these patterns is facilitated by using a beat to beat blood pressure monitor.

##### ***Pressure measurement***

The ambulatory monitoring of blood pressure in normal living conditions of the patient may reveal the coincidence between symptoms and arterial, postural, periprandial or situational hypotension. (37)

## **5. TREATMENT OF PATIENTS WITH SYNCOPE**

### **5.1. General guidance**

Knowing the cause of syncope and the pathophysiological mechanism that produces it, it is essential to guide the treatment. The objectives in patients with syncope are aimed at reducing mortality and morbidity as well as prevent recurrences. It will depend on the cause of syncope the importance of acquiring each of these objectives.

Treatment should always be directed to the last cause that causes TGCH. This may not have treatment, whereby this will focus on mechanisms that may cause the TGCH (for example, it may not be the cause of degenerative AV block, but may resolve the occurrence of syncope with the implant of a permanent pacemaker).

Once the identification of the cause and mechanisms of syncope is carried out, it is essential to perform a risk stratification. If it is concluded that syncope is of neurocardiogenic reflex mechanism, the risk will be determined only by the frequency of occurrence (recurrence); if it is a cardiac arrhythmia, specific treatment should be instituted for it and the risk will depend on the type of arrhythmia, as in the presence of structural heart disorder. However, if the syncope is of unknown cause and there is a higher risk of sudden death according to the structural underlying pathology (coronary artery disease, cardiomyopathy, and so on), it may be essential to assess the implantation of an ICD, according to specific guide that directs its usefulness.

## 5.2. Treatment of patients with reflex syncope and orthostatic intolerance

The reflex syncope and orthostatic intolerance syncope have similar strategies for the prevention of recurrence, although the involved pathophysiological mechanisms may be different, therefore, the therapeutic objective in these pathologies is the primary prevention of recurrence and associated injuries, in an attempt to improve the quality of life, but not the prolongation of life, since mortality is generally considered low.

The reflex syncope, as isolated abnormal of benign evolution, does not require specific treatment, especially when it has been single and has been out of risky situations.

Many patients are able to recognize the triggers and prodromal symptoms and learn to carry out maneuvers that correct, decrease or abort the symptoms. However, others are not able to do it. For them, the first indication is the information and training to recognize the prodromes, which is achieved by providing security at the onset of symptoms.

The passive body tilt testing has an essential role in this training, since some symptoms that go unnoticed, may highlight or relate to the 'triggers' of the episode during this test.

About the learning needs of patients with vasovagal syncope, a qualitative study conducted through surveys and interviews has shown that patients require knowledge about the etiology, management, natural evolution and prognosis of the entity. (38) Therefore, the treatment always begins with the reassurance of the patient combined with explanation of the 'trigger' mechanisms, the recognition of the prodromes (when they exist) and a clear conceptualization of the mildness of the disease.

One starting approach may be the advice on how to abolish dehydration, avoid prolonged periods of static

standing and recognition of precipitating factors to prevent traumas. It is important to try to avoid drugs that lower blood pressure (such as alpha blockers, diuretics and alcohol).

However, the patient should always be warned about the potential physical risks of injury and how to prevent and counteract them.

Secondly, the patient should be driven to drink fluids, minimal alcohol and caffeine and patients with significant basal hypotension should be indicated an increase in the amount of salt in the diet they do. These changes in lifestyle are crucial, and often sufficient to control symptoms. (39)

On the other hand, if the symptoms progress, part of the treatment should include the adoption of safe positions to avoid traumas, such as supine position indication in any situation that the patient is at the onset of symptoms (at home and social environments).

### **'Physical', non-pharmacological treatments**

They emerge as a new starting line of treatment for vasovagal syncope and is in this area where there have been major advances. These are called training programs with passive body tilt (tilt training), physical counterpressure maneuvers in preventing vasovagal syncope and increase orthostatic tolerance by physical training. They are described below.

#### ***Training by passive body tilt or tilt training***

When patients present recurrent vasovagal symptoms triggered especially by orthostatic stress (for example, prolonged standing), training by taking progressively longer periods of enforced upright posture such as standing, lying on a wall with feet to 30cm of it may reduce the recurrence of syncope.

This treatment, aimed particularly at young patients, requires maximum adherence and motivation and is obstructed by the low fulfillment to continue the treatment program for an extended period.

The randomized and controlled studies have failed to confirm the short-term efficacy of tilt training to reduce the rate of positive response, but it is recommended to be a therapeutic modality to consider for neurally mediated syncope patients with high recurrence. Its feasibility and simplicity are the major advantages of this resource. (40)

#### ***Physical counterpressure maneuvers***

Randomized and controlled studies to assess the benefit of these maneuvers in preventing the daily recurrent vasovagal syncope have concluded that physical counterpressure maneuvers are effective, without risk and its cost is low.

An essential prerequisite is that the patient has prodromes of sufficient duration and in the case of warning the imminence of syncope may carry out preventive maneuvers, such as crossing legs, squeezing hands tightly, a squatting position and tension of the arms.

It is important to warn patients about the physical counterpressure maneuvers require ongoing training,

to have adequate preparation in case one needs to use them against the threat of syncope.

As for the effectiveness of counter-maneuvers, was established to reduce the number of syncopal recurrences by 36% during a mean follow-up period of 14 months. In addition, only five patients needed to treat to obtain results in one of them. (41-43)

At present, the available information to propose a physical counterpressure maneuvers as a safe, simple and feasible method to prevent vasovagal syncope and suggest they join the first line of therapeutic indications.

### ***Increased orthostatic tolerance by physical training***

Physical training with increase aerobic capacity and muscle strength and the resistance of various muscle groups, especially the lower limbs, is a follow-up training programs with passive body tilt (tilt training) and physical counterpressure described above.

The evidence allows us to conclude that the aerobic training and muscle strength of the lower limbs is beneficial for patients with vasovagal syncope. The patient's adherence to the practice of the exercises and their continuity for many months is a fundamental requirement. (44, 45)

### ***Drug Treatments***

Many pharmacological treatments have been used in reflex syncope. The foundation of their indication was known pathophysiology of the episodes. Thus, we included beta blockers, clonidine, disopyramide, ephedrine, etilefrine, scopolamine, midodrine, inhibitors of serotonin and theophylline.

Although non-controlled or short-term clinical studies were successful in demonstrating their usefulness, several long-term, prospective, placebo-controlled clinical studies have been disappointing, with some exceptions. That is why we insist on the need for future randomized trials that allow us to assess the effectiveness of a particular drug in a significant number of patients.

The little or doubtful utility demonstrated for many of the assessed agents oblige to select drug/s on an individual basis to consider the concomitant diseases or complementary medication that the patient receives. Besides, one should keep in mind that any medication may make worse symptoms rather than better (prosyncopal effect).

Overall, chronic pharmacological treatment with an alpha agonist (etilefrine and midodrine) is useful only in reflex syncope and long-term treatment should not be advised for patients with occasional symptoms.

In some selected patients may be useful indication of a single dose before standing or having to perform an activity that may trigger syncope, but always as complementary therapeutic measures on lifestyle changes and physical maneuvers. However, this strategy has not been tested.

The indication of fludrocortisone do not have bibliography to support its use but, however, it has

been widely used in both children and adults with reflex syncope. Today it is not recommended.

The theory that justified the use of beta blockers has not been confirmed by the results of five of the six long-term clinical studies in which they were assessed, with the aggravating circumstance that may be prosyncopal or increase bradycardia in cardiodepressant syncope or hypersensitivity of carotid sinus.

Paroxetine (an antidepressant drug), even though it was proved effective in a placebo-controlled study, did not confirm this benefit in other studies. It may be helpful in reducing anxiety that may trigger episodes, but its use requires caution in patients without psychiatric illness.

Table 6 summarizes the most important trials of drug treatment with their results. Most placebo-controlled studies have shown no difference, while others show benefits in the treatment were not randomized. Clinical studies, randomized or not, were carried out on small samples and comprised only a short period of treatment or follow-up.

### ***Pacing or cardiac stimulation***

Artificial cardiac pacing in the treatment of reflex syncope was assessed in multicenter, randomized and controlled clinical studies, with conflicting results. (61-65)

The fact that they were not conclusive is due to episodes have a cardioinhibitory component and vasodepressor component and the predominance of one or the other is variable, so that electrical stimulation, which may only improve the cardioinhibitory component, would not have effect when vasodepressor component were dominant.

It was hypothesized that only the pause recorded during syncope and not the one obtained during the tilt test should be the basis for selection of patients for treatment with pacemakers.

The benefit of cardiac pacing in asystole, which mediates reflex syncope, documented by implantable event detector, was assessed in randomized clinical studies, which showed a significant decrease in the recurrence of syncope. (66, 67)

In short, the use of pacemakers for the treatment of reflex syncope seems to be useful only in patients in whom the role of bradycardia is presented as the primary mechanism in its genesis.

### ***Recommendations for treatment of vasovagal syncope***

#### **Class I Level of evidence B**

- In patients with prodromes, indicate isometric physical counterpressure maneuvers.

#### **Class I Level of evidence C**

- Explain the diagnosis, the risk of recurrence and reassure all patients.

#### **Class IIa. Level of evidence B**

- Cardiac pacing is indicated for patients with cardioinhibitory carotid sinus syndrome and those with common reflex syncope, age older than 40 years and documented spontaneous cardioinhibitory response by monitoring.

#### **Class IIb. Level of evidence B**

- Midodrine may be indicated in patients with vasovagal syncope that do not respond to lifestyle changes
- The tilt training may be helpful to educate patients, but long-term performance may be influenced by adhesion.

#### **Class IIb. Level of evidence C**

- Cardiac pacing may be indicated for patients older than 40 years with cardioinhibitory response to tilt-induced with frequent recurrent unpredictable syncope and failure to respond to alternative treatments.

#### **Class III. Level of evidence C**

- Cardiac pacing in the absence of documented cardioinhibitory reflex is not indicated.
- Beta-blockers are not indicated.

### ***Recommendations for the treatment of orthostatic intolerance syndromes***

#### **Class I Level of evidence C**

- Adequate levels of hydration and salt intake.

#### **Class IIa. Level of evidence B**

- Midodrine as adjunctive treatment.

#### **Class IIa. Level of evidence C**

- Fludrocortisone as adjunctive treatment.

#### **Class IIb. Level of evidence C**

- Physical maneuvers of isometric counterpressure.
- Sleep with the head slightly elevated ( $> 10^\circ$ ) to increase the volume of liquid.

### **5.3. Treatment of patients with carotid sinus syndrome.**

The recommendations for the treatment of this syndrome include the abolition of triggering events maneuvers (hyperextension of the head, external compression of the carotid sinuses, and so on) and suppress any medication that could help to vasodepression or cardioinhibition (such as vasodilators, beta blockers, cholinesterase inhibitors, and so on.)

Patients with syncope of this origin that have documented a cardioinhibitory response improve with pacemakers. We prefer to use pacemaker with sequential atrioventricular stimulation. (36, 68).

### **5.4. Treatment of patients with syncope and cardiac arrhythmias**

Ventricular and supraventricular arrhythmias may trigger syncope, which will depend on several factors, among which are heart rate, ventricular function, adequate vascular compensation and the magnitude of the neuromediated reflection. The objective of treatment is to improve the quality of life, prevent recurrence of symptoms and decrease mortality. We refer to the relevant guidelines for the review of the treatment of main syndromes that cause syncope related to arrhythmias.

#### ***Syncope in the presence of structural heart disease or cardiovascular disease***

The association of syncope with a congenital cardiovascular disease or underlying cardiopulmonary disease increases the risk of sudden cardiac death.

Although these patients may present symptomatically with intercurrent syncope, this does not imply that the cause of syncope is due invariably to the underlying pathology.

It is important to diagnose the underlying pathology, to identify precisely the mechanism of syncope and institute appropriate treatment for both. The precise mechanism of syncope may not be evident; in this case, the objective of treatment will be to reduce the risk of sudden death, rather than treat the underlying disease or find the cause of syncopal episodes.

In short, in the case of patients with an underlying disease at high risk of sudden death and at the same time syncopal episodes are associated, the recommendation is to carry out an exhaustive study of the cause of syncope and if possible establish specific treatment. In case this is not possible, it will treat any underlying disease or eventual arrhythmogenic mechanisms of the disease, knowing that the syncopal episodes, because they remain of unknown cause, may not disappear even though it has decreased the risk of sudden death.

The risk of sudden death in patients with coronary cardiomyopathy and systolic function of depressed left ventricle is high. In them should be assessed, and eventually resolved the ischemia. However, this does not assure to have solved the potential arrhythmogenic mechanism, which should be investigated.

Patients with syncope and heart failure have an increased risk of death regardless of the cause of syncope. Patients with an established indication for ICD according to current guidelines should receive this device even before and independently of the assessment of the mechanism of syncope. (69-71)

Hypertrophic cardiomyopathy is a hereditary disease with a penetrance and a very wide clinical expression. Hypertrophy and myocyte disarray, as well as fibrosis that characterizes it, favour the genesis of ventricular arrhythmias and sudden death associated with this syndrome. Syncope may occur at rest or during exercise and may be caused by multiple

**Table 6.** Pharmacological treatments tested in neurally mediated syncope and their results

Authors	Drug	Study Design	Population	Results
Sheldon, et al; POST Investigators (2006). (46)	Beta blocker (metoprolol vs. placebo)	Multicentric randomized, controlled trial vs. placebo	n = 208 (66% women), mean age 42 years	No benefits were observed in the group of patients treated with metoprolol
Ventura, et al. (2002). (47)	Beta blockers (metoprolol, propranolol vs. without treatment)	Prospective, randomized and controlled trial	n = 56 (64% women), mean age 44 ± 18 years	The group treated with beta blockers had a lower recurrence rate than the untreated group
Madrid, et al. (2002). (48)	Beta blocker (atenolol vs. Placebo)	Prospective, randomized, double- blind, and controlled trial	n = 50	There were no differences in the rate of recurrence and time to first episode
Flevari, et al. (2002). (49)	Beta blockers (propranolol, nadolol or placebo)	Randomized, crossover and controlled trial	n = 30 consecutive vasovagal syncope and positive tilt test (serial and randomized assignment to propranolol, nadolol or placebo for three months for each branch, with cross-linking 0)	After 9 months of follow up there was no difference in recurrence of syncope or presyncope in all three groups. All were effective in preventing vasovagal syncope
Mahanonda, et al. (1995). (50)	Beta blocker (oral atenolol. vs Placebo)	Randomized and controlled trial	n = 42 All at least 1 syncopal episode or 2 presyncope in the previous month and positive tilt test with isoproterenol	After a month of treatment: 62% of atenolol group. vs 5% of placebo group had negative tilt test (p = 0.0004), 71% of atenolol group and 29% of placebo group had symptomatic improvement (p = 0.02)
Takata, et al. (2002). (51)	Paroxetine 20 mg/ day vs. placebo for 6 weeks	A randomized, double-blind trial	n = 25 (19 completed the study: 9 with paroxetine, 10 with placebo)	Paroxetine did not attenuate sympathetic inhibition or vagotonia (did not prevent syncope)
DiGirolamo, et al. (1999). (52)	Selective inhibitor of serotonin reuptake inhibitors (paroxetine) 20 mg/day vs. placebo for 1 month	Randomized and controlled trial	n = 68 (42 women, 26 men), mean age 44.7 ± 16.5 years	61.8% of paroxetine group vs 38.2% of the placebo group had negative tilt test, 17.6% of paroxetine group vs 52.9% of the placebo group had spontaneous syncope (p <0.0001), paroxetine improved symptoms of vasovagal syncope
Moore, et al. (2005). (53)	Selective adrenergic agonist 1 (midodrine vs. placebo)	A pilot prospective double- blind, randomized, controlled study vs. placebo	n = 10 elderly people (6 women, mean age 75, range 66-86 years) with carotid sinus syndrome	In patients treated with midodrine for vasodepressor carotid sinus syndrome, the drug significantly reduces the frequency of symptoms, reduces the fall in BP after carotid sinus massage and mean 24-hour ambulatory BP increases
Kaufmann, et al. (2002). (54)	Selective adrenergic agonist 1 (midodrine vs. placebo)	A randomized double-blind, crossover trial vs. placebo	n = 12 (with recurrent neurally mediated syncope)	Midodrine significantly improves orthostatic intolerance during the tilt test in neurally mediated syncope patients (p <0.02)

Authors	Drug	Study Design	Population	Results
Pérez-Lugones, et al. (2001). (55)	Selective adrenergic agonist 1 (midodrine vs. liquids and salt tablets for 6 months)	Prospective randomized trial	n = 61	81% of midodrine group vs 13% of the group with liquids and salt tablets were asymptomatic (p <0.001)
Ward, et al. (1998). (56)	Selective adrenergic agonist 1 (midodrine vs. placebo for one month)	A randomized double-blind, controlled trial vs placebo	n = 16 (11 women), mean age 56 ± 18 years	Midodrine group had more symptom-free days and less positive tilt test vs. the placebo group
Mitro, et al. (1999). (57)	Selective adrenergic agonist 1 (midodrine)	Non-randomized prospective trial	n = 41 (23 women), mean age 34 years, with recurrent syncope and positive tilt test	95% had no presyncope or inducible syncope by repeated tilt tests. Mean follow-up 19 ± 9 months
Yu, et al. (1997). (58)	Anticholinergic (propantheline)	Non-randomized prospective study	n = 16 (11 men), mean age 48.8 ± 15.1 years	81% of patients had no syncope or inducible presyncope with repeated tilt tests on follow-up 15.2 ± 7.4 months
Salim, et al. (2005). (59)	Mineralocorticoid (fludrocortisone) and salt intake	Double-blind, randomized, controlled study vs. placebo	n = 32 (20 women), mean age 13.9 ± 2.5 years	Reduced recurrence of syncope in the placebo group (p <0.04)
Da Costa, et al. (1993). (60)	Mineralocorticoid (fludrocortisone)	Non-randomized prospective study	n = 11, mean age 83 ± 5 years, all patients had dizziness daily and vasodepressor carotid sinus syndrome	Fludrocortisone effectively reduced the vasodepressor response and relieved the symptoms of vasodepressor carotid sinus syndrome

mechanisms, including abnormal vascular reflexes, atrial and/or ventricular arrhythmias or obstruction in the outflow tract of the right ventricle. (72, 73) It is essential to try to recognize the underlying cause that provokes it and when it is not identified (unexplained cause of syncope) should be considered a greater risk factor in the assessment of the risk of sudden death. (74) The presence of syncope in patients with HCM has more meaning when it occurs in children or young patients, when it is recurrent or occurs during or immediately after exercise. (75)

The arrhythmogenic right ventricular cardiomyopathy is a genetic disease that may be presented with palpitations, syncope or sudden death. Risk stratification is extremely difficult. They are described as risk factors: being young, the presence of extensive right ventricular dysfunction, left ventricular commitment, the occurrence of ventricular tachycardia, the presence of late potentials, epsilon waves and family history of sudden death. (76, 77) In patients with arrhythmogenic right ventricular cardiomyopathy, syncope occurs in about one third of the derivatives to tertiary centers. Patients with arrhythmogenic right ventricular dysplasia who experience syncope, unable to exclude the VT / VF as its cause, they should receive an ICD. (Class IIa indication, level of evidence C). (73, 78)

Among the genetic syndromes that predispose

to VT or VF include the long and short QT interval syndromes, Brugada syndrome, catecholaminergic polymorphic VT and idiopathic VF. These primary electrical disorders occur in the absence of structural heart disease and predispose to potentially lethal ventricular arrhythmias. (79)

However, it is important to note that in a total population of patients with long QT syndrome that have phenotype of the condition and who are under treatment with beta-blocking agents, mortality over a 40-year follow-up was about 4%, that is to say, 0.1% per year. (73)

Among factors that predispose to an increased risk of adverse cardiac events are included patients who recovered from cardiac arrest, Jervell and Lange-Nielsen syndrome, a QTc interval ≥ 600 msec and patients with recurrent syncope despite beta-blockers.

A recent study shows that patients treated with beta blocking agents, the risk of recurrent syncope is low, but if there is, it increases between 6 and 12 times the chance of a fatal adverse event or near-fatal. (80)

Brugada syndrome is an inherited disease that may be presented with ventricular arrhythmias, syncope or sudden death in the presence of a typical electrocardiographic pattern that has the following characteristics: J-point elevation of the ST segment with negative T waves in right precordial leads.

Risk stratification of sudden death that have this

condition varies according to the authors in different series. However, there is agreement that the presence of syncope is a factor that significantly increases it.

In conclusion, in patients with diagnosis of Brugada syndrome and syncope, the recommendation to implant an ICD should be considered of Class IIa. (73)

Hereafter, there are listed the recommendations for the indication of an implantable cardioverter defibrillator in patients with syncope of unknown origin associated with different pathologies.

#### **Class I Level of evidence A**

- Dilated cardiomyopathy of ischemic or nonischemic origin with severe impaired LVFSF.

#### **Class IIa. Level of evidence B**

- Brugada syndrome with spontaneous ECG pattern of type I
- Long QT syndrome with beta-blockers to patients with high risk.
- Catecholaminergic polymorphic ventricular tachycardia.

#### **Class IIa. Level of evidence C**

- Hypertrophic cardiomyopathy at high risk.
- Right ventricular dysplasia at high risk.

#### **Class IIb. Level of evidence C**

- Ischemic dilated cardiomyopathy with severe impaired of LVFSF and negative programmed electrical stimulation.

## **6. SYNCOPE IN THE ELDERLY**

At present it is considered elderly any person aged older than 65 years, this definition, which is arbitrary, do not have health connotation, but it has to do with the age at which is acquired, in most countries, the retirement and some social benefits.

Syncope in elderly patients is a problematic entity. In the REDIFA study, 12% of elderly people reported having experienced a syncopal episode at the end of his life, (81) and visits for syncope in the emergency services, 80% corresponds to people older than 65 years. (82)

The problem with syncope in the elderly is the multiplicity of causes and their impact on the prognosis associated with falls. Elderly who has syncope is at high risk of fractures (especially hip), an increase in the rate of hospitalization, reduced independence with great negative impact on quality of life and a high mortality.

The most common causes of syncope in the elderly are orthostatic hypotension, reflex syncope (especially the carotid sinus syndrome), and cardiac arrhythmias. Orthostatic hypotension is a complex problem in the management of the elderly, it may be due to many causes in addition to age-related, its incidence is between 20% and 30%. (83, 84)

An important cause of orthostatic hypotension is antihypertensive medications and drugs used for neurological treatment with cholinesterase inhibitors. This makes difficult the management of patients in whom hypertension, senile cognitive impairment, and orthostatic hypotension coexist.

Carotid sinus syndrome is another frequent entity in the elderly and is due to sclerosis of the carotid bulb. It is often associated with cardiovascular disease, stroke and other comorbidities.

Finally, the most prevalent autonomic dysfunctions are the secondary ones, which are associated with diabetes and Parkinson's disease. The main element is the finding of postprandial hypotension or linked to drug taking. (85)

### **6.1. Diagnostic Assessment**

The diagnostic approach in elderly patients should not differ from that of the general population with syncope.

While questioning and physical examination are a valuable tool in the etiologic diagnosis of syncope, we should know that in the elderly the revenue may decrease. 5% to 20% of patients, depending on age, have cognitive impairment and besides there are no witnesses in most episodes.

Considering the most common causes of syncope in this age group, the assessment of orthostatic hypotension should be a priority.

Carotid sinus massage is another diagnostic tool with Class I indication in the elders. (1)

Most part of the bibliography agrees that all patients older than 65 years should be questioned about the relationship between syncope and intake, since the postprandial syncope is very common in clinical practice. The assessment of autonomic nervous system is also clinically useful.

No less important is the search for structural heart disease, since its finding guides for the diagnosis and eventual treatment.

The ambulatory recording of arterial pressure (MAPA) may be helpful in the diagnosis of tension changes, although its diagnostic value in syncope has not been assessed.

## **7. SYNCOPE IN CHILDREN AND ADOLESCENTS**

Nearly 15% of these patients experienced a syncopal episode before 18 years old. While most of the episodes are neurocardiogenic or reflex syncopes, syncope may be the first manifestation of congenital diseases with structural heart disease or not. (86)

The management of children and adolescents with syncope is, generally, similar to the management of the adult, except for some differences.

We describe two specific disorders that occur early in childhood. The first is infantile reflex syncopal attacks (also called pale apnea or anoxic reflex attacks), produced by a brief unpleasant stimulus, they are due to cardiac vagal inhibition. The second entity is transient loss of consciousness hypoxic

apneic type (also called cyanotic apnea), characterized by a expiratory cessation of breathing during crying, that produces cyanosis and often transient loss of consciousness.

The differentiation between epilepsy and syncope is sometimes complex, since the pediatric patient may respond to hypotension with seizures. There are guiding data to differentiate them, which are summarized in Table 3. The suggestive findings of epilepsy are the aura, the horizontal movement of the eyes and the absence of hypotension during the episode, after episode migraine headache and postictal period. It is important to highlight that urinary or fecal incontinence has no value to distinguish between these two entities. (87)

As in the adult, personal and family medical history should be thorough. The physical examination with the questioning (especially of the witness) has much diagnostic utility. When the clinical history focussing on a reflex syncope, episodes are infrequent, there is no family history and is not associated with structural heart disease, the diagnostic investigation may be finished at that point because of deeming low risk.

When family history provides relevant data or a history of heart disease, etiologic suspicion of syncope should be guided to the findings of a specific heredofamiliar heart disease.

In children, the conditions that cause syncope and are potentially dangerous, include: long and short QT interval syndrome, hypertrophic cardiomyopathy, arrhythmogenic dysplasia of right ventricle, myocardium non-compact, Brugada syndrome, catecholaminergic ventricular tachycardia and other less common types of infrequent congenital diseases, such as congenital palliated or operated heart disease. Some of these conditions do not usually have a suggestive family history. (88)

In general, a proper questioning (to the relative, the witness and the patient if is possible), a complete physical examination, an electrocardiogram and an echocardiogram may distinguish three different risk groups with prognostic differences:

- A low-risk group is the one who does not have heart disease or family history and also has isolated episodes.
- A second group of patients with most at risk is the one with heart disease, in which the cause of syncope should be investigated associated with underlying heart disease or with the obtained findings
- A third group, which is labeled as syncope of unknown origin.

The realization of a tilt test in pediatric patients is safe, although some authors recommend a shorter protocol and findings of the test should be taken with caution because the number of false positives and negatives. (89)

There is little evidence on drug treatment in pediatric and adolescent patients with syncope, so that its use should be careful. General preventive measures are, without doubt, the treatment of choice

when opting for a treatment and should be the first to be instituted.

In summary, the objective of the assessment of a pediatric patient with syncope is, in first place, to assess the presence or absence of macro-or microstructural cardiopathy. In the absence of heart disease, diverse psychological and clinical factors that may predispose to hypotensive or reflex syncopes should be assessed in collaboration with the pediatrician. In the presence of heart disease, the sequence of further diagnostic exploration depends on its etiopathogenesis.

## 8. ASSESMENT AND MANAGEMENT OF THE PATIENT IN THE EMERGENCY UNIT AND SYNCOPE UNIT

Current strategies to establish a definitive diagnosis in a patient with transient loss of consciousness are not uniform and generate a trend of hospitalization and the achievement of additional studies, not always indicated.

The objective of the Syncope Unit is to, through a diagnostic algorithm, prevent unnecessary admissions of patients attending the emergency department with syncope and achieve adequate diagnostic performance without affecting the prognosis of patients. (90)

As we have seen throughout this Consensus, the first approach to the patient with syncope includes questioning, physical examination and laboratory analysis in order to stratify risk in a period less than 24 hours.

According to the algorithm shown in Figure 2, the risk of morbidity and mortality in patients with syncope assessed in the emergency room is classified into high, intermediate and low.

Low risk (LR) corresponds to patients with a first episode, age <40 years, normal ECG, without heart disease, occupational risk or physical injuries, unrelated to exercise or with clear neurocardiogenic origin. These patients with LR should not remain hospitalized.

Intermediate risk (IR) corresponds to those with recurrent syncope, age > 40 years, occupational risk, with an implanted pacemaker without evidence of dysfunction, suffering from heart disease, present minor trauma or family history of sudden death.

High risk (HR) corresponds to patients who present with arrhythmias, with a history of severe arrhythmias, acute LBBB or RBBB, they are receiving antiarrhythmic with acute changes in the ECG, present a QTc  $\geq$  0.50 sec or have suffered more trauma. HR patients should be hospitalized.

Patients with IR require a reassessment. If they have a pacemaker, it is controlled: if is abnormal they should be hospitalized, whereas if it is normal and those who do not have a pacemaker, an echocardiogram is carried out.

At this point, the result of the echocardiogram determines whether is carried out a tilt test if normal or the patient is hospitalized in case it is abnormal. If the tilt test is positive, indicating the discharge and if negative the patient will undergo Holter ECG

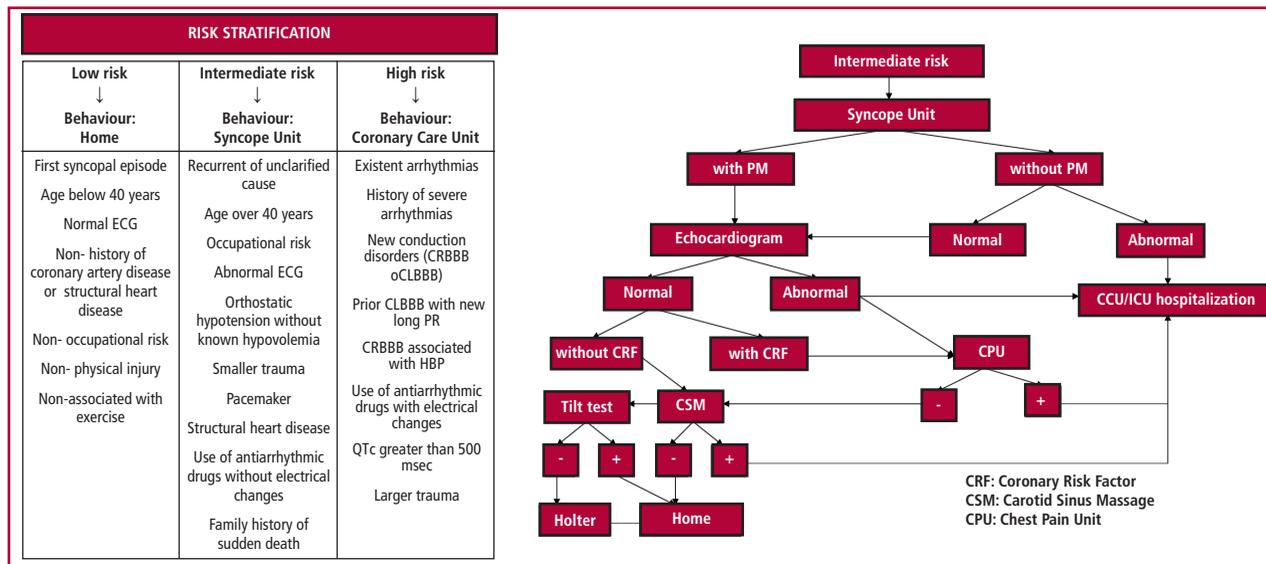
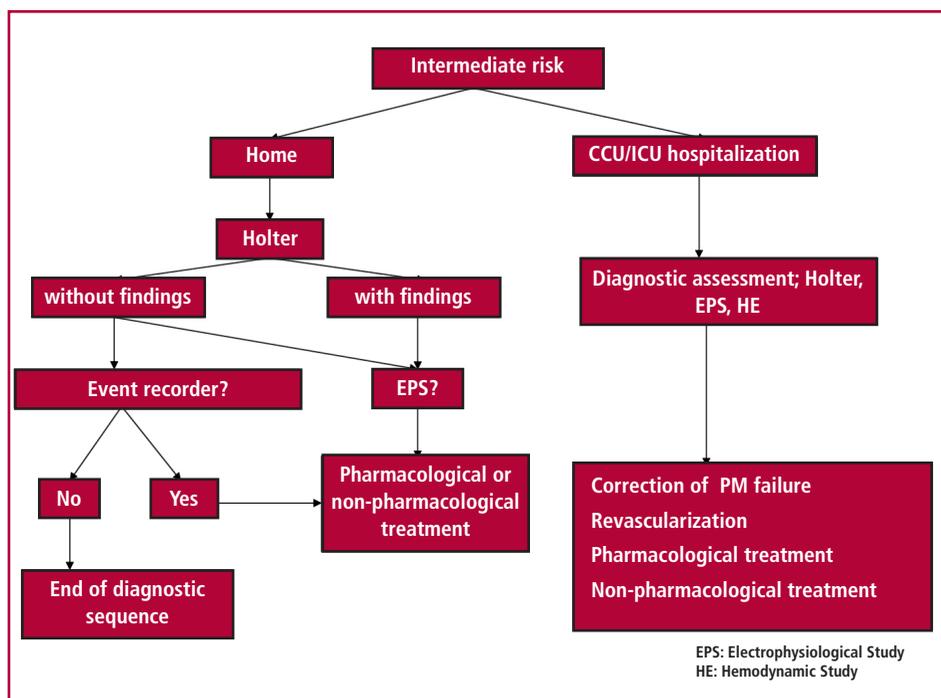


Fig. 2. Algorithm for assessment of syncope in the Emergency Room



recording prior to discharge.

Different studies have shown that Syncope Units reduce the need for hospitalizations without an increased incidence of adverse events during follow-up. (90-92) The experience in our country has shown that using these algorithms may prevent the hospitalization of 60% of patients with intermediate risk. (93)

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