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REVIEW

Arrhythmic syncope: From diagnosis to management

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Abstract

Syncope is a concerning symptom that affects a large proportion of patients. It can be related to a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. However, benign causes are the most frequent, and identifying high-risk patients with potentially severe etiologies is crucial to establish an accurate diagnosis, initiate effective therapy, and alter the prognosis. The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope is cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope. Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output and produce syncope. In this review, we summarized the main guidelines in the management of patients with syncope of presumed arrhythmic origin. Therefore, we presented a thorough approach to syncope work-up through different tests depending on the clinical characteristics of the patients, risk stratification, and the management of syncope in different scenarios such as structural heart disease and channelopathies.

Key Words: Syncope; Arrhythmia; Electrophysiological study; Loop recorder; Myocardiopathy; Atrioventricular conduction block

Core Tip: In this review, we summarized the most important and novel data on arrhythmic syncope, the value of the different diagnostic tests, the management, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. The review emphasized the importance of an appropriate stepwise approach work-up and intervention.

INTRODUCTION

Definition and causes

Syncope is a total loss of consciousness (T-LOC) secondary to cerebral hypoperfusion, characterized by rapid onset, short duration, and complete spontaneous recovery[1]. It must be differentiated from other T-LOC that do not meet these characteristics, such as T-LOC of traumatic origin, some types of epilepsy, or certain psychiatric disorders. It should be noted that syncope is a symptom that encompasses a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. Therefore, it should not constitute a final diagnosis. It is of great importance to stratify the risk and try to determine the cause.

The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope refers to cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope (Table 1). Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output, causing the syncope. Non-arrhythmic causes of cardiac syncope are usually related to structural heart diseases with obstruction of outflow and/or inflow of blood. These obstructions can restrict increases in cardiac output on exercise rendering this insufficient to maintain the circulation. Severe aortic stenosis (AoS), hypertrophic cardiomyopathy (HCM), mitral stenosis, atrial myxoma, or severe pulmonary hypertension are some examples of conditions that can cause cardiac syncope *via* this mechanism.

Furthermore, myocardial ischemia and acute ischemic syndromes may also precipitate syncope through multiple mechanisms. It is important to highlight that most of these heart diseases can also be associated with arrhythmias or reflex syncope, and therefore it is often challenging to determine the main cause of syncope in structural cardiac syncope[1-5]. In other words, the mere presence of structural heart disease associated with obstruction does not allow us to conclude that the syncope is due to this mechanism. In many cases, it will be necessary to rule out other possible causes, especially arrhythmic ones.

Epidemiology

It is estimated that almost one in two people will suffer at least one syncopal episode in their lifetime[1,6]. It is a front-line health problem with a high impact on the health system, even though it is known that only a small proportion of patients with syncope seek medical attention. An epidemiological study carried out in the United States showed that the prevalence of patients with syncope in the community requiring medical attention is 9.5 per 100 inhabitants, and that 1 in 10 required hospital admission[7].

The incidence of the first syncopal episode is distributed with a bimodal curve, with a first peak in youth (between 10-30 years of age) and a second peak over 65 years of age. Cardiac syncope is the third most common cause of syncope after reflex and orthostatic hypotension (OH)[1,8,9]. In the emergency department (ED), cardiac syncope accounts for 5%-21% of syncope. In the Framingham cohort, the prevalence of syncope and long-term prognosis were analyzed[10]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Reflex or vasovagal syncope is the most common cause in the general population. In the Framingham cohort it represented 21.0% of the cases, while cardiac syncope made up only 9.5%[10]. It is remarkable that the prevalence of cardiac syncope increases with advancing age[1,9-11]. Cardiac syncope causes less than 1% of syncope in youth (< 40 years)[12] and up to one-third in those over 60 years of age[10,12].

Prognosis

The prognosis of syncope is mostly related to the underlying cause and the presence of structural heart disease. While reflex syncope has an excellent prognosis in terms of survival, cardiac syncope is associated with an increased risk of mortality, especially if it is not identified and treated properly. Patients with reflex syncope have similar survival to patients without syncope[10], with a mortality rate between 4%-12% after 1 year (depending on the patient's age and comorbidities)[10,13-15]. By contrast, the 1-year mortality rate for cardiac syncope rises to 20%-30%[10,13-15]. In the Framingham cohort,

Table 1 Main cardiac causes of syncope

Cardiac syncope				
Arrhythmic causes	Bradyarrhythmia	Sick sinus syndrome/sinus node disfunction		
		Atrioventricular block		
	Tachyarrhythmia	Supraventricular tachycardia (AVNRT, AVRT, AT, fast AF, *etc.*)		
		Ventricular arrhythmias	Related to structural heart disease	
			Channelopathies and inherited arrhythmia syndromes	
Non-arrhythmic causes	Mechanical causes	Valvulopathies (aortic stenosis, mitral stenosis, *etc.*)		
		HCM		
		Atrial myxoma		
		Pulmonary emboli		
		Tamponade		
		Severe pulmonary hypertension		
Acute coronary syndrome				

AVNRT: Atrioventricular nodal re-entrant tachycardia; AVRT: Atrioventricular re-entrant tachycardia; HCM: Hypertrophic cardiomyopathy; AF: Atrial fibrillation; AT: Atrial tachycardia.

cardiac syncope was associated with a two-fold increase in the risk of death compared with those without a history of syncope, with an approximately 50% 5-year survival[10]. In this study, patients with syncope of unknown origin also had an increased risk of all-cause mortality compared with the general population [hazard ratio = 1.32, 95% confidence interval (CI): 1.09-1.60]. This observation was also made in other studies focused on specific populations[5]. This may be due to the fact that there are potentially serious causes for syncope left untreated due to a lack of diagnosis.

Importantly, in patients with syncope of unknown origin, the mere presence of structural cardiac abnormalities or the evidence of a conduction system disorder is associated with a poor prognosis, increasing the risk of death by a factor of more than five[1,9,16-19]. On the other hand, a structurally normal heart with a normal electrocardiogram (ECG) is usually associated with a benign etiology for syncope and a favorable prognosis[1,20-22].

DIAGNOSTIC APPROACH AND TEST

Initial evaluation, clinical history, physical examination, and ECG

T-LOC is a relatively common cause of presentation to the ED, and half of these episodes can be attributed to syncope[23]. However, it is important to distinguish it from other causes of T-LOC, to avoid unnecessary investigations in patients with benign causes, and to correctly detect and treat patients with cardiac syncope, which can lead to serious outcomes. The most common condition that can be confused with syncope is probably epilepsy. This confusion is an important phenomenon leading to misdiagnosis with rates ranging from 6%-67%[24]. This misdiagnosis contributes significantly to the numbers of patients with a questionable diagnosis of epilepsy and to those with apparently drug-resistant epilepsy. Syncope can be accompanied with urinary incontinence and/or muscular contractions that can resemble epileptic seizures, making it difficult to differentiate between the diagnoses. While in epilepsy muscular movements are generalized and appear from the beginning of the T-LOC and continue for a few minutes, syncope can also be associated with muscular contractions, which often tend to appear a few seconds after the collapse. They tend to be pleiomorphic and last only a short period of time. Some clinical findings have been suggested to differentiate seizures from convulsive syncope. Tongue biting and confusion on awakening are the most useful in predicting an epileptic origin[25]. In addition, clinical clues that should raise the suspicion for psychogenic pseudo-syncope include prolonged duration, eye closure during the episode, unusual triggers, no recognizable prodromes, and a high frequency of attacks[26].

Another common source of confusion in the ED is represented by falls, especially in the elderly population with non-witnessed T-LOC. On the one hand, elderly people with cognitive impairment and muscular weakness can present with falls as a manifestation of another illness, such as infections or

metabolic disorders[27]. On the other hand, these populations are usually treated with medications that can lower blood pressure (BP) and heart rate (HR) and tend to be dehydrated due to reduced water consumption. This combination of factors can promote orthostatic syncope. Additionally, in the elderly, there is a high prevalence of sinus node dysfunction, conduction disturbances, and structural heart disease, putting these patients at high risk of presenting with cardiac syncope[2]. For all these reasons, current guidelines recommend that repeated falls in elderly people without a reasonable explanation should be approached like unexplained syncope[1].

Once the syncope diagnosis has been established, special attention should be paid to determining the underlying cause. Syncope can be caused by three main different etiologies: Reflex mechanism (also known as neural-mediated syncope); OH; or cardiac syncope, which can be due to arrythmia or structural heart disease. The diagnostic approach should focus on detecting potential cardiac syncope, as it could be clinical manifestation of a primary cardiac disease with high risk of events.

Initial evaluation of any patient presenting with syncope should include three basic elements: (1) Careful history taking regarding the current and previous episodes (including eyewitness accounts); (2) Physical examination; and (3) ECG. Clinical history is probably the most important one, and it should be focused on past medical history, especially previous cardiac conditions, and symptoms related to the episode. Syncope during exertion or in a supine position accompanied by chest pain or palpitations have been described as high-risk factors and should raise the suspicion of cardiac syncope[28,29]. In addition, a family history of sudden cardiac death (SCD) at a young age or personal history of structural heart disease or coronary artery disease (CAD) have been considered high-risk factors. Physical examination does not usually show relevant findings, but it could reveal signs of heart failure or a systolic murmur suggesting structural heart disease. Performing an ECG is crucial, as it can show conduction disturbances, pathological Q waves, or repolarization abnormalities reflecting an underlying cardiac disease[15,30-32] (Figure 1). It is important to mention that every patient with syncope should have an ECG even if there is clear evidence that is a reflex syncope since there are some channelopathies such as long QT syndrome (LQTS) that can present with ventricular arrhythmias after emotional stimulus that can be confused with reflex syncope. Additionally, it has been described that patients with Brugada syndrome (BrS) are more prone to vasovagal syncope[33].

There are several scores developed for risk stratification according to clinical and ECG findings[34]. However, some of them have been tested with external validation cohorts showing poor sensitivity and specificity for detecting cardiac syncope, and they perform no better than clinician judgement at predicting short-term serious outcomes. Therefore, current guidelines do not recommend using them alone to make decisions in the ED. Most items included on these scales are those suggesting cardiac syncope, such as ECG abnormalities or signs or symptoms of structural heart disease.

Carotid sinus massage

Carotid sinus massage (CSM) consists of applying external pressure to the area of the neck where the carotid sinus is located and is indicated in patients over 40 with syncope. According to current clinical guidelines, carotid sinus hypersensitivity is defined by a sinus pause longer than 3 s or a drop in systolic BP (SBP) higher than 50 mmHg[1,9]. However, this condition is very common among older individuals with cardiovascular disease, even in the absence of syncope. To avoid misdiagnoses, it has been proposed that the diagnosis of carotid sinus syndrome requires reproduction of patient's symptoms and a sinus pause longer than 6 s or more or a drop in mean arterial pressure of 60 mmHg or more[35]. Patients fulfilling these criteria have been shown to have recurrent long pauses on monitoring and to respond well to cardiac pacing[36,37]. The worst complication of CSM is stroke, which is extremely uncommon.

Orthostatic challenge

Orthostatic challenge consists of measuring HR and BP changes between supine and upright positions. It is recommended to measure them during the first 3 min, but it can be extended to the first 10 min if there is a high suspicion of OH since retarded responses have been described[38]. OH is defined by a drop of more than 20 mmHg in SBP, or a drop of more than 10 mmHg of diastolic BP, or if SBP becomes lower than 90 mmHg, and always accompanied by symptoms[39]. OH is very common among elderly people, especially in patients taking anti-hypertensive medications and/or with autonomous nervous system diseases like Parkinson's disease or diabetes, and it represents an important cause of syncope in this population[2,40].

Tilt testing

Tilt testing is recommended in patients with suspected reflex syncope or autonomic failure, including delayed forms of OH or postural orthostatic tachycardia syndrome. The most frequently used protocol is the so called "Italian protocol," which includes a 20-min stabilization phase, followed by administration of sublingual nitroglycerin[41]. It is useful in patients with true reflex syncope, as it has been demonstrated that a positive cardioinhibitory response is highly predictive of asystolic spontaneous syncope[42]. However, it can also be positive in a high percentage of patients with unexplained syncope and even in patients with cardiac arrhythmic syncope. Therefore, it offers little diagnostic value in these
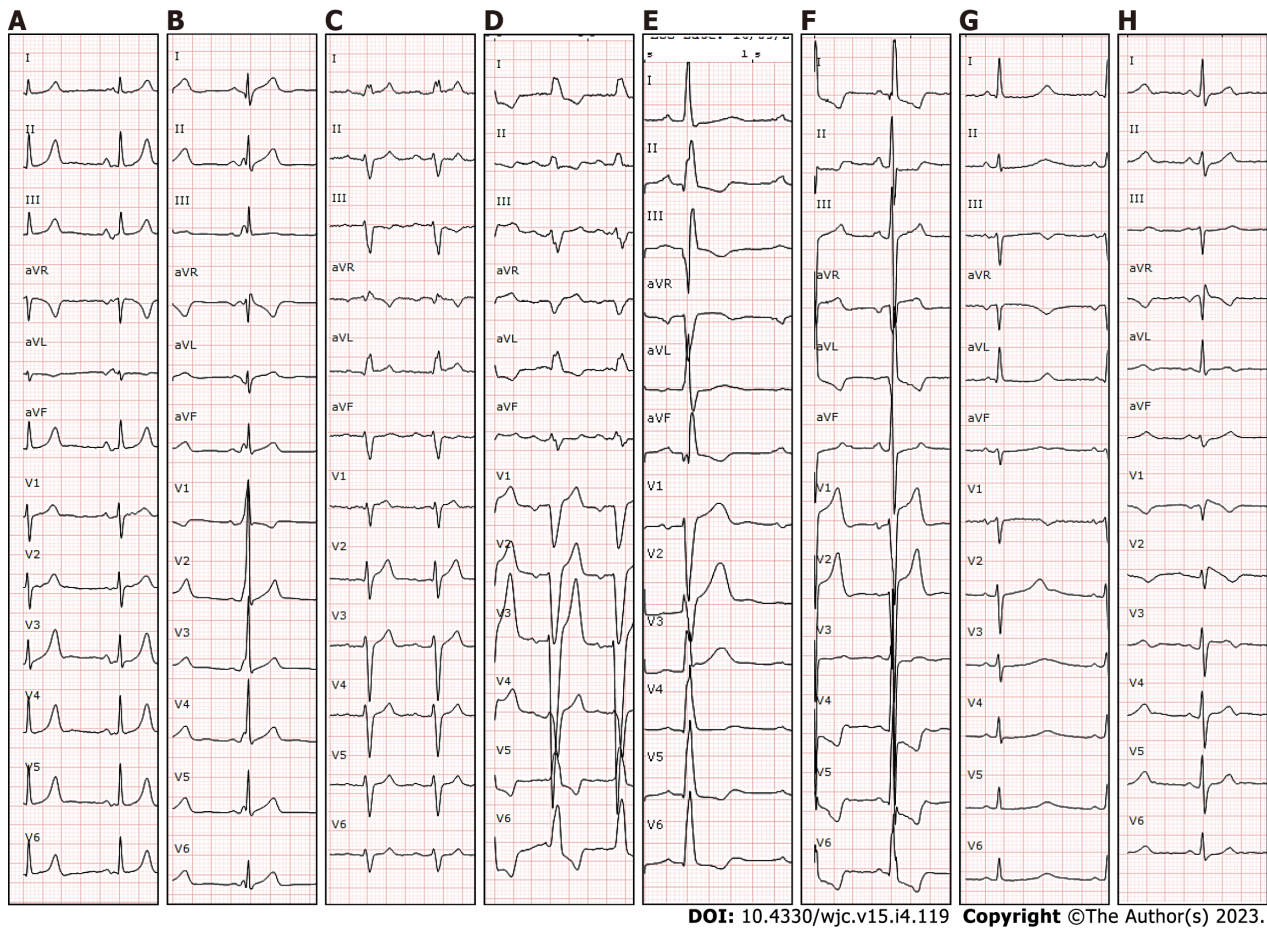
Figure 1 Examples of pathological electrocardiogram that should lead to suspicion of an arrhythmic origin of the syncope. A: Bayes Syndrome (biphasic p wave in inferior leads compatible with interatrial block, which is related with atrial arrhythmias); B: Pre-excitation syndrome; C: Long PR interval and left anterior fascicular hemiblock; D: Left bundle branch block; E: Inferior necrosis (Q waves); F: Hypertrophic cardiomyopathy; G: Long QT syndrome; H: Brugada syndrome. Suspected supraventricular tachycardia (A and B), suspected atrioventricular block (C and D), suspected ventricular tachycardia (E and F), and suspected polymorphic ventricular tachycardia (G and H).

populations and should not be performed routinely[1]. It has also been tested to evaluate treatment effectiveness, showing little value in this aspect. Finally, in recent years it has been demonstrated that cardiac denervation of parasympathetic ganglia can be highly effective in reducing cardioinhibitory reflex syncope, a technique known as cardioneuroablation[43]. Tilt test might play a crucial role in detecting suitable patients for this promising procedure[44].

Electrophysiological study

According to current European Guidelines[1], electrophysiological study (EPS) is indicated in patients with syncope and bifascicular block (BFB) or previous myocardial infarction or other scar-related conditions, when the etiology remains unexplained after non-invasive evaluation. It could also be considered when syncope is preceded by palpitations or in patients with sinus bradycardia, when the rest of the study has been negative. However, in patients with normal ECG and no structural heart disease, EPS is of poor diagnostic value, and other options like home monitoring are more appropriate. Additionally, a positive EPS is strongly predictive of the origin of the previous syncope, but a negative result cannot exclude arrhythmic events in the future. Therefore, it has a low negative predictive value [45,46].

Sick sinus syndrome is a heterogenous disease where sinus node does not function normally and includes some different kinds of bradycardia such as sinus pauses or junctional rhythm. However, these conditions are relatively common in elderly people, and it is crucial to correlate the bradycardia episodes with the patient's symptoms. A sinus node recovery time (SNRT) longer than 1600 ms is considered abnormal [or corrected SNRT (cSNRT) longer than 525 ms] and has been correlated with sick sinus syndrome[45], but its prognostic value remains unclear. There are few data supporting the benefit of pacing in patients with an abnormal SNRT.

Patients with intraventricular conduction disturbances like BFB or nonspecific conduction disturbance with a QRS greater than 120 ms are at higher risk of arrhythmic events due to His-Purkinje system disease, and in this population paroxysmal atrioventricular block (AVB) is the most common

cause of syncope[46-48]. In these patients with syncope suspected to be related to bradycardia, an HV interval longer than 70 ms or the development of second or third-degree AVB during incremental atrial pacing or pharmacological stress identifies a group with a high risk of developing AVB in the future [49], and pacing is recommended. In addition, some studies have evaluated the relationship between ECG conduction disturbance and the results of EPS, showing that PR interval prolongation and/or BFB patterns make a positive result in EPS more likely rather than a right bundle branch block (RBBB) pattern alone[50] (Figure 2).

Another important part of the EPS in the syncope work-up is programmed ventricular stimulation. In patients with previous myocardial infarction and syncope, the induction of monomorphic sustained ventricular tachycardia (MSVT) is strongly predictive of the cause of syncope and should be managed as spontaneous MSVT[51,52]. In contrast, the induction of polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) is considered a less specific finding, especially with aggressive stimulation protocols[53]. However, induction of PVT or VF may play a role in risk stratification of specific populations such as patients with repaired tetralogy of fallot[19,54-56] or BrS[57,58].

Electrocardiographic cardiac monitoring

ECG cardiac monitoring is one of the cornerstones of the etiological diagnosis of arrhythmic syncope. In addition, there are several areas of interest other than unexplained syncope in which monitoring devices have been investigated[54,59-72]. The objective of ECG monitoring is to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis. For this reason, the diagnostic yield of ECG monitoring is primarily related to the duration of monitoring and the frequency of symptoms. Since syncope is often an infrequent event, a long-term monitoring device is usually needed to have a chance of recording a syncopal episode. Moreover, the identification of significant asymptomatic arrhythmias (such as advanced AV block) can be important for the diagnosis. Therefore, as a general rule, ECG monitoring is indicated when there is a high pre-test probability of identifying an arrhythmia associated with syncope and after appropriate risk stratification. The choice of monitoring modality depends on the frequency of events.

In recent years, ECG monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-hr Holter monitor. This evolution of the ECG recording systems include, among other aspects, smaller devices, greater memory capacity for long-term monitoring, better quality of records, or remote monitoring capacity[70] (Table 2).

The main current ECG monitoring devices available are the following:

(1) In-hospital telemetry. In-hospital monitoring should be mandatory in patients with high-risk clinical features, especially if the monitoring is applied immediately after syncope. A recent study that evaluates the optimal ECG monitoring duration of ED patients with syncope found that a serious underlying arrhythmia was often identified within the first 2 h of ED arrival for low-risk patients and within 6 h for medium-risk and high-risk patients[73]. The diagnostic yield of ECG monitoring varies from 2%-20% depending on the patients' characteristics[1,9,69,73-75].

(2) 24/48-hr Holter monitoring. Despite likely being the most frequently used device, the diagnostic yield is as low as 1%-2% in unselected patients due to its short monitoring time[69,70]. Even the newest devices with a longer recording capacity (7-14 d) offer a very limited diagnostic yield. In the opinion of the authors of this review, at the present time, the 24/48-hr Holter should only be considered in patients with daily or very frequent symptoms[69,70]. In different circumstances, other modalities offer not only a greater diagnostic yield but also better cost efficiency per diagnosis.

(3) Loop recorders. These allow for more prolonged monitoring since they do not store a continuous recording. Even though they continuously monitor the ECG, the device just stores a few minutes, which is subsequently overwritten with a newer recording. Only when the device is activated (be it *via* manual activation or through an automatic arrhythmia detection algorithm), it stores from a few minutes before the start of the event until its end in another part of the memory. These stored episodes are protected from overwriting and available for review. In this way, several minutes before activation are stored in the device memory, and the likelihood of recording the trace at the time of the syncope episode is relatively high. Within this category, we have differentiated between external and implantable devices.

External loop recorders. The device uses cutaneous electrodes to record, like the 24 hr Holter monitor. The patients themselves position the electrodes daily. Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3-4 wk, although there are reports of more prolonged periods of time[70,76]). For this reason, in the setting of syncope, the diagnostic yield is no greater than 10%. They are especially useful for the investigation of symptoms that occur every 2-3 wk. Significantly, it has been found in various studies that early recorder use increased the likelihood of diagnostic events during external ECG monitoring[73,77].

Implantable loop recorders (ILR). These are small devices that are implanted subcutaneously, usually in the left parasternal region. They have the disadvantage of being minimally invasive since the latest models have been made significantly smaller. However, these devices allow for a more prolonged continuous monitoring of up to 3 to 4 years, making them especially useful in patients with syncope. Numerous studies have evaluated the diagnostic value and the usefulness of ILRs for the work-up and the diagnostic yield increases up to 30%-50%[5,48,59,62,78-82]. In a meta-analysis of five randomized controlled trials, it was found that initial implantation of an ILR in the work-up provided a 3.7-fold

Table 2 Main advantages, limitations, and indications of the most commonly used devices for electrocardiogram cardiac monitoring in patients with syncope

	Advantages	Disadvantages	Main indications
24-hr holter	Continuous recording: 12 leads with good correlation with surface ECG; low economic cost per study	Discomfort for the patient; artifacts; maximum recording of 24-48 h (low diagnostic yield); high economic cost per diagnosis	Very frequent (daily) symptoms; in-hospital monitoring (if ECG-telemetry not available)
Skin patches	Continuous recording of 7-14 d; good tolerability for patients	Single-use and greater economic cost; only one lead[1]; low diagnostic yield	Frequent (weekly) symptoms
External loop recorders	Loop recording (includes beginning and end of arrhythmic event); monitoring for 4 wk; low economic cost per study	Patient discomfort; requires education from healthcare professional on how to correctly place the electrodes; relatively low diagnostic yield	Frequent (weekly-monthly) symptoms
Implantable loop recorders	Loop recording; up to 3-yr monitoring (good diagnostic yield); patient does not have to do anything; remote monitoring	Invasiveness and associated complications (infection, bleeding, *etc.*); individual economic cost; single lead	Infrequent symptoms; most useful in syncope

[1]There are devices with more leads.

ECG: Electrocardiogram.
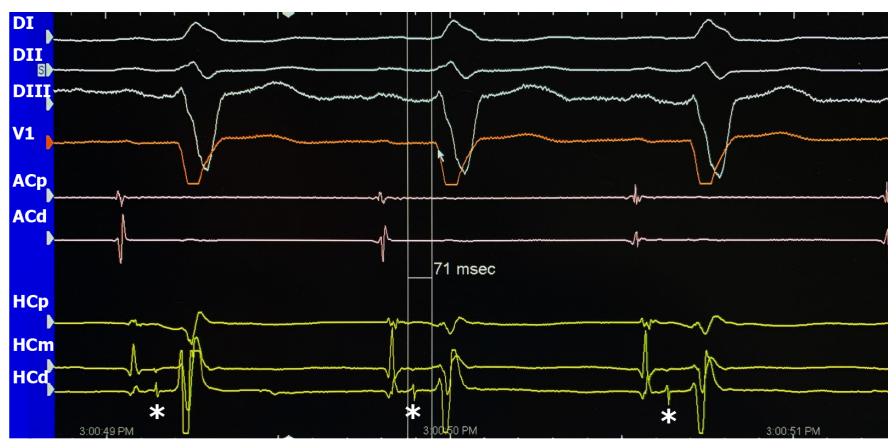
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Figure 2 Electrophysiological study of a patient with syncope and left bundle branch blocked. Surface electrocardiogram (DI, DII, DIII, V1) (top) and intracardiac electrograms at 100 mm/seg of an electrophysiological study to evaluate infra-Hisian conduction. A diagnostic catheter was placed in the right atrium (pink register: ACp and Acd) and in the His bundle zone (yellow register: HCp, HCm and HCd). ∗Indicates the His deflection. HV interval, from the onset of the His deflection to the onset of the QRS, is measured with the caliper (71 milliseconds in this case).

(95%CI: 2.7-5.0) increase in the relative probability of a diagnosis compared with the conventional strategy[1,71,83,84]. Different studies have also demonstrated that ILR was more cost-effective than the conventional strategy[69,81,83-85].

(4) Skin patches. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads that allow for a continuous ECG recording for 7-30 d of monitoring. Diagnostic yield and limitations are similar to external loop recorders. It should be noted that some new wearable devices like intelligent watches or other ECG prospective intermittent event recorders, which are quite popular nowadays, are generally not useful for syncope workup. These devices start recording only when the patient activates them. They have the limitation of not allowing for the recording of the onset of the episodes, which is often important for diagnosis. Furthermore, if the patient activates the device after recovering from the syncopal episode, in most cases the possible rhythm disorder would have resolved.

Other tests

Autonomic function tests like the Valsalva maneuver or deep breathing test can be considered to diagnose autonomic disfunction, but there is weak evidence that these tests may be useful in patients with syncope. Echocardiography should be performed in all patients with suspected valvular or structural heart disease, as it can detect some conditions that could present with cardiac obstructive syncope (*i.e.*, AoS or cardiac tamponade). Exercise testing is especially useful in patients that have experienced syncope during or shortly after exertion. The main purpose of these tests is to rule out ventricular arrythmias related to CAD or exercise-induced advanced AVB, which is usually located distally to the AV node. Cardiac biomarkers such as high sensitivity troponin and natriuretic peptides

can be elevated in patients with syncope and have been associated with worse outcomes in some case series[86,87]. However, such determinations are highly non-specific and rarely contribute to a certain diagnosis, and they may indicate serious illness rather than myocardial ischemia or heart failure. Therefore, it remains unclear whether they should be determined on a routine basis[88].

RISK STRATIFICATION

Cardiac syncope is a life-threatening condition. By consequence, the main goal of risk stratification is to identify those low-risk patients with benign causes that can be discharged home and only require medical education from those high-risk patients with syncope likely related with cardiac arrythmias or structural heart disease who require hospital admission for further investigation. This initial evaluation is especially necessary in the ED, where most patients with syncope first consult (Table 3).

For this purpose, several risk scores have been developed. In 2016, the Canadian Syncope Risk Score [34] was published. They included 4030 patients who presented to EDs of three centers in Canada for syncope and analyzed the occurrence of serious events including death, myocardial infarction, arrythmia, structural heart disease, pulmonary embolism, serious bleeding, and procedural intervention within 30 d from admission. Finally, they included nine predictors: (1) Predisposition to vasovagal syncope; (2) Heart disease; (3) Any systolic pressure reading in the ED < 90 or > 180 mmHg; (4) Troponin level above 99th percentile for the normal population; (5) Abnormal QRS axis (< -30° or > 100°); (6) QRS duration longer than 130 ms; (7) QTc interval longer than 480 ms; (8) ED diagnosis of cardiac syncope; and (9) ED diagnosis of vasovagal syncope. Those items suggesting reflex syncope conferred negative points, and those suggesting cardiac syncope conferred positive points. Each patient obtained a final score, with higher scores representing a greater risk of serious events (-3-0 points are considered low risk, while 0-3 points and 4-11 points are considered high and very high risk, respectively).

Recently, the same authors have validated this risk score in another large cohort of 3819 patients, showing very good correlation. Setting a threshold score of -1 point, they achieved very good sensitivity (97.8%) but poor specificity (44.3%) for serious events[89]. In addition, another group of researchers validated the same score in a cohort of 2283 patients from three continents also showing good correlation and better performance when compared with another European risk score[90]. However, they also observed that a simplified model including only the clinical classification (vasovagal, cardiac, or other), also achieved a similar degree of discrimination with regard to the primary outcome, showing that some of the predictors included may have a secondary role.

There are some other scales previously developed, such as the San Francisco Syncope Rule[91] or the EGSY score[29]. Both have shown similar results with good sensitivity but poor specificity. However, lack of reproducibility and remarkable heterogeneity in study design, variables, and outcome definitions of primary studies have prevented widespread use of these tools in clinical practice[92]. Moreover, recently some authors compared the EGSY score with clinical judgement, both alone and in addition to cardiac biomarkers, showing that clinical judgement has the highest diagnostic accuracy[93].

In summary, multiple risk scores have shown good sensitivity but poor specificity for predicting short-term serious outcomes, and they performed no better than clinical judgement. Therefore, they should not be used in isolation for the purposes of decision-making. It is also worth mentioning that, apart from risk scores, some other tests such as EPS, cardiac magnetic resonance (CMR), or stress test may be useful for risk stratification in selected groups of patients, as is discussed above in other sections of this article.

ARRHYTHMIC SYNCOPE IN SPECIFIC POPULATIONS

As previously mentioned, syncope could be the presenting symptom of an impending sudden cardiac arrest or can be related to more benign conditions such as neuro-mediated syncope or OH. Thus, it is important to correctly stratify the risk of each patient. For this reason, we need to understand the clinical scenario in which syncope takes place. Patients without overt structural heart diseases are at a lower risk of subsequent cardiac complications. Nonetheless, we must also consider some inherited heart diseases, which are primarily electrical, known as channelopathies and that can take place themselves in the absence of structural heart disease. In the following paragraphs we summarized some of those heart conditions that are associated with a higher risk of ventricular arrhythmias and sudden cardiac arrest.

Structural heart disease
Ischemic heart disease: Patients with ischemic heart disease (IHD) are at a higher risk of ventricular arrhythmias. It is necessary to differentiate between three stages in the ischemic evolution: (1) Acute ongoing ischemia. A patient suffering from an acute myocardial infarction might have VF and ventricular tachycardia related to the ischemic myocardium[1,19,94,95]. The acute ischemia induces a dispersion of the repolarization that may produce polymorphic ventricular arrhythmias and VF in the

Table 3 High-risk features suggesting cardiac syncope
High-risk features
Past medical history
Previous myocardial infarction
Previous cardiovascular condition (*i.e.*, BrS, hypertrophic cardiomyopathy, Long QT syndrome, *etc.*)
Syncopal event
Syncope during exertion or in supine position
Syncope associated with chest pain, palpitations, breathless, or abdominal pain
Physical examination
Signs of heart failure
Cardiac murmur suggesting specific condition (*i.e.*, aortic stenosis)
Signs of shock
Electrocardiogram
Conduction disturbance (AV block, bundle branch block)
Pathological Q waves
Long QT interval
Pre-excitation syndrome
Negative T waves

BrS: Brugada syndrome; AV: Atrio-ventricular.

acute setting. In the same way, some patients might present with monomorphic ventricular arrhythmias during acute myocardial infarction, in which a macro re-entrant circuit involving the ischemic tissue is a more probable mechanism. This latter mechanism is much less frequent than the former[94]; (2) In the subacute phase of ischemia, comprising hours to days after the ischemic event, Purkinje-related ectopia is a frequent mechanism for VF and acute cardiac arrest. The premature ventricular complexes are characterized by their very short coupling intervals and by the presence of a normal QT interval. It is believed that the ischemia induces an abnormal calcium release to the cytosol of Purkinje cells, which causes such early post depolarization[94]; and (3) In the chronic setting, which accounts for most patients with syncope and IHD, a frequent mechanism is a ventricular arrhythmia due to macro re-entry in well-established ventricular scars[1,19]. The risk of ventricular arrhythmias is much higher among those patients with IHD with low ventricular ejection fraction[1,19,96].

Ventricular arrhythmias should be suspected in patients with syncope and IHD[1,6,9,97]. If the patient has a left ventricle ejection fraction (LVEF) of < 35% despite optimal medical treatment, an implantable cardiac defibrillator (ICD) is indicated[18,19,98]. These patients have solid evidence of high arrhythmic risk independently of the invasive risk stratification, and an ICD implantation is strongly indicated even if the etiology of the syncope is treated subsequently. This recommendation is strongly supported by large randomized clinical trials (SCD-HeFT, MADIT-II)[99,100] and class 1A recommendation in the 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[101], and the 2019 Guidelines on Chronic Coronary Syndromes[102].

When the cause of the syncope remains unknown after an initial evaluation, and there is no apparent direct indication for ICD, an EPS with programmed ventricular stimulation should be performed. If MSVT are induced, the implantation of an ICD should be considered. The induction of polymorphic ventricular arrhythmias or VF has not been consistently related with ventricular arrhythmias or sudden cardiac arrest and no recommendation about ICD implantation can be made in this scenario. Despite the absence of solid evidence, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] recommends performing an EPS in patients with syncope and previous ST elevation myocardial infarction with a class IC recommendation. It is not clear if this recommendation is applicable to patients with a history of coronary revascularization without infarction or in the absence of late gadolinium enhancement in the CMR, and further studies are needed.

As we previously mentioned, the induction of a monomorphic VT in a patient with previous myocardial infarction presenting with syncope is an indication for an ICD implantation. On the other hand, the induction of VF has been traditionally considered as a non-specific result as these patients

appear to have a similar prognosis as patients without any ventricular arrhythmia induction. Brugada *et al*[103] demonstrated that non-sustained PVT and VF are nonspecific responses to an aggressive stimulation protocol including three to four extra stimuli. Brodsky *et al*[104], presenting the results of the AVID trial, were not able to demonstrate that the induction of VF or fast VT (rate > 200 bpm) is related with death or ventricular arrhythmia recurrence (*P* = 0.07), but the induction of slow VTs (HR < 200 bpm) was independently related with recurrences as monomorphic VT.

Mittal *et al*[53] also evaluated the prognosis of ventricular arrhythmia induction in a cohort of 118 consecutive patients with CAD presenting with syncope. The mean LVEF of their cohort was 42% ± 13%. VF was the only arrhythmia induced in 20 patients (17% of the cohort). There was a survival rate of 89% and 81% at 1 year and 2 years consecutively in the entire cohort, and there were no differences between patients with VF induction or no induced arrhythmia (*P* = 0.39). By contrast, Link *et al*[105] found contradictory results in their cohort where they followed 274 consecutive patients with CAD and syncope or presyncope. The risk of arrhythmia occurrence was evaluated at the time of presentation with syncope by an EPS. VF was induced in 23 patients (8%) and ventricular flutter (monomorphic tachycardia with CL < 230 ms) in 24 patients (9%). Overall, 41 patients (15% of the cohort) were inducible for monomorphic ventricular tachycardias. After a follow-up of 37 ± 25 mo, 34 patients had ventricular arrhythmias. VF was induced in the initial EPS in 3 out of 23 patients (13% of this group) and in ventricular flutter in 7 out of 24 patients (30% of this group). Considering these results together, the induction of VF/ventricular flutter was predictive of ventricular arrhythmias during follow-up (*P* ≤ 0.001 *vs* non-inducible patients)[105].

Nonetheless, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] only have clear recommendations for the induction of sustained monomorphic ventricular tachycardia. Thus, an ICD is recommended in patients with CAD and unexplained syncope with MSVT induced during EPS with a IIa B level of recommendation. The induction of polymorphic VT, VF, or non-sustained ventricular arrhythmias are considered non-specific responses, and considering the absence of solid evidence, no specific recommendations can be made.

Despite the fact that VT should be ruled out in patients with IHD, many other causes may be present in this set of patients[3,9,106,107]. In fact, VT is not the most common cause of syncope. Patients with IHD have some factors that predispose them to other causes. For example, they are often on different hypotensive drugs that predispose to OH or reflex syncope[2]. Also, some conduction disturbances are more frequent in patients with IHD[30,48,50]. In the presence of conduction disturbances on the ECG, advanced AV block is a common cause of syncope[46,50,108]. Importantly, if the EPS is negative, VT is unlikely to be the cause of syncope, with reflex and OH syncope being the most probable etiologies[3, 107].

Mid-range left ventricular dysfunction

Patients with left ventricular disfunction are at high risk of cardiac and arrhythmic syncope[6]. In observational studies, unexplained syncope in this population has been associated with an increased risk of sudden death[1,9,79,109,110], although the evidence for the benefit of an ICD is limited. In general, the direct implantation of an ICD is indicated in those patients who fulfil the primary prevention criteria (NYHA class II-III heart failure, with LVEF < 35% on optimized pharmacological therapy). The evidence regarding the management of syncope in patients with mid-range LVEF is even more scant. Current ESC syncope clinical practice guidelines[1], which are similar to ACC/AHA/HRS [9] guidelines, suggest a work-up in line with general recommendations and state that the implantation of an ICD should be considered in patients with systolic dysfunction and unexplained syncope. The implantation of a cardiac monitor (ICM) is an alternative that may be considered in patients with recurrent episodes. Newly published ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] suggest a conservative strategy based on risk stratification and ICM implantation in patients with no other direct indication for an ICD.

Our group has recently investigated a similar strategy based on a stepwise protocol[79]. In summary, the diagnostic work-up for syncope in this population is based on three steps. Step 1 consists of the initial assessment in the ED. In a systematic manner, a clinical history and physical examination are performed, including testing for OH and CSM (if not contraindicated), general bloodwork, chest x-ray, and 12-lead ECG, as well as 12-24-h telemetry monitoring and a transthoracic echocardiogram. In cases where no certain or highly probable diagnosis is reached, it is considered unexplained syncope, and the patient is admitted to the hospital. Step 2 involves the hospital admission with continuous ECG monitoring and carrying out an invasive EPS if the following criteria are fulfilled: (1) Presence of conduction disorder on baseline ECG [1st degree AV block, Mobitz type 1 s degree AV block, complete RBBB or left bundle branch block (LBBB), BFB, left anterior or posterior fascicular block]; (2) Clinical, electrocardiographic, and/or imaging evidence of myocardial scar (history of myocardial infarction, presence of Q waves on surface ECG, presence of late enhancement on cardiac magnetic resonance imaging, and/or presence of necrosis on myocardial perfusion single-photon emission computed tomography scan); and (3) History of palpitations prior to the syncopal episode. If these criteria are not fulfilled, the EPS is not carried out, and the patient moves on to Step 3. Step 3 involves implanting an implantable cardiac monitor with subsequent clinical monitoring (Figure 3).

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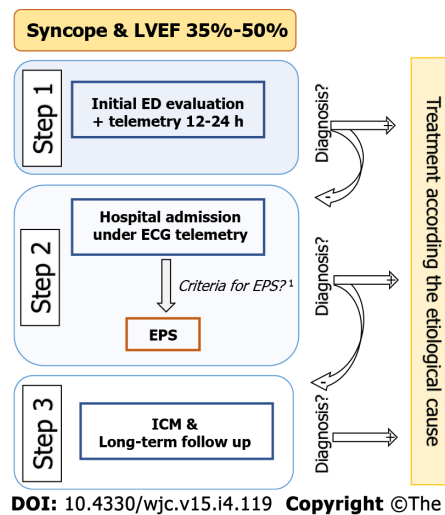
Figure 3 Proposed algorithm for the management of syncope in patients with mid-range left ventricular dysfunction. [1]Criteria for electrophysiological study: (1) Presence of conduction disorder on baseline electrocardiogram (1st degree atrioventricular block or Mobitz 1 s degree block, complete right or left bundle branch block, left anterior or posterior hemiblock); (2) Evidence of myocardial scar; and (3) Palpitations prior to the syncopal episode. ECG: Electrocardiogram; ED: Emergency department; LVEF: Left ventricle ejection fraction; EPS: Electrophysiological study; ICM: Implantable cardiac monitor.

In a recent published study that evaluated patients with unexplained syncope (excluding patients diagnosed in step 1), it was found that the application of this systematic protocol had a high diagnostic yield with a low rate of sudden death[79]. The overall diagnostic yield with both steps was 68.3%. Of note, the most common cause was arrhythmia. In 60 patients (57.7% of the total patients and 84.5% of the total diagnoses), a rhythm disorder was identified as the cause of the syncopal episode, with a high proportion of bradycardias, mostly due to AV block (47 patients, 45.2%). VT was the second most frequent cause, although it was significantly less common (9.6%). Most of the arrhythmias, be they AV block or VT, were able to be diagnosed in step 2. Another key finding of the study was that the diagnoses reached allowed treatment to be effectively guided. The sudden or unknown cause mortality rate of 0.9 per 100 person-years was comparable with general mortality rates published in the literature in patients with mid-range left ventricular dysfunction without syncope[106,111-113]. The findings of this study, in line with others on patients with structural heart disease[3,107,114], suggest that a stepwise diagnostic strategy and prolonged monitoring may be a safe and effective management alternative, reducing the number of patients requiring an ICD.

HCM
The hallmark of HCM is the abnormal increase of left ventricular wall thickness unrelated to abnormal loading conditions such as high BP, valvular heart diseases, or congenital heart disease. At the histopathological level, HCM is characterized by an increase in the size of myocardial cells and disordered myocardial cell organization with interstitial fibrosis that may predispose patients to suffer from ventricular arrhythmias. HCM carries a mortality rate that ranges from 1%-2%. New data from cohorts of patients with ICDs suggest that the mortality rate might be even lower (about 0.8%) and that it is related with several risk factors summarized in the HCM-SCD score[115]. The eight variables included in the risk score are: Age, LV wall thickness, left atrial size, left ventricular outflow tract (LVOT) gradient, nonsustained ventricular tachycardia, unexplained syncope, and family history of SCD.

HCM patients may have different syncope etiologies such as: Hypovolemia, conduction system disorders, sustained ventricular tachycardia, LVOT obstruction, and abnormal vascular reflexes, *etc*[116-118]. After ruling out non-cardiogenic and neural-mediated causes, arrhythmic syncope is one of the more worrisome causes for syncope in those patients. Patients with unexplained syncope should be tested with at least 24-hr Holter recording and exercise time-to-exhaustion to rule out LVOT obstruction on exertion. After an extensive evaluation of causes of syncope in those patients without clear diagnosis, an ILR should be implanted[1,117]. Routine tilt table testing in patients with HCM may be associated with an unacceptable number of false positives, and its use should be limited to selected cases[117].

Syncope of unknown origin is included in the risk score with an independent hazard ratio of 2.05 (1.48, 2.82; $P < 0.001$)[115]. Patients with intermediate-risk and low-risk clinical profiles should be evaluated for additional risk factors not included in the score, following 2022 ESC guidelines[19]. LV systolic dysfunction, apical aneurysm, > 15% of LV mass with late gadolinium enhancement on CMR, and several sarcomeric mutations have demonstrated a higher risk of ventricular arrhythmias in different studies and should be considered when evaluating the risk profile of a given patient[117,118]. The risk of ventricular arrhythmias is nonetheless dynamic and needs to be reassessed at every clinical

visit. Those patients with syncope and a high-risk clinical profile (SCD HCM risk score > 6%) or intermediate risk and other risk factors should be considered for ICD implantation (IIa B level of recommendation)[116], and those with intermediate risk (SCD HCM risk score 4%-6%) may be considered for ICD implantation (IIb B level of recommendation)[19].

Valvulopathies

A hemodynamic origin of syncope should be suspected in patients with valvular heart disease. However, other causes are possible[1,5,9,119-123]. The valvular heart disease with the highest risk of syncope is AoS[5,124,125]. Syncope is more frequent in severe stages of AoS but can occur in patients with moderate severity when suffering from other hemodynamic disturbances. Pharmacologic hypotension and atrial arrhythmias are also a frequent cause of syncope in patients with moderate and severe AoS[5,72,121,126]. In a recent study performed by our group in a cohort of patients with severe AoS and syncope, we observed that in 65% of the patients, the stenosis per se was initially identified as the likely cause of syncope, but later only 17.5% of the total cohort of patients was confirmed as having AoS as their final diagnosis. Conduction system disease and vasovagal etiologies were a more frequent cause of syncope in this population[5]. Importantly, syncope in the setting of a severe AoS has been suggested as having prognostic implications.

In a study published in 2019, these patients had a greater risk of mortality after aortic valve replacement in both the short-term (hazard ratio = 2.27; 95%CI: 1.04-4.95) and the long-term (hazard ratio = 2.11; 95%CI: 1.39-3.21) compared with patients who did not have syncope[127]. Although patients with syncope had somewhat different characteristics on echocardiography (smaller aortic valve area, smaller cardiac chambers, and lower ejection volumes), we believe that this rise in mortality was also partially due to the presence of other causes for the syncope such as underdiagnosed arrhythmias. In the cohort studied by Francisco-Pascual *et al*[5], those patients in whom it was not possible to precisely determine the cause of the syncope had more than triple short-term and medium-term mortality.

Furthermore, several studies have observed a high incidence of syncope and SCD after transcatheter aortic valve replacement (TAVR)[66,67,72,126,128]. It is theorized that induced conduction system delays after TAVR may predispose patients to suffer from electrical re-entry within the His-Purkinje system favoring a rare type of cardiac arrhythmia called bundle-branch re-entry in which the electrical impulse circulates between both branches of the conduction system with a slight delay often happening in the left bundle in the retrograde arm of the tachycardia. This arrhythmia is very rapid and frequently compromises the patient hemodynamically producing syncope or sudden cardiac arrest. The real incidence of this problem is unknown, but it needs to be kept in mind when evaluating a patient after a TAVR with some degree of conduction system delay.

Another significant but infrequent cause of syncope in patients with valvular heart disease is the presence of VF in patients with mitral valve prolapse, which has been named "the malignant mitral valve prolapse syndrome". In a recent meta-analysis carried out by Nalliah *et al*[129], they reported the population prevalence of mitral valve prolapse (MVP) of 1.2% and the prevalence of MVP in SCD autopsies of 11.7%. Nonetheless an incidence of 0.14 SCD events per 100 patient-years in the community MVP cohort, deserves an in-depth investigation of other risk factors for ventricular arrhythmias such as the presence of myocardial fibrosis or frequent complex ventricular ectopy, as has been proposed.

Conduction disturbances

In patients with conduction disturbances and syncope, the presence of bradyarrhythmia is always a concern although other causes may also be present. For example, in a recent cohort of 503 patients with unexplained syncope and BBB, arrhythmic syncope was identified in 57.9% patients, mostly secondary to AV block (51.3%). However, 12% were due to reflex syncope or an OH mechanism, 1.4% were due to ventricular tachycardia, and 10% were secondary to other causes[108].

The optimal management of patients with unexplained syncope and BBB is still controversial[1,9,46-48,130,131]. In fact, the 2017 ACC/AHA Guidelines[9] suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies, while ESC guidelines[1] recommend opting for a stepwise approach. The systematic stepwise approach (that includes an EPS and long-term follow-up with an ICM) was initially evaluated in the B4 study[47]. This study found that the diagnostic approach is safe and achieves a high rate of etiological diagnosis allowing for the selection of specific treatment and avoiding the implantation of unnecessary pacemakers. The results of the B4 study have been confirmed by several subsequent studies, some of them with a relatively high number of patients and long-term follow-up[80,108,132-134].

On the other hand, the strategy of direct pacemaker implantation was recently evaluated in the SPRITELY trial. This study randomized 105 patients older than 50 years with BFB (41 LBBB and 74 RBBB plus left fascicular block) and at least one syncope in the previous year to receive ICM or empirical pacemaker implantation. In the 33-mo follow-up period, the 57 patients randomized to the pacemaker arm showed a lower primary composite endpoint (cardiovascular death, syncope, bradycardia resulting in an intervention, and device complications) than the ILR arm; [20 (35%) *vs* 44 (76%); *P* < 0.0001]. However, the presence of syncope during follow-up was similar in both groups (29% *vs* 26%; *P* = 0.95)[135].

It must be highlighted that in the SPRITELY trial, EPS was not systematically carried out before ICM implantation, and therefore it cannot be considered as a direct comparison with the stepwise approach. Similar findings were previously found in the PRESS study[136], where patients were randomized to pacemaker in pacing mode (DDD at 60 bpm) or backup pacing mode (drug-drug interaction at 30 bpm). The primary endpoint of this study was a composite endpoint of syncope, presyncope with device intervention, or documented bradycardia and AVB, and patients allocated to active pacing had a significant reduction of this composite endpoint. However, when only syncope recurrences were analyzed separately, there were no differences between the two groups. Furthermore, there are some studies that have analyzed the recurrence rate in patients with syncope and BBB, in whom a pacemaker has been implanted, showing that syncope recurrence is higher in those patients in whom a pacemaker was implanted empirically than in those in whom a pacemaker was implanted after a positive EPS or a documented AVB[137,138].

With the available evidence, the authors of this review continue to support the stepwise approach to manage these patients. Nevertheless, direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment (Figure 4). According to the newest 2021 ESC guidelines for cardiac pacing and resynchronization[18], in patients with sinus bradycardia and syncope of unclear origin after a thorough work-up, an exercise test to evaluate chronotropic competence and an EPS to evaluate for sinus node overdrive suppression pathologic responses might be indicated. cSNRT (basal cycle length; normal value 525 ms) has demonstrated good predictive value in patients with sinus bradycardia despite the presence of symptoms (overall accuracy of cSNRT in predicting serious sinus node disease regardless of the presence of symptoms: 90%, 100% in the presence of symptoms; sensitivity of the test: 66%). Patients presenting with a ventricular rate below 40 bpm have a 70% probability of having an abnormal cSNRT. In patients with a basal HR of 50 to 55 bpm, the probability of finding an abnormal response in cSNRT test is 24%[139]. However, it should be noted that pacing patients with sinus node dysfunction has not demonstrated improved survival so far[18,131].

EPS diagnostic yield is higher in patients with sinus bradycardia or BFB and structural heart disease and is lower in patients with a normal ECG and no structural heart disease[46,50]. Thus, it is preferable to perform EPS in patients with higher pretest probability and implant a loop recorder in those with lower pretest probability. Patients with first degree AV block and second degree type I (Wenckebach) block presenting with syncope without a firm diagnosis after extensive study should be offered an EPS. The presence of second degree type II block or third degree AVB constitutes a clear indication for cardiac pacing. Patients with 2:1 AV block can be evaluated by increasing the sinus node rate (atropine 1 mg or exercise test). If the degree of block increases by increasing of the sinus rate, an infra-Hisian origin must be suspected, and pacemaker implantation should be considered. Patients with syncope and BFB represent a group whose risk of syncope is especially difficult to stratify. Therefore, in patients with BFB and syncope of unknown origin an EPS should be performed.

In the presence of an HV interval longer than 70 ms (basal) or > 100 ms after infusion of 2 mg/kg of flecainide (or other Vaughan Williams class I antiarrhythmic drugs), cardiac pacing should be considered[140]. The absence of high-risk characteristics in the EPS of patients with syncope and BBB or BFB does not preclude the development of paroxysmal AV block, and an ILR needs to be considered. Roca-Luque *et al*[50] demonstrated that the most predictive combination of conduction disorders were LBBB or RBBB + long PR interval + left fascicular block [odds ratio = 4.5 (1.06-20.01); $P < 0.042$], LBBB + prolonged PR interval [5.2 (1.52-17.74); $P < 0.001$], and RBBB + prolonged PR interval [3.8 (1.7-8.7); $P < 0.001$] in their 271 patient cohort in 2018.

Channelopathies and inherited arrhythmia syndromes

Cardiac channelopathies are a group of diseases in which a mutation of different regulatory proteins of the action potential may predispose a patient to suffer from ventricular arrhythmias and SCD. Syncopal episodes in these patients might be due to non-sustained polymorphic VT or VF. In this section, we discussed the implications of the presence of syncope in patients with BrS, LQTS, and catecholaminergic PVT.

BrS

BrS was first described by the Brugada *et al*[141] in their elegant paper published in JACC in 1992. In their first publication of this syndrome, they described a cohort of 8 patients with RBBB and ST elevation in leads V1-V2-3 that suffered from aborted episodes of SCD[142].

Even though the mechanism of the electrical dysfunction leading to VF is not completely understood, it is believed that an increase in early repolarizing currents (Ito current) or a reduction in depolarizing currents (INaT) may lead to a phase II dispersion of repolarization and early post-depolarizations, which might generate phase II re-entries, possibly triggering VF. This electrical disorder seems to be more accentuated in the anterior part of the right ventricular outflow tract obstruction, where Ito current has been shown to be higher than in other heart sites. This latter observation might explain the isolated ST elevation in precordial leads and the effectiveness of ablation on the right ventricular outflow tract in patients with BrS and arrhythmic storm[143].
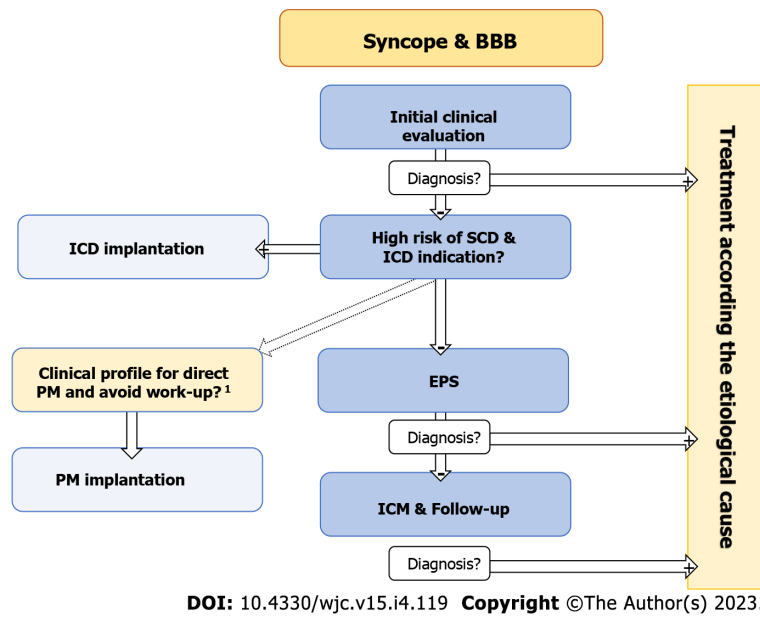
Figure 4 Proposed algorithm for the management of syncope in patients with bundle branch block. [1]Direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment. SCD: Sudden cardiac death; BBB: Bundle branch block; EPS: Electrophysiological study; ICD: Implantable cardiac defibrillator; PM: Pacemaker; ICM: Implantable cardiac monitor.

Patients with BrS pattern on ECG and syncope have a four-fold risk of sudden cardiac arrest, representing a 1.5% annual risk of sudden cardiac arrest. When the syncope cannot be classified as neuro-mediated or a cardiac origin is a possibility, ICD implantation should be considered[19]. Therefore, it is usually not necessary to perform an EPS to stratify the risk in the presence of unexplained syncope, as it is assumed to be high risk.

However, patients with sodium channel dysfunction may exhibit conduction system dysfunction as well. It is not infrequent for patients with those specific mutations to exhibit sinus bradycardia and/or BBB. Furthermore, reflex syncope is also frequent in young patients with BrS[144]. For these reasons, some authors have also suggested a more conservative approach, where implantation of a loop recorder can be considered in BrS patients with an unexplained syncope (not clearly cardiac) and without other indications for an ICD[19,145].

LQTS

The hallmark of the LQTS is an inadequately prolonged corrected QT interval, measured from the beginning of the QRS complex to the point at which the descending limb of the T wave crosses the isoelectric baseline of the ECG. The measure is frequently performed in leads II or V5-6 where the T wave and the isoelectric baseline are often well demarcated. The diagnosis of LQTS is made in the presence of a cQT interval of ≥ 480 ms or a Schwartz score (including several clinical and electrocardiographic parameters) of > 3. In the presence of a cardiogenic syncope, the presence of a cQT ≥ 460 ms is sufficient to reach the diagnosis.

The mechanism of arrhythmogenicity in patients with LQTS seems to be related with dispersion of the repolarization. The prolongation of the repolarization is not homogeneous among the different layers of myocardium. Therefore, early post depolarization occurring over the T wave may generate functional re-entry patterns of conduction ultimately generating fibrillatory conduction.

Up to 17 different mutations leading to LQTS have been described. The majority of them are produced by three specific mutations. LQTS1 is produced by mutation in the α subunit of the delayed rectifier potassium channel with slow opening kinetics. This mutation comprises 40%-55% of cases. LQTS1 patients are prone to suffering from ventricular arrhythmias during sports or physical activity (especially during swimming). LQTS2 is caused by a mutation in the α subunit of the delayed rectifier potassium channel with rapid opening kinetics. This mutation is present in up to 30%-45% of cases, and ventricular arrhythmias are frequent during loud noises and in the postpartum period in females. The activating mutation in the α subunit of the sodium channel (INaT) keeps the channel opened beyond phase 0, increasing late sodium currents (INaL), thus prolonging repolarization and therefore the QT interval. This mutation is present in 5%-10% of patients and is related to fatal events during rest or sleep [146].

It has been observed that LQTS patients respond favorably to beta-blockers; thus every patient with a diagnosis of LQTS should be treated with beta-blockers. Apparently, non-specific beta-blockers, such as propranolol or nadolol, have shown better results with a lower incidence of ventricular arrhythmias. If patients suffer from syncope despite the use of beta-blockers, an ICD must be implanted for the

prevention of SCD[147].

Catecholaminergic PVT

Catecholaminergic PVT (CPVT) is an inherited channelopathy in which several mutations may affect the intracellular handling of calcium release-uptake. The overload of cytoplasmatic calcium leads to cell membrane voltage instability leading to delayed depolarizations that lead to the characteristic arrhythmia of this disorder, bidirectional ventricular tachycardia (also seen in digitalis toxicity), or VF.

The mutation in the ryanodine receptor gene, inherited in an autosomal dominant manner, is the cause of 50%-55% of cases. A new mutation in the calsequestrin gene has been described and has an autosomal recessive inheritance pattern. The ryanodine receptor gene mutation generates an aberrant ryanodine channel that permeabilizes the channel to calcium release. The calsequestrin proteins work close to the ryanodine channel, regulating its function.

Patients with CPVT are prone to ventricular arrhythmias related to exercise. Ventricular arrhythmias usually occur with HR over 130 bpm. With increasing levels of exercise, patients may exhibit monomorphic ectopy, polymorphic ectopy, non-sustained VT, bidirectional VT, and finally, if the exercise continues, VF. CPVT is a highly arrhythmogenic condition with a cardiac event rate of up to 80% at 40 years. Therefore, a low threshold for ICD implantation is advised. The use of non-selective beta-blockers has been shown to reduce the incidence of ventricular arrhythmias from 25% to 11% at 8 years[148].

Probably due to small cohorts, no single risk factor has demonstrated sufficient prognostic value to be used routinely. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend implantation in patients with CPVT who have survived a cardiac arrest (class I C) and should be considered in patients with CPVT and either arrhythmic syncope or presence of polymorphic VT or bidirectional VT on maximal tolerated doses of beta-blockers (class IIa C)[19].

CONCLUSION

Syncope is a symptom that involves a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. The highest mortality and SCD risk occur when syncope is associated with underlying cardiac disease, in particular when the main cause of syncope is not well established and treated properly. Arrhythmia is the most common cause of cardiac syncope. Appropriate risk stratification and work-up to determine the main cause of the event is warranted to improve the prognosis of patients. This review provided an update on the important and novel data about arrhythmic syncope, the value of the different diagnostic tests, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. This review emphasized the importance of an appropriate stepwise approach work-up and interventions.

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FOOTNOTES

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