

## Update: Arrhythmias (VIII)

# Syncope

Ángel Moya-i-Mitjans,\* Nuria Rivas-Gándara, Axel Sarrias-Mercè, Jordi Pérez-Rodón, and Ivo Roca-Luque

Unidad de Arritmias, Servicio de Cardiología, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain

### Article history:

Available online 3 July 2012

### Keywords:

Syncope  
Transient loss of consciousness  
Transient cerebral hypoperfusion

### ABSTRACT

Syncope, which can be defined as a transient loss of consciousness caused by transient global cerebral hypoperfusion and characterised by rapid onset, short duration, and spontaneous complete recovery, is a common condition. This definition is useful for differentiating syncope from other clinical conditions that also involve real or apparent transient loss of consciousness, but in which the mechanism is not global cerebral hypoperfusion, such as epilepsy, falls, or psychiatric pseudosyncope. We reviewed the etiological classification of syncope and found that reflex syncope is the most common etiology in the general population, with a good prognosis, whereas cardiac syncope increases with age and has a worse prognosis. We also reviewed the role and limitations of different tests, specifically referring to the interpretation of the results of carotid sinus massage, the role of tilt-table testing, the diagnostic strategy in patients with syncope and bundle branch block, the adenosine test, and the emerging role of prolonged electrocardiographic monitoring. Furthermore, we reviewed the different therapeutic options available. The importance of establishing syncope units with the aim of improving the diagnostic process and optimizing resources is also emphasized.

© 2012 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

### Síncope

### RESUMEN

El síncope, definido como una pérdida transitoria de conciencia que cursa con recuperación espontánea y sin secuelas que se debe a una hipoperfusión cerebral general y transitoria, es un cuadro clínico muy prevalente. Esta definición permite diferenciar el síncope de otras entidades que cursan con pérdida de conciencia transitoria, real o aparente, en las que el mecanismo no es una hipoperfusión cerebral, como la epilepsia, las caídas accidentales o el seudosíncope psiquiátrico. Se revisa la clasificación etiológica del síncope, con especial hincapié en que el síncope reflejo es el más frecuente y tiene buen pronóstico, mientras que el síncope cardiogénico aumenta con la edad y tiene peor pronóstico. Se hace una revisión crítica de las principales exploraciones, con especial énfasis en las dudas sobre la interpretación del masaje del seno carotídeo, las limitaciones de la prueba en tabla basculante, la estrategia a seguir en pacientes con síncope y bloqueo de rama, la administración de adenosina y el papel de la monitorización electrocardiográfica prolongada. Asimismo se revisa el estado actual del tratamiento y se destaca la importancia de establecer unidades de síncope con la finalidad de mejorar el proceso diagnóstico optimizando los recursos.

© 2012 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

### Palabras clave:

Síncope  
Pérdida transitoria de conciencia  
Hipoperfusión cerebral transitoria

### Abbreviations

BP: blood pressure  
CSM: carotid sinus massage  
EPS: electrophysiology study  
HR: heart rate  
ICD: implantable cardioverter defibrillator  
TTT: tilt-table test

### INTRODUCTION

Syncope is a very prevalent condition<sup>1,2</sup> and is frequently the cause for seeking medical attention both in primary care<sup>3</sup> and emergency departments.<sup>4</sup> Although in the majority of cases syncope is due to a reflex mechanism and has a good prognosis,<sup>1,2</sup> recurring episodes may occur in certain patients, with a severe impact on their quality of life.<sup>5</sup> Between 6% and 30% of patients, according to age and context, have syncope of a cardiac origin. It may constitute the first manifestation of disease and can serve as a marker for poor prognosis, with the risk of sudden death.

These patients can undergo their first evaluation in primary care or emergency departments, and can then be referred to neurology, internal medicine, or cardiology units. In this context, given the high number of patients seeking medical care for episodes of loss of consciousness, there is a high risk of

\* Corresponding author: Unidad de Arritmias, Servicio de Cardiología, Hospital Universitario Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain.

E-mail address: [amoya@vhebron.net](mailto:amoya@vhebron.net) (A. Moya-i-Mitjans).

overdiagnosis in patients with benign causes, leading to increased costs, and on the other hand, a risk of underdiagnosing those patients with possibly severe and often treatable conditions.

With the objective of standardizing and optimizing the process of diagnosing and treating these patients, several clinical practice guidelines have been published in recent years on the topic of syncope.<sup>6-9</sup> However, there are several unresolved aspects, as well as new developments, that often make managing patients with syncope a difficult challenge.

In this update, we review the primary recommendations from the guidelines, placing special emphasis on unresolved aspects as well as new data and expectations.

## DEFINITION AND CLINICAL CONTEXT

One of the first definitions published for syncope came out in the 2001 guidelines of the European Society of Cardiology.<sup>6</sup> This definition included the fundamental concepts of syncope, which are transient loss and spontaneous recovery of consciousness, with no need for treatment and an absence of sequelae. This definition also established that, for a transient loss of consciousness to be labeled as syncope, the causal mechanism had to be transient cerebral hyperperfusion.

This definition is important because it places syncope in the context of a number of clinical conditions that involve a real or apparent transient loss of consciousness.<sup>6-9</sup> Patients usually describe symptoms as falls, dizziness, or fainting, and are often incapable of attesting to whether or not they lost consciousness. Table 1 lists the different sets of clinical symptoms that are usually associated with real or apparent transient loss of consciousness that can be confused with syncope. We will expand more on those conditions that most frequently create problems in the differential diagnosis.

### Syncope and Epilepsy

From the point of view of clinical descriptions, both of these entities share many characteristics that define episodes of syncope, since epilepsy involves transient loss of consciousness in which the patient recovers spontaneously and without sequelae. Epileptic seizures involve tonic-clonic convulsions, but patients with syncope may have muscle contractions during episodes of syncope that can be confused with an epileptic seizure.<sup>10</sup> From a pathophysiological point of view, the difference between these two entities lies in the underlying mechanism: syncope is the result of cerebral hypoperfusion<sup>6,7</sup> and epilepsy is caused by uncontrolled discharges from neurons of the cerebral cortex.<sup>11</sup>

In epilepsy, seizures appear at the start of symptoms, with widespread movements that affect the entire limb, whereas syncope initially involves hypotonia, and only after several seconds of cerebral hypoperfusion can muscle movements be observed, to a lesser degree than in epileptic seizures, normally affecting the distal ends of the arms.<sup>10</sup> In the medical literature

concerning neurology, results suggest that in a substantial proportion of patients initially labeled as epileptic the diagnosis is later switched to syncope.<sup>12</sup> The importance of a correct differential diagnosis is twofold: on the one hand, in addition to the negative connotations for the patient, a diagnosis of epilepsy involves treatment that usually has side effects and on the other hand, once the incorrect diagnosis is made (in this case epilepsy), the diagnosis of a potentially severe and eventually treatable cause of syncope can be delayed or never even reached.

### Syncope and Falls

Another entity that must be differentiated from syncope is falls. Elderly patients suffer frequent inexplicable falls, many of which cause fractures that can mark the start of clinical deterioration, with substantial loss of independence and reduced quality of life. In the majority of cases the fall is assumed to be incidental or the result of a loss of balance because, as it normally occurs so rapidly, the patient and family members rarely report a loss of consciousness.<sup>13</sup> Many of these patients are under treatment with several medications that can reduce blood pressure (BP) and heart rate (HR). Additionally, many of these patients have reduced perception of thirst, often leading to some level of dehydration. Furthermore, these patients have a high incidence of cardiopathy and electrocardiogram (ECG) abnormalities in the form of conduction disorders and sinus node dysfunction, which can cause syncope. Many of these patients are directly treated in trauma-orthopedic emergency rooms, where the suspicion of syncope is lower than in medical emergency rooms. This probably leads to an improper diagnosis of many cases of syncope. The consequence of this misdiagnosis is that we are unable to establish a specific treatment that would avoid subsequent episodes and their consequences.

### Psychiatric Pseudosyncope

There are patients who suffer falls that appear to lack any connection with their environment and who show no evidence of cerebral perfusion. This has been documented during tilt-table tests (TTT) in some patients in which a pseudosyncope episode was triggered with no hypotension or bradycardia. In these cases, the cause is believed to be of psychiatric origin. The differential diagnosis can be difficult but there are some clinical signs that can aid in defining the episode as a psychiatric pseudosyncope, such as when a patient suffers multiple episodes even on the same day, when longer episodes last up to several minutes, and when the patient's eyes are closed during the episode, contrasting with syncope, in which patients tend to have partially open eyes.<sup>14</sup>

## RISK STRATIFICATION AND ETIOLOGICAL DIAGNOSIS

Once the patient has been confirmed to be suffering from syncope, a diagnostic approach must be decided upon.

**Table 1**  
Clinical Conditions That Lead to Transient Loss of Consciousness (Real or Apparent) and Can Be Confused With Syncope

Loss of consciousness	No loss of consciousness
Epilepsy	Falls (especially in the elderly)
Metabolic alterations such as hypoglycemia or hyperventilation with hypocapnea	Drop attack
Intoxication	Psychogenic pseudosyncope
Vertebrobasilar transient ischemic attack	Cataplexy

## Etiological Classification

Syncope can be caused by 3 different etiologies (Table 2): a reflex or neurally mediated mechanism; a cardiogenic origin, which can involve arrhythmia or some type of structural cardiopathy; or orthostatic hypotension, which can be due to primary autonomic dysfunction, secondary to an underlying condition, or triggered by hypotensive drugs or hypovolemia. In any case, although the cause of syncope tends to be one of the three aforementioned mechanisms, on occasion it is caused by multiple mechanisms. For example, there is a vasodilatory component and a cardioinhibitory component to neurally mediated syncope, and in syncope caused by tachyarrhythmia, transient hypotension, a reflex mechanism caused by poor adaptation to the initial sudden onset of the tachyarrhythmia, has been observed (Fig. 1).<sup>15-17</sup>

## Initial Evaluation of Patients Treated for Transient Loss of Consciousness

The initial evaluation of any patient treated for the first time for transient loss of consciousness consists of a detailed clinical history focused on certain aspects of the syncope episode, a physical examination focused on evaluating the possibility of a cardiopathy that may have caused the syncope, and an ECG.<sup>7,8</sup>

Since syncope is a transient phenomenon that does not leave sequelae, in the majority of cases no objective test is available to confirm whether or not the patient has suffered an episode of syncope or to establish its cause.<sup>18,19</sup> The only information that we can obtain is provided by the clinical history, with a detailed description of triggering factors, previous symptoms, what occurred during the episode, and the recovery process. In addition, data on the chronology of the episodes of syncope, duration and frequency of the episodes suffered in the previous months and years, the patient's history of cardiopathies and other diseases, pharmacological history, and family history are of utmost importance in order to establish whether or not the patient has suffered syncope, a diagnosis of the etiology, or a risk stratification that will allow us to make the correct decisions. This information can only be obtained through a detailed interview with the patient and any witnesses of the episode.

The physical examination is also very useful, but provides little information regarding the etiology of the episode unless it reveals evidence of aortic stenosis, signs of heart failure, or a clearly

pathologic response to active orthostasis or carotid sinus massage (CSM).

All patients who seek medical care for an episode of syncope must undergo an ECG, at least the first time, even when their clinical history clearly suggests a reflex syncope. This is of great importance because even though it is true that an emotional trigger is one of the characteristics of vasovagal syncope, some cardiogenic conditions such as congenital long QT syndrome and catecholaminergic ventricular tachycardia can be triggered by an adrenergic stimulus that may be confused with an emotional trigger of a reflex syncope. On the other hand, since a certain degree of overlap has been described between reflex syncope and other forms of channelopathy, such as Brugada syndrome,<sup>20,21</sup> ECG abnormalities must be ruled out in all of these patients.

Table 3 lists the circumstances that can be considered diagnostic for the different etiologies of syncope following an initial evaluation. Table 4 describes those abnormalities that, while indicative of syncope, do not provide sufficient evidence to establish a definitive diagnosis, requiring further testing to rule out or confirm the etiology.

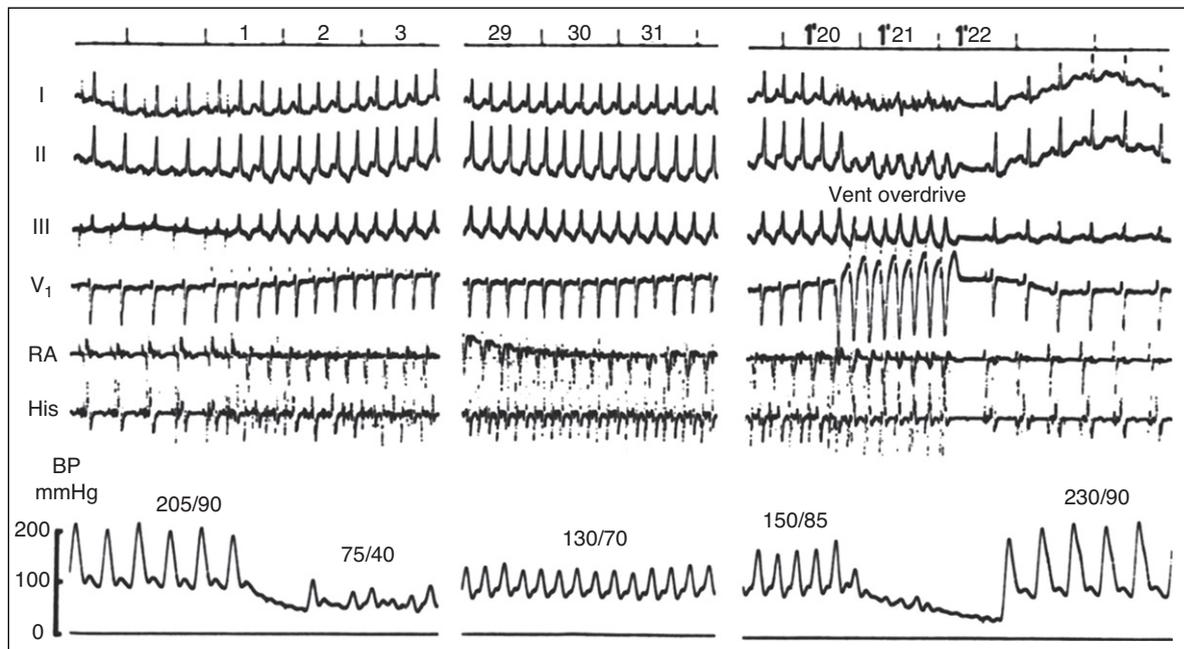
## Risk Stratification

In recent years, several publications have identified a number of predictive variables of short- to mid-term severe cardiovascular events, including death, in patients with a history of syncope.<sup>22-24</sup> For this reason, the most recent guidelines<sup>7,8</sup> have placed special emphasis on the initial risk stratification of patients who have suffered an episode of transient loss of consciousness without receiving an etiological diagnosis based on the initial evaluation. Table 5 summarizes the criteria for patient risk, which in general coincide with the conditions associated with cardiogenic syncope. Using these variables, patients with syncope can be classified as low or high risk.

Low-risk patients have a very low probability of suffering cardiogenic syncope. In the majority of cases, if the patient has suffered a first episode of syncope or infrequently occurring episodes, further examination is not usually necessary, especially if the patient is young. These patients should be informed about the benign nature of their situation. Only in the case of recurrent and unexpected episodes that affect the patient's quality of life should other tests be performed in order to diagnose possibly unexpected etiologies or to perform a detailed evaluation of the underlying mechanisms of each particular case in order to provide personalized treatment.

**Table 2**  
Etiological Classification of Syncope

<i>Reflex or neurally mediated</i>	
Vasovagal	Triggered by adrenergic discharge Triggered by standing
Situational	Related to coughing, gastrointestinal stimulus, urination, postprandial, after exercise or laughter
Carotid sinus syndrome	With or without apparent stimulus of the carotid sinus
Atypical forms	No apparent trigger
<i>Cardiogenic</i>	
Bradyarrhythmia	Sinus node dysfunction, atrioventricular block
Tachyarrhythmia	Supraventricular or ventricular tachycardia
Structural cardiopathy	Aortic stenosis, hypertrophic cardiomyopathy, atrial myxoma, pericardial tamponade, aortic dissection
<i>Orthostatic hypotension</i>	
	Primary autonomic dysfunction
	Secondary to diabetes mellitus, amyloidosis, spinal lesions
	Induced by drugs (vasodilators, diuretics, antidepressants)
	Hypovolemia (insufficient water intake, hemorrhage, diarrhea)



**Figure 1.** Transient reflex hypotension during induced accessory pathway reciprocating tachycardia. A sudden drop in blood pressure from 205/90 mmHg to 75/40 mmHg at the moment of tachycardia induction (left) manifests clinically as presyncope. After several seconds of tachycardia (center), blood pressure stabilizes at 130/70 mmHg, despite sustained tachycardia. Before tachycardia is halted (right), blood pressure is 150/85 mmHg, and when tachycardia ends there is a sudden increase in blood pressure. The fact that the patient initially has hypotension and recovers from it despite sustained tachycardia suggests that the hypotension is due to a poorly adapted reflex mechanism, rather than the tachycardia itself. BP, blood pressure; RA, right atrium. (Courtesy of Dr Roberto Garcia Civera, Hospital Clínico de Valencia, Valencia, Spain.)

**Table 3**  
Diagnostic Criteria Following the Initial Evaluation

Vasovagal syncope	Emotional triggers and typical prodromes, in the absence of cardiopathy, with a normal ECG, and no family history of sudden death
Situational syncope	When clearly associated with coughing, urination, abdominal pain, in the absence of cardiopathy, with a normal ECG, and no family history of sudden death
Syncope from orthostatic hypotension	When spontaneously occurring in relation to changes in posture, along with a documented symptomatic orthostatic hypotension
Syncope due to bradycardia or sinus node dysfunction	When persistent sinus bradycardia is documented at <40 bpm during waking hours, or in the presence of episodes of sinoatrial block or sinus pauses $\geq 3$ s
Syncope secondary to AVB	Complete AVB or second degree Mobitz II block Alternating right and left bundle branch block
Syncope secondary to tachycardia	Sustained VT or rapid SVT Uncontained VT in patients with long QT syndrome In patients with a Brugada type I ECG pattern and no data diagnostic of another aetiology
Syncope secondary to structural cardiopathy	Severe aortic stenosis, atrial myxoma, pulmonary embolism, or aortic dissection

AVB, atrioventricular block; ECG, electrocardiogram; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

High-risk patients should be immediately evaluated for several reasons. First, the cause of syncope could be a severe arrhythmia that could threaten the patient's life if left unchecked. Second, syncope can be a marker of cardiac disease. Following an initial complete evaluation, if arrhythmia is not clearly confirmed as the cause of syncope and severe cardiopathy is ruled out, these patients can be monitored in an outpatient context.

Once the process of risk stratification is completed, certain complementary tests must be performed, some of which are directed towards confirming or ruling out cardiopathy and establishing its severity, and other more specific tests are focused on determining the underlying mechanism of syncope in certain patients. In suspected cases of cardiogenic syncope, an echocardiogram must be performed. Based on the results from this test and the clinical suspicion, other examinations will be indicated, such as

imaging tests in order to rule out specific types of cardiopathy, or a coronary angiography in the case of suspected ischemic heart disease. A stress test is usually indicated in patients with physical exercise-related syncope. For low-risk patients, these examinations are only indicated if the syncope recurs frequently and is clinically severe, or when there is a high risk of trauma due to professional or leisure activities.

### A CRITICAL VIEW OF THE DIFFERENT COMPLEMENTARY EXAMINATIONS IN PATIENTS WITH SYNCOPE OF UNKNOWN CAUSE

In this section, we will analyze the role of the majority of the complementary examinations that tend to be carried out in

**Table 4**  
Criteria Suggestive, but not Diagnostic, of the Aetiology of Syncope

Reflex syncope	Absence of cardiopathy, normal ECG, and no family history of sudden death Long history of syncope Nausea and vomiting Preprandial or postprandial After exercising Caused by rotation of the head or compression of the neck
Syncope due to orthostatic hypotension	When syncope occurs with changes of posture from lying or seated to standing When coinciding with changes in doses of vasodepressors or diuretics
Cardiac syncope	Bifascicular bundle branch block (LBBB or RBBB with AHB or PHB) or interventricular conduction disorder with $QRS \geq 120$ ms Asymptomatic sinus bradycardia $\leq 50$ bpm Second-degree Mobitz I AVB Uncontained VT Ventricular preexcitation Long or short QT segment Brugada ECG pattern Q-waves suggestive of myocardial necrosis Syncope appears during exercise Family history of unexplained sudden death at a young age Palpitations that precede the episode of syncope Syncope occurs in decubitus History of cardiopathy

AHB, anterior hemiblock; AVB, atrioventricular block; ECG, electrocardiogram; LBBB, left bundle branch block; PHB, posterior hemiblock; RBBB, right bundle branch block; VT, ventricular tachycardia.

the assessment of patients with syncope of an unknown cause, based on the guideline recommendations. However, we will highlight some controversial aspects in light of novel results that have appeared in the recent literature, and will comment on where future research will take us.

One of the issues is that the majority of the examinations of patients with syncope consist of provocation tests. Although these tests attempt to produce physiological alterations that cause syncope, doubts are raised in the interpretation of the results because it is impossible to establish a causal relationship with the spontaneous episode of syncope suffered by the patient. Recently, the availability of prolonged ECG recording systems has allowed us to obtain more diagnostic information for select patients and provides a new framework for interpreting the value of several of these tests, leading to a better understanding of the mechanism behind syncope in certain groups of patients.

**Table 5**  
Risk Criteria Requiring Immediate Evaluation or Hospitalization

Ischaemic heart disease or dilated cardiomyopathy with $EF < 35\%$
History of myocardial necrosis
Heart failure
Episode of NSVT
Bifascicular bundle branch block (LBBB or RBBB and AHB or PHB) or $QRS \geq 120$ ms
Preexcitation
Long or short QT
Family history of sudden death
Brugada pattern ECG

AHB, anterior hemiblock; ECG, electrocardiogram; EF, ejection fraction; LBBB, left bundle branch block; NSVT, non-sustained ventricular tachycardia; PHB, posterior hemiblock; RBBB, right bundle branch block.

### Carotid Sinus Massage

Applying external pressure to the area of the carotid sinus, a maneuver known as CSM, will slow the HR, prolong the PR interval, and produce a drop in BP. Classically, a pause  $\geq 3$  s or a drop in systolic BP  $\geq 50$  mmHg from baseline values is defined as an abnormal response, suggesting hypersensitivity of the carotid sinus. The problem faced when interpreting this finding is that this type of response is relatively frequently observed in elderly patients and those with any one of several different types of cardiovascular disease, and that have never suffered syncope.<sup>25-27</sup> Since the response to CSM includes slowed HR and a possible drop in BP, the BP must also be measured during the massage.

Given the high rate of hypersensitivity of the carotid sinus observed in some patients who have never suffered an episode of syncope, and with the end goal of increasing the specificity of the test, it has been proposed that CSM must, in addition to producing pauses or hypotension, reproduce the patient's symptoms, in this case syncope, in order to consider the response to CSM to be the causal mechanism of syncope.<sup>28</sup> In patients with a negative CSM test while lying down, the test should be repeated in an upright position so as to better evaluate the presence of symptoms during massage.

The 2009 guidelines recommend performing CSM on all patients older than 40 years with syncope of an unknown cause, considering the response to be positive if the patient has an asystole period  $\geq 3$  s and/or a drop in systolic BP  $\geq 50$  mmHg, with the reproduction of spontaneous symptoms.

However, there continue to be doubts surrounding whether these cut-off values, especially the pause  $\geq 3$  s, are excessively sensitive and thus overdiagnose hypersensitivity of the carotid sinus. Recently, an exhaustive review was published on the origin of this cut-off value and the pathophysiologic data that support it, and the authors concluded that the cut-off value was based on historical data with little pathophysiologic rigor, which probably has led to an excessive number of false positives. In this review, the expert panel proposed a revision of these values, establishing a

new cut-off at 6 s.<sup>29</sup> This observation, which also lacks supporting evidence, demonstrates the need for a review of these criteria and caution when interpreting the results of CSM.

### Orthostatic Testing

This category of tests includes those that analyze BP and HR in response to changes from lying down to upright positions. The two most commonly used tests are active orthostasis and TTT.

#### Active Orthostatic Test

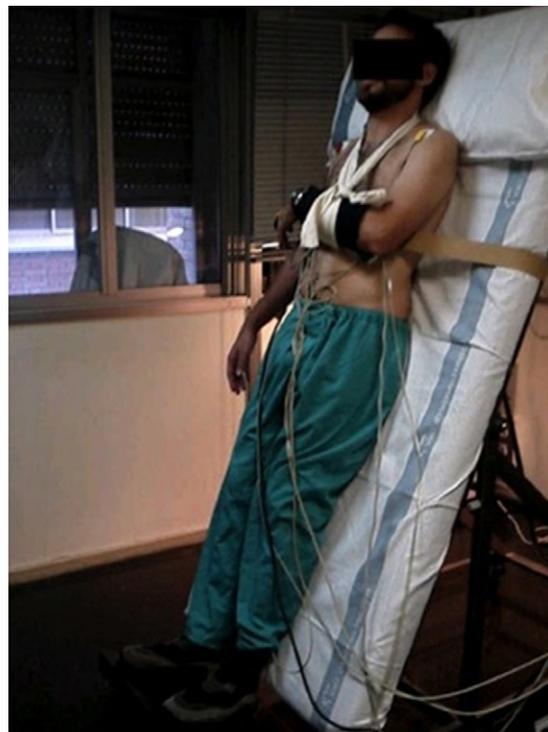
The active orthostatic test consists of analyzing response in BP and HR in the moment when the patient actively moves from lying down to a standing posture. This is the basic test indicated for patients who suffer episodes of syncope caused by changes in posture, whether immediately or a few minutes after changing positions. Despite the fact that these symptoms do occasionally occur in young patients, they are much more frequent in elderly patients, especially in people with diseases that affect the autonomous nervous system, such as diabetes mellitus and Parkinson disease, or who are being treated with hypotensive drugs. In orthostatic hypotension tests, BP and HR are repeatedly measured, ideally manually, with the patient lying down and for 3 min after assuming an active standing position. However, delayed forms of orthostatic hypotension have been described in which the drop in BP can occur even later than 5 min after changing position; in cases where such a response is suspected, the BP and HR measurements must be extended to 5 to 10 min following the test.

An active orthostatic test is considered to be diagnostic of the condition when, along with symptoms, there is a drop  $\geq 20$  mmHg in systolic BP or  $\geq 10$  mmHg in diastolic BP while lying down, or if systolic BP values fall below 90 mmHg in terms of absolute values.<sup>30</sup> Asymptomatic drops in BP are more difficult to interpret.

#### Tilt Table Test

In 1986, Kenny et al.<sup>31</sup> first described the use of a TTT as a diagnostic tool in patients with vasovagal syncope. In contrast to active orthostatic tests, TTT involves a passive change in posture: the table is inclined without the patient performing any active movement (Fig. 2), and it is kept at an inclination of 60° to 70°, in contrast to the vertical position held during active orthostasis. With this maneuver, there is less muscle activity in the legs, which facilitates a greater accumulation of fluid and a consequent drop in central volemia and can trigger a reflex response in susceptible patients.

During the late 1980s and '90 s, TTT was very useful for better understanding the pathophysiology of reflex syncope because it facilitated an analysis of the behavior of BP and HR before and during the episode of syncope and the identification of cardio-inhibitory and vasodepressor components of reflex syncope. One of the issues with the use of TTT is that several protocols have been elaborated with varying durations, inclinations in posture, and the use of different enhancing drugs, which has led to difficulties in comparing results from different studies.<sup>6,32</sup> In recent years, at least in our field, the so-called "Italian protocol" has been put into effect, in which patients are inclined at 70° for 20 min; if this does not trigger syncope, sublingual nitroglycerin is administered through aerosol and the patient is left at the same inclination for another 20 min (Fig. 2). Another problem that has arisen in the interpretation of TTT results is the difficulty in assessing the sensitivity and specificity of the test. While we have assumed



**Figure 2.** Tilt-table test. The patient lies face-up on a bed and is then inclined to 70° from horizontal, with the feet supported by a board. Blood pressure and electrocardiogram readouts are continuously monitored. The patient is strapped to the bed in order to prevent a fall in the event of an episode of syncope. After 20 min, if there has been no syncope, a dose of sublingual aerosol nitroglycerin is administered.

that the rate of positive responses observed in healthy individuals allows us to calculate specificity, which is estimated at 90%, sensitivity is more difficult to calculate, since we have no reference values with which to compare TTT results.<sup>32</sup>

During the first few years in which TTT was used, its usefulness was examined not just as a diagnostic tool for reflex syncope but also to characterize the contribution of the cardio-inhibitory and vasodepressor components during syncope,<sup>33</sup> as well as to evaluate the response to various therapeutic interventions.<sup>34,35</sup> The role of TTT in evaluating therapeutic interventions has been ruled out because controlled studies that compared certain drugs with placebos revealed a high rate of negative TTT results, both with drug treatment and placebos,<sup>18,35</sup> and other studies demonstrated low reproducibility of the TTT results.<sup>36</sup> In recent studies comparing the results of TTT with the findings from long-term assessment of ECG monitors, TTT was likely to have a low

sensitivity both for the diagnosis of neurally mediated syncope and for the identification of patients with an important cardio-inhibitory component.<sup>37,38</sup>

Although TTT has provided us with a better understanding of the pathophysiology of reflex syncope, its use as a diagnostic tool currently has several limitations. According to the guidelines, its use is primarily indicated in non-high-risk patients with syncope of an unknown etiology that recurs frequently. In many cases, it can be a useful tool to help the patient recognize prodromes and train them to perform counter-pressure maneuvers, as well as in certain cases of orthostatic hypotension.

### Electrophysiology Study

In a similar manner to TTT, an electrophysiology study (EPS) is an indirect method of testing the patient, with debatable interpretations of the results. Currently, in patients with no structural cardiopathy and a normal ECG, EPS has a very low diagnostic value and is not indicated.

The primary objectives of EPS are the detection of a possible bradyarrhythmic mechanism for syncope, whether due to sinus node dysfunction or a conduction disorder, or to inducibility of supraventricular or ventricular tachyarrhythmias.

#### Detection of Bradyarrhythmias

EPS has a very limited role in the diagnosis of sinus node dysfunction. Sinus node recovery time is the only test involving EPS that is currently used for this purpose. Although this test has a relatively high specificity, it has a low sensitivity, meaning that the diagnosis is made using a baseline ECG or Holter monitor in the majority of cases.

Regarding conduction disorders, EPS is most useful in detecting altered infrahisian conduction because it has little diagnostic value for abnormal nodal conduction. An analysis of infrahisian conduction in syncope is indicated in patients with altered intraventricular conduction as revealed by a baseline ECG, whether with morphology indicative of a bifascicular bundle branch block (left bundle branch block or right bundle branch block along with anterior or posterior left hemiblock) or a nonspecific conduction disorder and a  $QRS \geq 120$  ms.

There is controversy regarding the best strategy to use for this group of patients. On the one hand, the most common cause of syncope in these patients is paroxysmal atrioventricular block.<sup>39</sup> However, they also can suffer neurally mediated syncope or syncope caused by ventricular tachyarrhythmia, even in the absence of structural cardiopathy.<sup>39</sup> In this context, and since there is no consensus on the optimal strategy to use for these patients, both the syncope management guidelines<sup>7</sup> and the cardiac pacing guidelines<sup>40</sup> of the European Society of Cardiology recommend direct implantation of a pacemaker (level IIa recommendation). The syncope guidelines also propose (level IIa) performing an EPS, and pacemaker implantation in the case of altered parameters of distal conduction. In order to properly address this issue, a prospective study has commenced involving patients with syncope and bundle branch block that will be randomized into one of these two treatment strategies.<sup>41</sup>

#### Inducibility of Arrhythmia

Another unresolved aspect of EPS is its role in inducing arrhythmia. As we have already mentioned, in patients with no cardiopathy the induction of ventricular arrhythmia is very rare,

and at the most we might expect to see induction of supraventricular arrhythmia. Since this finding is so rare and is usually suspected due to the presence of palpitations or because it has been directly documented, an EPS should not be performed with this goal in patients with no cardiopathy.

However, patients with ischemic heart disease or dilated cardiomyopathy and a low ejection fraction already have an indication for an implantable cardioverter defibrillator (ICD), regardless of the presence of syncope, and so EPS would have little impact on the decision for treatment. This indication could be justified in cases of severe conduction disorders, with the objective of inducing a possible ventricular tachycardia that could be treated using ablation, especially for the branch-to-branch reentrant type. On the other hand, the usefulness of inducing ventricular arrhythmia in patients with dilated cardiomyopathy with a preserved ejection fraction, or with hypertrophic cardiopathy, is debatable.

As such, EPS would be indicated for diagnostic purposes in patients with ischemic heart disease and ventricular function  $>35\%$ , and could possibly be indicated in patients with other types of cardiopathy.

### Adenosine Test

The administration of adenosine initially slows sinus rhythm with a total but very short atrioventricular nodal block, followed by a phase of sinus tachycardia.<sup>42</sup> Studies analyzing the response to administering adenosine in the normal population with no history of syncope have defined the abnormal response to adenosine as a pause  $>10$  s. There is a group of patients with syncope of unknown cause in which asystole  $>10$  s has been observed following the administration of adenosine. The interpretation of this response has been the subject of much discussion, especially since prolonged ECG monitoring has revealed an absence of concordance between the response to adenosine and the behavior of the ECG during spontaneous syncope.<sup>38,43</sup>

It has recently been observed that some patients with syncope of an unknown origin, with no cardiopathy and a normal ECG, have a sudden atrioventricular block during the episode of syncope, with no prior sinus bradycardia or progressive elongation of the PR interval, which suggests that this is not a typical reflex mechanism, but rather some intrinsic atrioventricular nodal phenomenon. Brignole et al.<sup>44</sup> found that patients with this type of response have greater plasma concentrations of adenosine than patients with typically vasovagal syncope, which points toward a different purinergic profile. Flammang et al.<sup>45</sup> recently published a controlled study of a cohort of patients with syncope, no cardiopathy, a normal ECG, and asystole  $>10$  s in the adenosine test, in which the implantation of a pacemaker significantly reduced the recurrence of syncope.<sup>45</sup>

With this in mind, the syncope guidelines published in 2009<sup>7</sup> do not recommend the use of the adenosine test because the available studies at the time found no correlation between the response to adenosine and clinical syncope. Given the more recent data, we must await the currently ongoing studies to establish in which groups of patients the adenosine test should be applied, and especially to select those candidates that could possibly benefit from cardiac pacing.

### Outpatient Electrocardiographic Monitoring

The only reference data for the etiological diagnosis of syncope should be those obtained during spontaneous syncope. Since the behavior of an episode of syncope is unpredictable, it is difficult to

obtain ECG and BP values during an episode of spontaneous syncope.

Until now, the only variable that can be monitored for a relatively long period of time is the ECG. A conventional 24-h or 48-h Holter monitor has shown poor diagnostic value, generally <5%. It is widely accepted that conventional Holter monitoring is only indicated in patients with very frequent syncope episodes.<sup>46</sup>

Prolonged ECG monitoring systems for prospective events (the ECG is recorded from the moment the patient activates the device) are not particularly useful in syncope, which is a transient phenomenon. By the time the patient is capable of activating the device, the potential alteration that could be observed in an ECG and that may have caused the episode tends to have already normalized.

In recent years, loop recorders have been developed that, at the moment the patient activates the device, will save the ECG results from the previous time period (usually about 12 min); ie, the readout is of the time period in which the patient suffered the episode of syncope.<sup>47</sup> Also, all currently available devices have an automatic recording system that is triggered by an altered HR that goes above or below the programmable cut-off point and can automatically record episodes of tachyarrhythmia and bradyarrhythmia, even if they are asymptomatic episodes or episodes of syncope in which the patient was incapable of activating the device.

Implantable recording devices have not only allowed physicians to establish the diagnosis of syncope in a large number of patients, but also have provided new understanding of the mechanisms behind syncope in several different groups of patients and the value of certain provocation tests. As such, in cases of recurrent syncope, no cardiopathy, and a normal ECG, in which a neurally mediated cause could have been clinically suspected, as many as 50% of patients have asystole >3 s, regardless of the results from the TTT test.<sup>37,38,43</sup> On the other hand, whereas the majority of patients with syncope, intraventricular conduction disorders, no cardiopathy, and normal EPS results have a paroxysmal atrioventricular block during the episode of syncope, in a certain percentage of these patients no arrhythmia is documented, suggesting a probable reflex origin, and some patients have syncope secondary to ventricular arrhythmia.<sup>39,48</sup>

As such, prolonged ECG monitoring with looped recorders plays an important role in the study of the mechanisms behind syncope in certain groups of patients. Perhaps the patients who will benefit the most would be those with no underlying cardiopathy and a normal ECG, with recurrent syncope that interferes with their quality of life despite taking all conventional measures. In these patients, the indication for a recording device could prevail over performing a TTT. On the other hand, an event recorder should be indicated in cases of suspected arrhythmic syncope, but in which initial examinations have not been able to confirm a diagnosis, and when there is no risk of sudden death that would indicate ICD implantation.

The type of recording device, external or implantable, depends on the frequency of the patient's symptoms. Remote monitoring of implantable recorders helps eliminate false positives created by noise and improve the diagnostic value of these devices.<sup>49</sup>

## TREATMENT

In order to provide the appropriate treatment for episodes of syncope, the underlying cause of the syncope and the mechanism of a given episode must be determined. In addition to treating the

mechanism causing the episodes of syncope, a specific treatment must be given for the underlying cardiopathy, and on occasion measures must be taken to prevent sudden death, such as implanting an ICD.

### Cardiac Syncope

In principle, cardiogenic causes are the easiest to treat, despite being the most serious. In cases of syncope associated with obstructive cardiopathy, such as aortic stenosis or myxoma, a surgical intervention can resolve the patient's problem. In cases of syncope secondary to arrhythmia, treatment tends to resolve recurrences through the implantation of a pacemaker in patients with bradyarrhythmia, or by ablation or anti-arrhythmia medication in the case of supraventricular tachyarrhythmia and for certain ventricular arrhythmias. We should point out that the implantation of an ICD for preventing sudden death is not a treatment of episodes of syncope, since its mechanism is to recognize and halt ventricular arrhythmia when syncope has already been produced. Since syncope tends to occur at the start of arrhythmia, it usually has already been produced by the time the ICD starts to counteract the tachycardia. As such, patients with an ICD for episodes of syncope but who still have recurrence should have the device programmed for antitachycardia pacing as early as possible, along with an added strategy in the form of ablation or anti-arrhythmic drugs, in order to avoid a recurrence of arrhythmia.

### Reflex Syncope

The reflex mechanism is the most common cause of syncope, is benign in terms of survival, and often tends to be self-limiting. In the majority of cases, it occurs in the form of isolated episodes, usually triggered by specific circumstances, and is preceded by prodromes that are recognizable by the patient. In general, this condition does not require special therapeutic measures; instructing the patient regarding the benign nature of the condition in many cases is sufficient to reduce the anxiety produced by syncope and aids the patient in recognizing and avoiding the triggers. Several different drugs have been tested in randomized trials, such as alpha mimetics,<sup>34</sup> serotonin reuptake inhibitors,<sup>50</sup> and beta blockers,<sup>51</sup> but none have demonstrated their effectiveness, and so there are no clear indications for their use. The only drug that has proven effective is midodrine,<sup>52</sup> although the studies that have analyzed this drug involved mixed groups of patients clearly experiencing reflex syncope and others with orthostatic hypotension. In addition, this drug is very limited and expensive in Spain, as it is not subsidized by the public health system.

It has recently been shown that counter pressure maneuvers (Fig. 3), which can involve isometric arm contraction maneuvers or contracting the quadriceps and gluteal muscles, can avoid or at least delay the hypotension and bradycardia that cause syncope. In a high percentage of patients with syncope that are preceded by prodromes, these maneuvers reduce the rate of recurrence, whereas in others they can at least help prevent serious falls, which in turn can lower the risk of trauma.<sup>53</sup>

However, some patients have recurrent, sudden episodes with no prodromes, which can cause trauma. In these patients, implantable event recorders have demonstrated prolonged asystole periods in as many as 50% of cases. These cases are considered for implanting a pacemaker. Currently, despite conflicting data in the medical literature,<sup>54</sup> it appears that we are starting to establish which patients would benefit from this treatment. The majority of previous studies used TTT for the

selection of possible candidates,<sup>54</sup> although, as we have mentioned, this test is not particularly sensitive for this task.<sup>38,43</sup> In recent years, however, the use of prolonged ECG monitoring has allowed us to identify patients that are in asystole during a spontaneous episode of syncope,<sup>55</sup> while also recognizing a subgroup of patients with sudden atrioventricular block who probably would benefit the most from cardiac pacing.<sup>45</sup>

Other measures have been proposed, albeit with insufficient data to support or reject them, such as water intake and tilt training, which consists of repeated TTT until the results are negative, followed by the patient performing inclination maneuvers in a position similar to a tilt table once or twice per day at home. There is little evidence in the medical literature regarding the possible effectiveness of this training, although in some studies this may be due to nonadherence.<sup>56</sup> For this reason, and due to the logistic difficulties of implementing such a program in the hospital

and at home, tilt training should be indicated only for extremely symptomatic patients and those expected to adhere to the training protocol.

### Orthostatic Hypotension

This clinical situation is becoming ever more prevalent, since it usually occurs in elderly patients who tend to have comorbidities affecting the autonomous nervous system and use several drugs, including hypotensive and diuretic drugs, in addition to having a reduced sensation of thirst, which can increase hypovolemia. In these patients, antihypertensive treatment must be reduced, hydration increased, and compression stockings should be applied to the legs.<sup>57</sup>

### SYNCOPE UNITS

In recent years, a series of articles have been published demonstrating that an organized care system for patients with syncope improves the rate of diagnosis, reducing hospitalization rates and the rate of nonspecific tests for the analysis of syncope.<sup>58,59</sup>

This concept is based on an optimization and reorganization of diagnostic and therapeutic tools that are commonly available, rather than some new physical infrastructure or acquiring new devices.

These units apply mandatory algorithms based on clinical practice guidelines and provide coordinated care by one or two responsible physicians for each patient, preferential access for high-risk patients, and easier access to the necessary tests. Strict adherence to these directives increases the rate of diagnosis and reduces the use of unnecessary tests and hospitalizations.

As such, we believe that the implementation of these units in our hospitals lead to better patient management and resource management, with minimal investment.

### CONFLICTS OF INTEREST

None declared.

### REFERENCES

1. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. *N Engl J Med.* 2002;347:878–85.
2. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, Van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35–60 years. *J Cardiovasc Electrophysiol.* 2006;17:1172–6.
3. Olde Nordkamp LR, Van Dijk N, Ganzeboom KS, Reitsma JB, Luitse JS, Dekker LR, et al. Syncope prevalence in the ED compared to general practice and population: a strong selection process. *Am J Emerg Med.* 2009;27:271–9.
4. Baron-Esquivias G, Martínez-Alday J, Martín A, Moya A, García-Civera R, Paz López-Chicharro M, et al. Epidemiological characteristics and diagnostic approach in patients admitted to the emergency room for transient loss of consciousness: Group for Syncope Study in the Emergency Room (GESINUR) study. *Europace.* 2010;12:869–76.
5. Rose MS, Koshman ML, Spreng S, Sheldon R. The relationship between health-related quality of life and frequency of spells in patients with syncope. *J Clin Epidemiol.* 2000;53:1209–16.
6. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J.* 2001;22:1256–306.
7. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J.* 2009;30:2631–71.



**Figure 3.** Counter pressure maneuvers: two types of maneuvers have proven effective in preventing reflex syncope. Top: isometric arm contraction. Bottom: quadriceps contraction. The patient should be instructed in how to perform both maneuvers, and should alternate between them or use the one they prefer.

8. Cooper PN, Westby M, Pitcher DW, Bullock I. Synopsis of the National Institute for Health and Clinical Excellence Guideline for management of transient loss of consciousness. *Ann Intern Med.* 2011;155:543-9.
9. Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA, et al. AHA/ACC Scientific Statement on the evaluation of syncope: from the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: in collaboration with the Heart Rhythm Society: endorsed by the American Autonomic Society. *Circulation.* 2006;113:316-27.
10. Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. *Ann Neurol.* 1994;36:233-7.
11. Van Dijk JG. Conditions that mimic syncope. In: Benditt D, Blanc JJ, Brignole M, Sutton R, editors. *The evaluation and treatment of syncope.* New York: Futura; 2003. p. 184-200.
12. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D; Medical Research Council MESS Study Group. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet.* 2005;365:2007-13.
13. Cronin H, Kenny RA. Cardiac causes for falls and their treatment. *Clin Geriatr Med.* 2010;26:539-67.
14. Benbadis SR, Chichkova R. Psychogenic pseudosyncope: an underestimated and provable diagnosis. *Epilepsy Behav.* 2006;9:106-10.
15. Leitch JW, Klein GJ, Yee R, Leather RA, Kim YH. Syncope associated with supraventricular tachycardia. An expression of tachycardia rate or vasomotor response? *Circulation.* 1992;85:1064-71.
16. Brignole M, Gianfranchi L, Menozzi C, Raviele A, Oddone D, Lolli G, et al. Role of autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. *J Am Coll Cardiol.* 1993;22:1123-9.
17. Garcia-Civera R, Morell-Cabedo S, Sanjuán-Mañez R, Ruiz-Granell R. Syncope due to paroxysmal junctional tachycardia. In: Garcia-Civera R, Barón-Esquivas G, Blanc JJ, Brignole M, Moya i Mitjans A, Ruiz-Granell R, et al., editors. *Syncope cases.* Oxford: Futura; 2006. p. 194-6.
18. Alboni P, Brignole M, Menozzi C, Raviele A, Del Rosso A, Dinelli M, et al. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol.* 2001;37:1921-8.
19. Sheldon R, Hersi A, Ritchie D, Koshman ML, Rose S. Syncope and structural heart disease: historical criteria for vasovagal syncope and ventricular tachycardia. *J Cardiovasc Electrophysiol.* 2010;21:1358-64.
20. Yokokawa M, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, et al. Neurally mediated syncope as a cause of syncope in patients with Brugada electrocardiogram. *J Cardiovasc Electrophysiol.* 2010;21:186-92.
21. Letsas KP, Efremidis M, Gavrielatos G, Filippatos GS, Sideris A, Kardaras F. Neurally mediated susceptibility in individuals with Brugada-type ECG pattern. *Pacing Clin Electrophysiol.* 2008;31:418-21.
22. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart.* 2008;94:1620-6.
23. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med.* 1997;29:459-66.
24. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M; OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J.* 2003;24:811-9.
25. Brignole M, Gigli G, Altomonte F, Barra M, Sartore B, Prato R, et al. Cardioinhibitory reflex provoked by stimulation of carotid sinus in normal subjects and those with cardiovascular disease. *G Ital Cardiol.* 1985;15:514-9.
26. Brown KA, Maloney JD, Smith CH, Haritzler GO, Ilstrup DM. Carotid sinus reflex in patients undergoing coronary angiography: relationship of degree and location of coronary artery disease to response to carotid sinus massage. *Circulation.* 1980;62:697-703.
27. Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern Med.* 2006;166:515-20.
28. Puggioni E, Guiducci V, Brignole M, Menozzi C, Oddone D, Donato P, et al. Results and complications of the carotid sinus massage performed according to the "method of symptoms". *Am J Cardiol.* 2002;89:599-601.
29. Krediet CT, Parry SW, Jardine DL, Benditt DG, Brignole M, Wieling W. The history of diagnosing carotid sinus hypersensitivity: why are the current criteria too sensitive? *Europace.* 2011;13:14-22.
30. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res.* 2011;21:69-72.
31. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet.* 1986;1:1352-5.
32. Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, et al. Tilt table testing for assessing syncope. American College of Cardiology. *J Am Coll Cardiol.* 1996;28:263-75.
33. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, et al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncope phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. *Europace.* 2000;2:66-76.
34. Moya A, Permanyer-Miralda G, Sagrista-Sauleda J, Carne X, Rius T, Mont L, et al. Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. *J Am Coll Cardiol.* 1995;25:65-9.
35. Morillo CA, Leitch JW, Yee R, Klein GJ. A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol.* 1993;22:1843-8.
36. Sagristà-Sauleda J, Romero B, Permanyer-Miralda G, Moya A, Soler-Soler J. Reproducibility of sequential head-up tilt testing in patients with recent syncope, normal ECG and no structural heart disease. *Eur Heart J.* 2002;23:1706-13.
37. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, et al.; International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation.* 2001;104:1261-7.
38. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al.; International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. *Eur Heart J.* 2006;27:2232-9.
39. Moya A, Garcia-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, et al. Bradycardia detection in Bundle Branch Block (B4) study. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *Eur Heart J.* 2011;32:1535-41.
40. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, et al.; European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace.* 2007;9:959-98.
41. Krahn AD, Morillo CA, Kus T, Manns B, Rose S, Brignole M, et al. Empiric pacemaker compared with a monitoring strategy in patients with syncope and bifascicular conduction block—rationale and design of the Syncope: Pacing or Recording in The Later Years (SPRITELY) study. *Europace.* 2012. <http://dx.doi.org/10.1093/europace/eus005>
42. Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine. Basic and clinical concepts. *Circulation.* 1991;83:1499-509.
43. Deharo JC, Jégo C, Lanteaume A, Djiane P. An implantable loop recorder study of highly symptomatic vasovagal patients: the heart rhythm observed during a spontaneous syncope is identical to the recurrent syncope but not correlated with the head-up tilt test or adenosine triphosphate test. *J Am Coll Cardiol.* 2006;47:587-93.
44. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L, et al. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. *J Am Coll Cardiol.* 2011;58:167-73.
45. Flammang D, Church TR, De Roy L, Blanc JJ, Leroy J, Mairesse GH, et al. Treatment of unexplained syncope: a multicenter, randomized trial of cardiac pacing guided by adenosine 5'-triphosphate testing. *Circulation.* 2012;125:31-6.
46. Bass EB, Curtiss EI, Arena VC, Hanusa BH, Cecchetti A, Karpf M, et al. The duration of Holter monitoring in patients with syncope. Is 24 hours enough? *Arch Intern Med.* 1990;150:1073-8.
47. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace.* 2009;11:671-87.
48. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation.* 2001;104:2045-50.
49. Furukawa T, Maggi R, Bertolone C, Ammirati F, Santini M, Ricci R, et al. Effectiveness of remote monitoring in the management of syncope and palpitations. *Europace.* 2011;13:431-7.
50. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 1999;33:1227-30.
51. Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, et al. Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation.* 2006;113:1164-70.
52. Perez-Lugones A, Schweikert R, Pavia S, Sra J, Akhtar M, Jaeger F, et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. *J Cardiovasc Electrophysiol.* 2001;12:935-8.
53. Van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *J Am Coll Cardiol.* 2006;48:1652-7.
54. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med.* 2007;120:54-62.
55. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J.* 2006;27:1085-92.

56. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. *Europace*. 2004;6:199-204.
57. Podoleanu C, Maggi R, Brignole M, Croci F, Incze A, Solano A, et al. Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. *J Am Coll Cardiol*. 2006;48:1425-32.
58. Brignole M, Ungar A, Casagrande I, Gulizia M, Lunati M, Ammirati F, et al. Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospitals. *Europace*. 2010;12:109-18.
59. Rodríguez-Entem F, González-Enríquez S, Olalla-Antolín JJ, Cobo-Belaustegui M, Expósito-García V, Llano-Cardenal M. Manejo del síncope en el servicio de urgencias sin ingreso hospitalario: utilidad de un protocolo coordinado con la unidad de arritmias. *Rev Esp Cardiol*. 2008;61:22-8.