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# Unexplained Syncope: The Importance of the Electrophysiology Study

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**Abstract:** Syncope of cardiac origin may be associated with an increased risk of sudden cardiac death if not treated in a timely and appropriate manner. The diagnostic approach of syncope imposes a significant economic burden on society. The investigation and elucidation of the pathogenetic mechanism of syncope are of great clinical importance, as both prognosis and appropriate therapeutic approaches depend on these factors. The responsible mechanism of presyncope or syncope can only be revealed through the patient history, baseline clinical examination and electrocardiogram. The percentage of patients who are diagnosed with these tests alone exceeds 50%. In patients with a history of organic or acquired heart disease or/and the presence of abnormal findings on the electrocardiogram, a further diagnostic electrophysiology inclusive approach should be followed to exclude life threatening arrhythmiological mechanism. However, if the patient does not suffer from underlying heart disease and does not show abnormal electrocardiographic findings in the electrocardiogram, then the probability in the electrophysiology study to find a responsible cause is small but not absent. The role of a two-step electrophysiology study inclusive risk stratification approach for the effective management of the former is thoroughly discussed in this review.

**Keywords:** syncope; presyncope; pacemaker; electrophysiology study; sinus node dysfunction; atrioventricular node disease



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## 1. Introduction

Syncope is a clinical syndrome defined as the transient loss of consciousness, associated with the inability to maintain postural tone and accompanied by a fall to the ground, with rapid and spontaneous recovery. It is caused by a period of inadequate cerebral nutrient flow, most often the result of various factors causing an abrupt drop of systemic blood pressure. Typically, the inadequate cerebral blood flow is of relatively brief duration (at least 8 s) and, in syncope, is, by definition, spontaneously self-limited [1,2].

Presyncope is the prodromal phase of syncope, characterized by dizziness, lightheadedness, weakness, nausea, with transient alteration of consciousness, without complete loss, and without necessarily falling on the ground [2]. Syncope of cardiac origin, whether arrhythmic or mechanic obstructive, may be associated with an increased risk of sudden cardiac death if not treated in a timely and appropriate fashion [3,4]. The role of a two-step

electrophysiology study inclusive risk stratification approach for the effective management of the former is thoroughly discussed in this review.

## 2. Significance

The diagnostic approach of syncope implies a notable economic burden on society [5,6]. Healthcare expenditure is essential since syncope is an ordinary symptom with a variety of underlying causes leading to patient visits to physicians, the emergency department, and to hospitalizations after syncope [7]. Syncope was the fifth most common reason for an emergency department visit in the United Kingdom according to the Hospital Episode Statistics 2011–2012. The diagnostic tests undertaken to determine the cause of syncope are important drivers of the cost.

Updated guidelines and/or consensus documents display recommendations on which diagnostic tests are most relevant and likely to lead to a diagnosis while, at the same time, less effective measures can be replaced [2,8]. Guidelines are dynamic documents that are updated as new research produces evidence that justifies changes in recommendations. However, the dissemination and permeation of the meanings of guidelines and expert consensus documents are far from satisfactory, and clinical practice adjusts slowly [9].

The investigation and elucidation of the pathogenetic mechanism of syncope or presyncope are of great clinical importance, as both prognosis and appropriate therapeutic approach depend on these factors. The clarification and identification of cardiac-induced syncope or presyncope are essential because many arrhythmias as well as other cardiac disorders implicated in these episodes can be effectively treated. In addition, an episode of loss of consciousness may often be the first symptom of an underlying cardiac disorder [2].

The episodes of loss of consciousness (either partial or complete) of unknown etiology constitute a common clinical problem that may be encountered by physicians of different specialties or general practitioners. Such episodes are the reason for presentation in 3% of all patients visiting the outpatient department and the reason for hospitalization in 1–6% of those, who need to be hospitalized [10–12]. It has been estimated that 30% of the general population will experience such an episode during their lifetime [13]. Framingham's study reported that 6.2 per 1000 patients/year presented with first-episode syncope [13]. Among them, 30% will experience similar episodes in future, and, in approximately 10%, an underlying cardiac cause will be diagnosed [14]. Studies undertaken in Europe and Japan share similar results, showing that such cases account for the 1–3.5% of all cases presenting in the emergency department [15].

## 3. Epidemiology

The incidence of these episodes is higher in younger as well as in advanced aged populations. In a study of 268 patients, electrophysiology evaluation revealed positive findings in 38% in general and 50% in the subgroup of patients older than 70 years. Growing age correlated with increased diagnostic value of the electrophysiology examination [3,16].

Recurrent episodes of loss of consciousness occur in approximately 30% of patients with at least one episode in the past [2,4,13,14,17,18]. The majority of these cases are not life-threatening, as they usually do not have serious neurological or cardiological background. However, it is worth noting here that the occurrence of cardiac-induced syncope or presyncope is correlated with worse prognosis and 50% 5-year survival rate, unless appropriate treatment is applied [1,10]. In the majority of patients with sudden cardiac death, the main cause is ventricular tachycardia, often triggered by acute coronary syndromes in patients without until then known heart disease, or associated with structural heart disease [19]. In the emergency department of some centers, a special syncope assessment unit is available, improving the diagnostic approach and reducing the need for admission of these patients [20,21].

## 4. Consequences

The episodes of partial or complete loss of consciousness may often induce moderate or severe physical trauma in patients themselves, due to a fall to the ground, as well as trauma to other people and involvement in traffic accidents caused by patients experiencing an episode while driving. Furthermore, the quality of life of patients who experience such episodes, especially if they tend to occur frequently, is reduced, on the one hand, because of the fear of recurrence and, on the other hand, because of the anxiety. Hence, they limit their activities, their performance at work is impaired, and they are overwhelmed with anxiety or may even develop severe psychiatric syndromes, such as depression, neurosis and psychosis. Moreover, these people should not be employed or must leave their jobs if they are employed in specific occupations, such as aircraft pilots, car drivers, or workers with high-altitude tasks, such as building cleaners, builders, crane operators etc. [2,22].

## 5. Etiology

The pathological conditions that cause syncope or presyncope episodes are many and heterogeneous. The episodes can occur if there is a significant reduction in blood flow to the reticular formation of medulla oblongata of short duration (8 to 10 s). It has been estimated that cerebral oxygen ($O_2$) supply should be reduced below 3.5 mL per 100 gr tissue per minute [23,24]. Normal levels are estimated at 50–60 mL/100 g/min and are maintained throughout life by self-regulatory mechanisms of brain homeostasis, while their integrity depends on homeostatic mechanisms for the regulation of blood pressure and heart rate.

The causes are divided into cardiac and non-cardiac. The first are distinguished in turn into obstructive and arrhythmic. Non-cardiac causes include broader categories, such as neurally-mediated or reflex syncope, disorders of the autonomic nervous system (including pharmacogenic orthostatic hypotension), vascular or non-vascular diseases of the central nervous system, metabolic diseases and psychiatric disorders. The majority of patients with presyncope or syncope episodes without suffering from heart disease and with a normal electrocardiogram have more common neurological etiology versus psychiatric diseases (Table 1) [1,2,25].

**Table 1.** Etiological classification of unexplained syncope [2].

| Reflex (Neurally Mediated) Syncope | Orthostatic | Cardiovascular |
|---|---|---|
| **Vasovagal**<br>• Orthostatic VVS: standing, less common sitting<br>• Emotional: fear, pain, blood phobia | **Primary autonomic failure**<br>• Pure autonomic failure<br>• Multiple system atrophy<br>• Parkinson's disease | **Tachycardia**<br>• Supraventricular<br>• Ventricular |
| **Situational**<br>• Laughing, cough, sneeze<br>• Gastrointestinal stimulation (swallow, defecation)<br>• Urination<br>• Post-meals<br>• Post-exercise | **Secondary autonomic failure**<br>• Diabetes, amyloidosis, kidney failure<br>• Spinal cord injuries<br>• Auto-immune autonomic neuropathy<br>• Paraneoplastic autonomic neuropathy | **Bradycardia**<br>• Sinus node dysfunction<br>• Atrioventricular conduction system disease |
| **Carotid Sinus Syndrome (CSS)** | **Drug-induced**<br>• Vasodilators<br>• Diuretics<br>• Phenothiazine<br>• Antidepressants<br>• Alcohol | **Structural cardiac**<br>• Aortic stenosis<br>• Acute myocardial infarction<br>• Hypertrophic cardiomyopathy<br>• Myxoma<br>• Pericardial disease<br>• Congenital anomalies of coronary arteries<br>• Prosthetic valve dysfunction |
| **Non-classical forms**<br>• Without prodromes/without apparent triggers/atypical presentation | **Volume depletion**<br>• Haemorrhage<br>• Diarrhoea<br>• Vomiting | **Cardiopulmonary and great vessels**<br>• Pulmonary embolus, pulmonary hypertension<br>• Acute aortic dissection |

VVS: Vasovagal syncope.

## 6. Diagnostic Approach

The responsible mechanism of presyncope or syncope can only be revealed by history, baseline clinical examination and electrocardiogram [26,27]. The echocardiogram or the electroencephalogram offer additional confirmatory help. The percentage of patients who are diagnosed with these tests alone, exceeds 50%.

If the electrocardiogram is within normal limits, the chances of the cause of the presyncope or syncope being an arrhythmia are usually small [28]. If this initial diagnostic approach does not help to reveal the mechanism of episode, further diagnostic tests will have to be performed depending on whether organic heart disease or abnormal electrocardiographic findings coexist. Thus, in patients with a history of organic or acquired heart disease or/and the presence of abnormal findings on the 12-lead or/and 24-h Holter monitoring or/and signal averaged electrocardiogram, a further diagnostic electrophysiology inclusive approach should be followed to exclude life threatening arrhythmiological mechanisms [29,30].

However, if the patient does not suffer from underlying heart disease or does not show abnormal electrocardiographic findings in the 12-lead electrocardiogram or the 24-h Holter monitoring, then the probability in the electrophysiology study to find a responsible cause is small but not absent [31]. Among such elderly syncopal patients, occasionally HV interval prolongation or/and other atrioventricular node conduction disease criteria or/and carotid sinus syndrome are revealed leading to device therapy [3]. In these cases, the possibility of finding reflex etiology during the tilt table test is more likely, which should be the exam of choice for the examiner [22,32–36].

If the episodes are recurrent and remain unexplained with a negative tilt table test, then special diagnostic techniques of long-term electrocardiographic recording (implantable loop recorder) can be applied, which occasionally reveals the cause and mechanism of these episodes [37–41]. These patients should also be suspected of having a psychiatric condition [42–45], provided a thorough electrophysiology investigation has ruled out the presence of a life threatening and provocative arrhythmia substrate, which can be safely and adequately addressed even among such patients [46].

Although epilepsy is not considered syncope, as it is not associated with transient loss of consciousness, there are reported cases of epilepsy patients responding to antibradycardia pacing [47] while it is well known that some epilepsy patients die suddenly implicating arrhythmia mechanism of central origin [48]. It is uncommon to encounter syncopal patients exhibiting several syncope mechanisms, either benign or potentially malignant during a thorough diagnostic approach [41]. In such cases, the operating mechanism may be revealed by an implantable loop recorder, thus, leading the patient to the safest and most appropriate treatment plan [41].

It has been suggested to follow an implantable loop recorder policy in cases of suspected arrhythmic mechanism when the electrophysiology study is non diagnostic. However, recent evidence investigating the prognostic significance of a number of sinus node disease and atrioventricular node conduction disease defined electrophysiology criteria of positivity, which are thus far non-proposed in the guidelines, suggest the early implantation of rhythm management devices [49,50]. It would be interesting to compare such an electrophysiology-guided versus the implantable loop recorder policy in a randomized control trial in terms of cost effectiveness, ethics and safety in the near future [30,49,50].

Based on the diagnostic approach analyzed above, at the "Hippokration" General Hospital of Athens, we follow a two-step diagnostic approach [27,41,49,50]. In the first step, which is the non-invasive one, the goal is to increase the sensitivity of the simple 12-lead surface electrocardiogram in combination with signal-averaged electrocardiogram (SAECG) and the 24-h Holter monitoring. Findings from these two methods that guide the diagnostic tactics to investigate the possibility of serious presyncope or syncope arrhythmic causes are the following.

### *6.1. A. Standard 12-Lead Body Surface Electrocardiography (ECG)*

The 12-lead ECGs were analyzed and divided in the following categories according to the pathological findings:

1. Sinus bradycardia with a heart rate <60 bpm.
2. Presence of left anterior (LAFB) or left posterior fascicular block (LPFB) or complete right bundle brunch block (RBBB).
3. Presence of left bundle branch block (LBBB).
4. Presence of first degree atrioventricular block with PR interval >200 ms.
5. Presence of bifascicular block (RBBB with either LAFB or LPFB, first degree AV block with either LAFB or LPFB).
6. Presence of trifascicular block (RBBB and first degree atrioventricular block combined with either LAFB or LPFB).
7. Presence of LBBB with first degree atrioventricular block.
8. Presence of right ventricular repolarization abnormalities such as ST segment and T wave changes in right precordial leads V1-V2-V3, indicative of Brugada syndrome or arrhythmogenic right ventricular cardiomyopathy with epsilon wave (ARVC).
9. Presence of delta waves.
10. Presence of Q waves or poor R wave progression in the precordial leads, indicative of an old myocardial infarction.
11. Presence of late potentials (LPs) in the signal-averaged electrocardiogram (SAECG).
12. "Dagger-like" Q waves in inferior +/− lateral leads and deep inverted precordial T waves in apical hypertrophic cardiomyopathy.

### *6.2. B. 24-h ECG Holter Monitoring*

24-h Holter monitor recordings were analyzed and divided to the following categories according to the results:

1. Mean 24-h heart rate (day and night) <60 bpm, indicative of persistent sinus bradycardia pointing to sinus node disease as the arrhythmia cause of transient loss of consciousness [49].
2. Presence of episodes of supraventricular tachycardia with a heart rate >140 bpm [41].
3. Presence of frequent complex premature ventricular contractions ($\geq$30 bpm), isolated, in form of pairs and or in form of non-sustained ventricular tachycardia (NSVT) ($\geq$3 beats with heart rate $\geq$120 bpm) [51,52].
4. Presence of sinus pauses of $\geq$2 and $\leq$2.5 s.
5. Episodes of second degree atrioventricular block type I or type II, including 2:1 atrioventricular block [50].
6. Presence of non-conducted premature atrial conductions.

In patients who have a history of either known organic heart disease, or at least one of the above noninvasive ECG findings in the absence of such a known disease, we proceed to the second step of the diagnostic approach, which is the electrophysiology study (Figure 1) [27]. In this step, the application of extended electrophysiology criteria, which, although not included in the current guidelines for the selection of patients for implantation of an anti-bradycardia pacemaker, can contribute to the early detection and selection of these patients. During the study, the following parameters were tested in an attempt to increase the sensitivity of the method again as studies have shown in the past [3,53,54]:

### *6.3. C. Electrophysiology Study*

1. Snus node function.

(a) Corrected sinus node recovery time (CSNRT) $\geq$525 ms.
(b) Sinoatrial conduction time (SACT) $\geq$140 ms.
(c) Chronotropic response to atropine or isoproterenol $\leq$90 bpm.

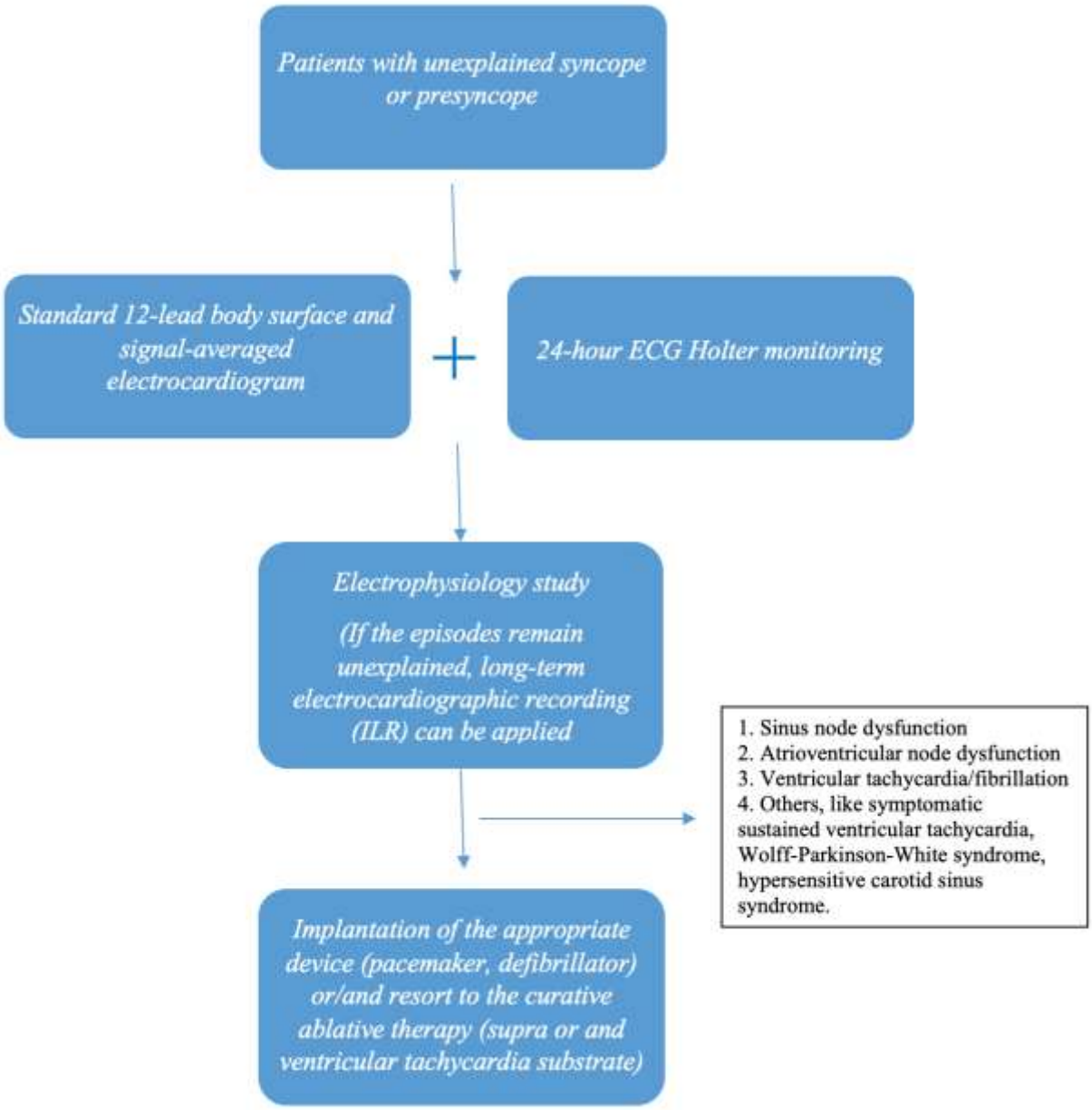


**Figure 1.** The steps of the diagnostic approach in patients with unexplained syncope.

2. Atrioventricular node and His bundle function.

(a) HV interval $\geq$ 60 ms.
(b) Weckenbach phenomenon and 2:1 atrioventricular block $\geq$500 and 400 ms, respectively.
(c) Atrioventricular node effective refractory period $\geq$450 ms.
(d) Presence of split His potentials.
(e) Induction of infranodal block in atrial pacing.
(f) Induction of bifascicular or trifascicular block in atrial pacing.

3. Programmed ventricular stimulation with extra stimuli: Induction of sustained ventricular tachyarrhythmia requiring either antitachycardia pacing or shock for its termination.

4. Programmed supraventricular stimulation with extra stimuli inducing symptomatic sustained supraventricular tachyarrhythmia.

5. In the presence of apparent preexcitation (delta wave) with an antegrade effective refractory period of the accessory connection fast enough ($\leq$250 ms), its elimination through radiofrequency catheter ablation at the same electrophysiology session should follow.

6. Carotid sinus massage: The test is characterized as abnormal if pauses ≥3 s occur [55].

The following conditions were considered as abnormal findings of the electrophysiological study:

1. Sinus node dysfunction.
2. Atrioventricular node dysfunction.
3. Ventricular tachycardia/fibrillation induction.
4. Others, such as symptomatic sustained ventricular tachycardia induction, Wolff–Parkinson–White syndrome (WPW), hypersensitive carotid sinus syndrome.

Sinus node dysfunction was defined as the presence of sinus bradycardia in standard 12-lead ECG or in 24-h Holter monitoring combined with the detection of at least one abnormal parameter associated with sinus node dysfunction in an electrophysiological study [49].

Atrioventricular node dysfunction was defined as the presence of at least one abnormal parameter in the atrioventricular node function assessment during electrophysiological study [50]. The presence of increased likelihood of developing ventricular tachycardia/fibrillation was defined as the reproduction of sustained ventricular tachycardia and/or fibrillation in electrophysiology study.

## 7. Future Perspectives

Implantation of a permanent pacemaker is a therapeutic intervention commonly employed when a bradycardic etiology is revealed in the clinical and laboratory workup of the patient with syncope, and there are different levels of recommendation according to particular pathophysiologic substrates—including atrioventricular block, sinus node dysfunction, vasovagal syncope etc. The official guideline recommendations for permanent pacing are based on observational studies [56–58] and not on randomized clinical studies, and the evidence of electrophysiology study (EPS) to assess atrioventricular node conduction disease or/and sinus node disease in patients with syncope depends only on the baseline H-V interval, second- or third-degree His-Purkinje block during incremental atrial pacing or with pharmacological challenge and prolongation of the corrected sinus node recovery time [2,59].

Other means of EPS-derived evidence of atrioventricular node conduction disease or/and sinus node disease, such as the point of effective refractory period of the atrioventricular node, split his activity or the appearance of bifascicular block on atrial stimulation, sinoatrial conduction time (SACT) and the chronotropic response to atropine [27], have not been included in the European and American guidelines for the management of unexplained syncope patient [2,59,60]. Furthermore, we still lack clear answers to seemingly simple questions including the appropriate use of EPS and the exact criteria for pacing based on the results.

## 8. Conclusions

Among patients with a history of unexplained syncope, a set of positivity criteria for the presence of electrophysiology study defined atrioventricular node disease or/and sinus node disease identifies a subset of patients who will benefit from permanent pacing. A randomized control study of a combined electrophysiology study inclusive guided approach is needed in order to better define the best strategy of treating such patients, namely with electrophysiology study guidance or an implantable loop recorder documentation policy or even a combination of these in a more systematic diagnostic approach [58].

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