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REVIEW

Brugada syndrome and syncope: a practical approach for diagnosis and treatment

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Abstract Syncope in patients with Brugada electrocardiogram pattern may represent a conundrum in the decision algorithm because incidental benign forms, especially neurally mediated syncope, are very frequent in this syndrome similarly to the general population. Arrhythmic syncope in Brugada syndrome typically results from a self-terminating sustained ventricular tachycardia or paroxysmal ventricular fibrillation, potentially leading to sudden cardiac death. Distinguishing syncope due to malignant arrhythmias from a benign form is often difficult unless an electrocardiogram is recorded during the episode. We performed a review of the existing literature and propose a practical approach for diagnosis and treatment of the patients with Brugada syndrome and syncope.

Keywords Syncope • Neurally mediated syncope • Brugada syndrome • Sudden death • Ventricular fibrillation • Tilt testing • Electrophysiologic study • Implantable loop recorder • Implantable cardioverter-defibrillator

The diagnosis of Brugada syndrome

Since its recognition as a clinical entity in 1992,[1] Brugada syndrome (BrS) has attracted the attention of many physicians for its circadian pattern of ventricular arrhythmias (VAs), mostly occurring at rest. In a patient presenting with syncope, BrS is diagnosed when the electrocardiogram (ECG) shows the Type 1 morphology (coved type, a downward ST segment elevation ≥2 mm followed by negative T waves) in ≥1 lead among the right precordial leads V1–V2 positioned in the 2nd, 3rd, and 4th intercostal space, occurring either spontaneously or after provocative drug test.[2–4] Type 2 and 3 saddlebacks ECG patterns are only considered suspicious but not diagnostic for the disease.[2–4]

Syncope in Brugada syndrome: incidental vs. aborted sudden death

Syncope is a powerful symptom influencing prognosis in BrS.[2] Nevertheless, a history of syncope is a non-specific finding because incidental benign forms, especially neurally mediated syncope (NMS), are common, both in the general population as well in BrS population.[5,6] Conversely, arrhythmic syncope in BrS is extremely rare, representing the expression of self-terminating paroxysmal VF, e.g. a spontaneous arrhythmic event with duration sufficient to cause loss of consciousness (potentially >5 s), but not sustained enough to cause sudden cardiac death (SCD). This condition has only been described in a few case reports.[7–10] Syncope due to self-terminating VF has also seldom been reported in patients who had already received

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an implantable cardioverter-defibrillator (ICD) or a loop recorder.[11] In a 20-year single-centre experience, the rate of appropriate defibrillator shocks was similar in asymptomatic BrS populations as well as in those with syncope.[12] In patients with presumed moderate arrhythmic risk, no arrhythmic event was documented in 27 patients who had received an implantable loop recorder in an Italian community-based prospective study,[13] as well as among eight patients in the study of Sacher *et al.*[11] Kubala *et al.*[14] reported the outcome of 11 patients with implantable loop recorder and clinical suspicion of life-threatening arrhythmias among 36% of patients experiencing syncope during monitoring, only atrioventricular block and sinus bradycardia were reported, confirming the pre-disposition to vasovagal mechanism. Finally, Sakhi *et al.*[15] found an atrial arrhythmia or a bradycardia in 11/20 patients in BrS patients who had syncope or palpitations; a sustained ventricular arrhythmia was never documented.

The evaluation of syncopal BrS is also complicated by the fact that, since NMS is so frequent,[6,16] a 'true positive' BrS patient may suffer from both reflex and arrhythmic syncopes.[11] Moreover, no single feature from history taking is sufficient for differential diagnosis. Indeed, triggers or prodromes can be concomitant in neurally mediated as well as in arrhythmic syncope in patients affected by channelopathies,[17,18] and palpitations often precede also non-arrhythmic syncope.[17,19]

The recent European Society of Cardiology (ESC) guidelines on syncope[20] give recommendations for diagnosis and risk stratification of unexplained syncope. Aim of this article was to perform an overview of the literature and to propose a practical approach to the patients with BrS and syncope.

Overview of current publications

The results of a comprehensive review of articles that assessed arrhythmic events in the follow-up are listed in *Table 1*.[11,13,21–28] Most articles reported the results of large multi-centre registries. Six articles[11,13,22,26–28] gave a quite homogeneous definition of suspected arrhythmic syncope. In brief, the common clinical characteristics used for such definition were abrupt onset without prodrome and triggers, short duration, and prompt recovery, syncope during sleep (nocturnal agonal respiration), concomitant usage of drugs that were known to facilitate BrS. Although severe trauma, urinary incontinence, tonic–clonic activity, older age, and male gender were more in favour for an arrhythmic syncope, these factors were not considered for the definition.[11,27] When the patients did not meet such characteristics, syncope was classified as vasovagal/NMS (when typical triggers and prodroms were present) or as undefined/unknown/doubtful syncope (when the clinical features did not allow to classify into one of the above forms). All the studies had a homogeneous definition of arrhythmic events during the follow-up, defined as SCD or appropriate ICD shock. Pooled together, 44/279 (15.7%) patients affected by suspected arrhythmic syncope had arrhythmic events during a median follow-up of 60 months, corresponding to 2.8 per 100/person year. Conversely, 4/541 (0.7%) patients without such features had arrhythmic syncope, corresponding to 0.2 per 100/person year (*P* value: 0.0001).

Two other studies[21,25] defined the study population as affected by 'suspected arrhythmic syncope' but did not give a precise definition of it and two studies[23,24] included patients with unspecified syncope. Taken together, these patients had a rate of arrhythmic events slightly lower than that of patients with suspected arrhythmic syncope: 39/544 (7.2%) during a median follow-up of 39 months, corresponding to 2.2 per 100/person year.

Practical approach to diagnosis and treatment

The results of the studies reported in *Table 1* show that, in BrS patients, the risk of arrhythmic events at follow-up can be stratified during the initial clinical assessment. The probability of arrhythmic events is exceptionally low in patients with only established neurally mediated forms, similar to the value of 0.23 per 100 person year observed in the lowest risk group of asymptomatic individuals without syncope with drug-induced Type 1 BrS ECG pattern.[30] Therefore, ICD can be safely avoided in these patients.

On the other hand, patients with suspected arrhythmic syncope or with undefined syncope have a significantly higher risk of life-threatening events. However, the relatively low predictive value of the clinical diagnosis of 'suspected' arrhythmic syncope warrants an accurate multi-parametric assessment to restrict the number of ICD candidates. In *Table 1* which summarizes the present evidence, the number of patients with suspected arrhythmic syncope or undefined syncope is unrealistically higher than that of patients with non-arrhythmic syncope (823 vs. 541, respectively). Indeed, owing to the relative rarity of BrS, the registries were assembled by few tertiary centres, collecting cases from several referrals. It is likely that many cases of typical NMS were not referred to tertiary centres, configuring a selection bias: by diluting the arrhythmic events among the general population of patients with syncope, the prognostic yield of syncope is likely to be even lower, pointing to the need of a better definition of the nature of the syncopal event.

Critical points and open questions: the role of cardiac autonomic nervous system and tilt testing

The autonomic nervous system function could impact BrS patients.[31–38] Endomyocardial biopsies have shown reduced cAMP and norepinephrine concentrations in BrS patients, consistent with autonomic dysfunction.[33] An increased cholinergic tone could exert its proarrhythmic effects in BrS through increasing dispersion of transmural repolarization.[37] The clinical features of the episodes of cardiac arrest as well as ECG fluctuations under autonomic modulation[36] suggest a potential role of the cardiac vagal tone in the pathogenesis of arrhythmias, potentially explaining the higher incidence of cardiac arrest at night.[38] Yet, deep baroreflex stimulation using phenylephrine injection failed to induce life-threatening arrhythmias or ST-segment elevation.[36] Arrhythmias following vasovagal symptoms have been reported in a few case reports, suggesting a potential cause–effect relationship.[34,35] However, the connection between autonomic dysfunction, NMS, and risk of arrhythmias remains uncertain. Kasanuki *et al.*[34] reported episodes of aborted cardiac arrest in six BrS patients who had a history of presumed vagal activity. Nevertheless, the clinical features of the syncopal episodes make unlikely a diagnosis of vasovagal syncope among these

Table 1 Principal studies in Brugada syndrome evaluating patients with syncope

Study	Patients with syncope (% of total population)	Median FU (months)	Syncope type	Patients with arrhythmic events during FU *
FINGER registry 2010[21]	313 (30)	34	Suspected arrhythmic (undefined)	19 (6%) 2.2 per 100/person year
Delise *et al.* 2011[23]	105 (34)	40	Any syncope	10 (10%) 2.9 per 100/person year
PRELUDE registry 2012[22]	64 (21)	34	Suspected arrhythmic	7 (11%) 2.5 per 100/person year
Sacher *et al.* 2012[11]	57 (28)	65	Suspected arrhythmic: 23 (40%)	6 (26%) 1.1 per 100/person year
			Typical vasovagal syncope: 17 (30%)	0 (0%)
			Doubtful origin (intermediate clinical features): 17	0 (0%)
Hiraoka *et al.* 2013[24]	17 (4)	43	Syncope (unspecified)	2 (12%) 3.5 per 100/person year
J-IVFS registry 2013[25]	109 (24)	52	Suspected arrhythmic (unspecified)	8 (7%) 1.7 per 100/person year
Olde Nordkamp *et al.* 2015[27]	118 (84)	54	Suspected arrhythmic: 33 (28%)	4 (12%) 2.7 per 100/person year
			Neurally mediated: 67 (57%)	0 (0%)
			Unknown cause (intermediate clinical features): 18 (15%)	0 (0%)
Giustetto *et al.* 2017[13]	195 (100)	62	Suspected arrhythmic: 77 (39%)	7 (9%) 1.7 per 100/person year
			Neurally mediated: 118 (61%)	2 (2%) 0.3 per 100 person/year
Florez *et al* 2018[26]	251 (100)	74	Suspected arrhythmic: 16 (6%)	4 (25%) 4.0 per 100/person year
			Neurally mediated: 235 (94%)	1 (0.4%) 0.03 per 100/person year
Hernandez-Ojeda *et al.* 2020[28]	135 (28, 5)	92	Suspected arrhythmic: 66 (48.9%)	16 (24%) 3.1 per 100/person year
			Neurally mediated: 51 (38%)	1 (2%) 0.2 per 100/person year
			Undefined: 18 (13%)	0 (0%)
Total	1364	56	Suspected arrhythmic: 279 (20%)	44 (15.7%) 2.8 per 100/person year
			Suspected arrhythmic undefined: 544 (40%)	39 (7.2%) 2.2 per 100/person year
			Non-arrhythmic: 541 (40%)	4 (0.7%) 0.2 per 100/person year

Modified with permission from [29]Mascia *et al.* Brugada syndrome and syncope: a systematic review. *J Cardiovasc Electrophysiol* 2020.

patients, since syncope had occurred at rest, without typical triggers and prodromes.[34] Similar findings were observed in a 44-year-old man with BrS and VF at rest[35]: VF was associated with an autonomic disorder, but it was never causally linked to an episode of NMS. Giustetto *et al.*,[13] in a group of 195 BrS patients with clinical features suggesting a NMS, documented only two patients with arrhythmic events at follow-up. One patient had history of recurrent syncope after meals and another had a history of positive head up tilt test (HUTT); both patients had documented VF induction during electrophysiological study (EPS). Thus, to date, no firm evidence that in BrS a NMS may trigger an arrhythmic cardiac arrest exists.[11,27,28]

Another critical point is the importance of a proper HUTT indication. HUTT aims at obtaining an autonomic correlation for transient loss of consciousness, providing an addendum to history taking if the initial evaluation is compatible with a NMS.[39] Head up tilt test is useful to distinguish between neurally mediated and arrhythmic syncope.

Table 2 Principal studies in Brugada syndrome evaluating the clinical outcome of patients without prophylactic implantable cardioverter-defibrillator

Reference (years)	Total no. of BrS patients	No. of patients with ICD in primary prevention/total no.	No. of patients with Type 1 ECG and no previous ICD	FU (median)	No. of patients with no previous ICD, who suffered aborted SCD during FU	Syncopal patients with no previous ICD, and aborted SCD during FU
Brugada *et al.*[46] (2003)	547	177/547	370	37	16	3/16
Mok *et al.*[51] (2004)	50	6/50	36	30	1	1/1
Kamakura *et al.*[47] (2009)	245	70/245	130	48	1	0/1
Probst *et al.*[21] (2010)	1029	388/1029	579	31,9	2	0/2
Priori *et al.*[22] (2012)	308	137/308	171	34	1	0/1
Takagi *et al.*[25] (2013)	460	193/460	183	44	2	1/2
Sieira *et al.*[49] (2017)	400	176/400	224	80,7	1 (successfully reanimated)	1/1
Letsas *et al.*[50] (2019)	111	34/111	77	55	0	0
Total	3150	1181/3150	1770	45	24/1770 (1.4%)	6/24 (25%)

Indeed, in the study of Sacher *et al.*,[11] and in the study of Take *et al.*,[40] HUTT was significantly more frequently positive in patients with clinical features suggesting a NMS (in 79% and 54% of cases, respectively) than patients with a history of suspected arrhythmic syncope (38% and 10%, respectively). Nevertheless, in patients with a history of suspected arrhythmic syncope, a positive response to HUTT simply suggests that also a neurally mediated susceptibility is possible, but it cannot rule-out an associated arrhythmic form. Therefore, in BrS, HUTT should never be used as a substitute for history taking nor isolated from history taking.[40] A practical algorithm for the appropriate utilization of HUTT based on 2018 ESC guidelines[20] is shown in *Figure 1*.

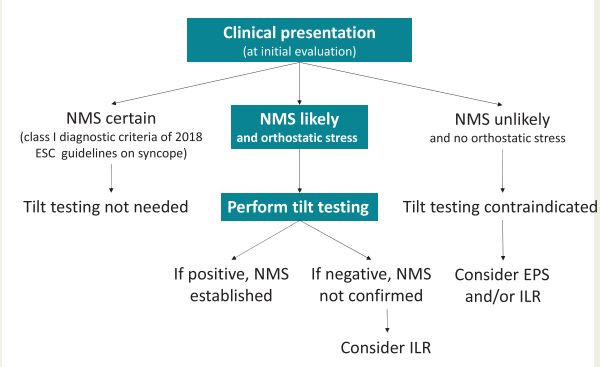

Figure 1 Proper indications for the use of tilt testing, ILR, and EPS in patients with Brugada syndrome and suspected NMS. EPS, electrophysiological study; ILR, implantable loop recorder; NMS, neurally mediated syncope.

Critical points and open questions: the role of implantable loop recorder, electrophysiological study, and genetic testing

Due to the importance of ECG documentation obtained during episodes, implantable loop recorder is today considered an important tool in subjects with recurrent unexplained syncope following a negative workup at baseline.[11,13–15] In BrS patients considered at low risk for SCD, the implantable loop recorder may allow to rule out an arrhythmic cause of syncope as the potential mechanism of atypical syncope. Nevertheless, implantable loop recorder should not be used in patients at high risk of cardiac arrest.

The role of EPS in risk stratification has been discussed in multiple studies over 25 years and is actually one of the most discussed topics in this intriguing disease entity. In a systematic review and pooled analysis of prospective observational studies of BrS patients (8 studies comprising 1312 patients who experienced 65 cardiac events). Sroubek *et al.*[30] found that arrhythmias induced with EPS were associated with future arrhythmic risk, while lack of induction was not necessarily associated with low risk. In particular, the lowest risk occurred in individuals without syncope and with drug-induced Type 1 patterns (0.23% for no induced arrhythmia with up to double extrastimuli vs. 0.45%, for induced arrhythmia), and the highest risk occurred in individuals with syncope and spontaneous Type 1 patterns (2.55% for no induced arrhythmia vs. 5.60%, for induced arrhythmia).

Thus, EPS increases the predictive accuracy of a history of suspected arrhythmic syncope.

Many genes have been so far identified in association with BrS, but only *SCN5A* contributed to a significant number of patients and has information regarding its possible role in the risk stratification.[41] In young BrS patients ≤18 years of age, the absence of a SCN5A mutation may denote a lower risk of events. Andorin *et al.*[42] studied 106 patients, 15 of whom had history of syncope: all patients who experienced life-threatening events had a SCN5A mutation, whereas none of the 17 genotype-negative patients had events. Yamagata *et al.*[43] analysed a population of 415 BrS probands (average age 46 years), 24% of them with a syncopal events, and showed that the presence of a mutation in the pore region of SCN5A was associated with significant higher risk of life-threatening arrhythmias, including the subgroup with history of syncope. Therefore, there are data supporting the role of genetic in risk stratification; however, a validation in larger and independent cohorts is probably needed.

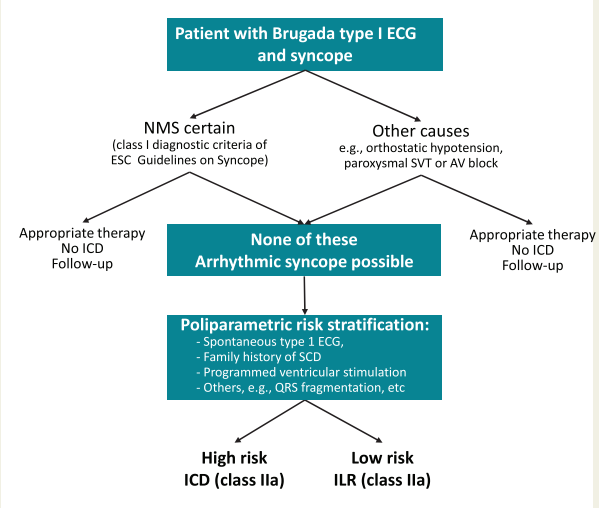

Figure 2 Proposed practical algorithm for a proper selection of patients with Brugada syndrome and syncope candidates for ICD. ICD, implantable cardioverter defibrillator; NMS, neurally mediated syncope; SCD, sudden cardiac death; SVT, supraventricular tachycardia.

Implantable cardioverter-defibrillator: when to implant in a Brugada syndrome patient with syncope?

Implantable cardioverter-defibrillator is the only measure proven to prevent death in BrS population.[2] ICD-recorded fast VAs are only a surrogate of SCD, as malignant tachycardias are potentially self-terminating and may not lead to death.[44,45] Therefore, the real incidence of arrhythmic SCD that can potentially benefit from an ICD, is probably lower.[21,22,25,46–50] Syncope *per se* is a weak risk factor, which was present in only one quarter of patients with events (*Table 2*). In addition, since the device itself is burdened by a non-negligible complication rates,[45,51] an extensive indication is not justified. The issue of inappropriate shock is particularly important in young patients with inherited arrhythmia syndromes. In a systematic review and meta-analysis,[52] inappropriate shocks occurred in 20% of patients (crude annual rate of 4.7% per year). In the recent randomized PRAETORIAN trial,[53] compared with transvenous ICD, subcutaneous ICD showed a reduction of device-related complications from 9.8% to 5.9% but a slight increase in the rate of inappropriate shocks (most frequently precipitated by oversensing of T waves) and death (with an equal number of SCD). T-wave oversensing is an issue in BrS because of the dynamic nature of the electrocardiographic morphology[54]; such a risk is probably decreased using SMART Pass[55] and screening test during drug challenge and exercise.[56] The potential benefit of a longer lead longevity of subcutaneous ICD, which would be particularly useful in young BrS patients, need to be assessed during the long-term follow-up. The proportion of BrS patients with syncope who have been unnecessarily treated with an ICD is high, estimated from 84% to 89%.[9,10,42] Finally, ICD implantation does not prevent recurrent vasovagal symptoms.[2]

On the other hand, in BrS patients with unexplained syncope and high risk for malignant arrhythmia, an ICD should be offered to the patients even in doubtful cases. In this patient population, physicians should balance the benefit with the potential long-term device-related complications.[45] To improve patient selection, some important multi-parametric risk stratification algorithms have been developed.[23,28,49,57–59] They include syncope in conjunction with other variables in the estimation of the global risk of SCD. Delise *et al.*[57] developed a simple algorithm that included, besides syncope, familial sudden death, spontaneous Type 1 BrS pattern, and positive EPS. This author found that the higher is the number of risk factors per patient, the higher is the risk of arrhythmic events. In general, a limitation of these algorithms is that they do not made any attempt to distinguish the type of syncope. More recently, in a multi-centre study enrolling 1110 patients with BrS and no history for cardiac arrest, multiple parameters recognized in previous studies as risk markers in BrS were evaluated.[58] Specifically, the authors considered: age at diagnosis, gender, probable arrhythmia-related syncope, diagnosis by family screening of SCD, spontaneous Type 1 Brugada ECG pattern, SCN5A mutation, positive programmed ventricular stimulation, ventricular effective refractory period >200 ms, sinus node dysfunction, atrial fibrillation/flutter, early repolarization in peripheral leads, Type 1 brugada ECG in peripheral leads, aVR sign, significant S wave in lead I, QRS duration >120 ms in V2, QRS fragmentation. Among these risk factors, those associated with a higher risk of life-threatening arrhythmias were probable arrhythmia-related syncope, spontaneous Type 1 ECG, early repolarization, and Type 1 Brugada ECG pattern in peripheral leads. Surprisingly, despite most studies in the literature distinguished between suspected arrhythmic and non-arrhythmic syncope, the '2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD'[28] used the generic term of 'syncope' in the recommendations regarding BrS: 'an ICD implantation should be considered in patients with a spontaneous diagnostic Type 1 ECG pattern and history of syncope' (Class IIa, level of evidence C).[4] The '2017 AHA/ACC/HRS guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death'[60] are more restrictive, recognizing a Class I indication for ICD implantation in BrS patients with a spontaneous Type 1 ECG pattern and a recent history of syncope presumed due to VAs, but missed to define the diagnostic criteria. The most recent '2018 ESC guidelines for the diagnosis and management of syncope'[20] are as restrictive and, in addition, provide instructions to distinguish benign NMS from potentially lethal arrhythmic syncope (*see Appendix 1*). Unexplained, potentially arrhythmic syncope is defined as 'syncope that does not meet the Class I diagnostic criteria'. In the presence of spontaneous Type 1 BrS ECG pattern, unexplained syncope is considered a risk factor for life-threatening arrhythmias and the guidelines recommend ICD implantation with a Class IIa, level of evidence B.[20] Such indication is consistent with the data from the literature (*Table 1*). On the contrary, ICD is not indicated in patients with a Class I diagnosis of NMS. In patients with recurrent episodes of unexplained syncope and low SCD risk, these guidelines also consider the alternative option of the implantable loop recorder (Class II, level of evidence B).[20] The proposed management is shown in *Figure 2*. Such more restrictive indication will hopefully reduce the number of patients who receive a useless ICD implantation while maintain those patients who need it.

Conclusions

The association of BrS and NMS is frequent in consideration of high prevalence of this latter in young subjects. The distinction between incidental benign NMS and aborted sudden death is one of the most difficult challenges for electrophysiologists as misdiagnosis can have serious consequences. When the implantation of an ICD is considered, a careful history taking should be integrated in a multiparametric risk stratification that includes, spontaneous Type 1 ECG, family history, EPS, and other known risk factors.[23,28,49,57–59] At the same time, any decision should be shared with the patient acknowledging the patient's beliefs, expectations, preferences, and values.

Conflict of interest: none declared.

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Appendix I Class I diagnostic criteria of the 2018 ESC Guidelines on Syncope[18]

Recommendations	Class	Level
Diagnostic criteria with initial evaluation		
Vasovagal syncope is highly probable if syncope is precipitated by pain or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea).[8,13–17]	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers.	I	C
Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant OH.	I	C
Arrhythmic syncope is highly probable when the ECG shows:	I	C
• Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 s in the awake state and in the absence of physical training		
• Mobitz II second- and third-degree AV block		
• Alternating left and right BBB		
• VT or rapid paroxysmal SVT		
• Non-sustained episodes of polymorphic VT and long or short QT interval		
• Pacemaker or ICD malfunction with cardiac pauses.		
Carotid sinus syndrome		
Carotid sinus syndrome is confirmed if carotid sinus massage causes bradycardia (asystole) and/or hypotension that reproduces spontaneous symptoms, and patients have clinical features compatible with a reflex mechanism of syncope.	I	B
Active standing		
Syncope due to Orthostatic hypotension is confirmed when there is a fall in systolic blood pressure from baseline value ≥20 mmHg or diastolic blood pressure ≥10 mmHg or a decrease in systolic blood pressure to <90 mmHg that reproduces spontaneous symptoms.[6,20,]	I	C
Electrocardiographic monitoring		
Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected.	I	B
Exercise testing		
Syncope due to second- or third-degree AV block is confirmed when the AV block develops during exercise, even without syncope.	I	C
Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension.	I	C