

## Review Article

# Use of Implantable Loop Recorders to Unravel the Cause of Unexplained Syncope

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### Abstract

Syncope is a symptom of many underlying disease states, which range from the relatively benign to the life threatening. There are numerous investigations done for patients with recurrent unexplained syncope which may have very low yield when it comes to making a definitive diagnosis. Recently, the implantable loop recorder (ILR) for continuous monitoring of the cardiac rhythm has been launched in India. This review will briefly discuss these current available strategies and focus on the usefulness of an ILR in the definitive diagnosis and treatment of patients with a recurrent unexplained syncope.

**Key words:** Syncope, implantable loop recorder

### Introduction

Syncope is an abrupt and transient loss of consciousness (TLOC) associated with loss of postural tone that follows a sudden fall in cerebral perfusion. Syncope is a symptom of many underlying disease states, which range from the relatively benign to the life threatening [1]. At assessment, patients are often asymptomatic and the diagnosis is unclear, culminating in frequent hospitalization and resulting in expensive and often repeated investigations, most of which are inconclusive [2].

Syncope accounts for approximately 3% of emergency room visits and 1-6 % of hospital admissions. The prevalence of syncope increases with age from 0.7% in men aged 35-44 to 5.6% in men over the age of 75. In long- term care institutions, the annual incidence is approximately 6 % [3]. The elderly represent the population at greater risk for most causes of syncope.

Once it has been established that the patient has true syncope, it is useful to further classify into 4 categories: 1) reflex neurally mediated; 2) cardiac; 3) orthostatic hypotension; or 4) unexplained. The major causes of syncope are enumerated in **Table 1**.

**Table 1:** Different causes of syncope**Neurally-mediated (reflex)**

- i- Vasovagal syncope (common faint)
- ii- Carotid sinus syncope
- iii- Situational syncope
  - cough, sneeze
  - gastrointestinal stimulation (swallow, defecation, visceral pain)
  - micturition (post-micturition)
  - post-exercise
  - post-prandial
- iv- Glossopharyngeal neuralgia

**Orthostatic hypotension**

- i- Autonomic failure
  - primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)
  - secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy)
  - post-exercise
  - post-prandial
- ii- Drug (and alcohol)-induced orthostatic syncope
- iii- Volume depletion

**Cardiac Arrhythmias as primary cause**

- i- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- ii- Atrioventricular conduction system disease
- iii- Paroxysmal supraventricular and ventricular tachycardias
- iv- Inherited syndromes (e.g., long QT syndrome, Brugada syndrome)
- v- Implanted device (pacemaker, ICD) malfunction
- vi- Drug-induced proarrhythmias

**Structural cardiac or cardiopulmonary disease**

- i- Obstructive cardiac valvular disease
- ii- Acute myocardial infarction / ischemia
- iii- Obstructive cardiomyopathy
- iv- Atrial myxoma
- v- Acute aortic dissection
- vi- Pericardial disease/tamponade
- vii- Pulmonary embolus / pulmonary hypertension

**Cerebrovascular**

- } Vascular steal syndromes

Investigation of patients with recurrent unexplained syncope may include electrocardiography, ambulatory Holter monitoring, treadmill exercise testing, neurologic testing, tilt table testing and electrophysiological testing. Recently, a new device, an implantable loop recorder (ILR) has been developed for continuous monitoring of the cardiac rhythm to unravel the cause of unexplained syncope. This review will briefly discuss these current available strategies and focus on the usefulness of an ILR in the definitive diagnosis and treatment of patients with a recurrent unexplained syncope.

More commonly, a focused initial evaluation of syncope leads to a suspected diagnosis, which needs to be confirmed by directed testing. If a diagnosis is confirmed by specific testing, treatment may be initiated. On the other hand, if the diagnosis is not confirmed, then patients are considered to have unexplained syncope. The strategy of evaluation varies according to the severity and frequency of the episodes. The majority of patients with single or rare episodes probably have neurally mediated syncope and tests for confirmation are usually not necessary.

If it is not clear that it was syncope, the term 'transient loss of consciousness (TLOC) is preferable and reappraisal is warranted.

### Approach to assess unexplained syncope

History, physical examination, and electrocardiography are the core of the investigations of syncope with a combined diagnostic yield of 50%. Neurological testing is rarely helpful unless additional neurological signs or symptoms are present and the diagnostic yield for electroencephalography, computed tomography, and Doppler ultrasound is only 6% [4].

### Clinical history and physical examination

History should focus on postural symptom, palpitations, family history and should include the use of medication particularly in the elderly patients. Physical examination should focus on orthostatic blood pressure, cardiac murmurs and specific cardiac disorders e.g. aortic or mitral stenosis. The clinical features suggestive of a particular cause of syncope are enumerated in **Table 2**.

**Table 2:** Clinical features suggestive of specific causes of syncope

#### Neurally-mediated syncope:

- | Absence of cardiac disease
- | Long history of syncope
- | After unpleasant sight, sound, smell or pain
- | Prolonged standing or crowded, hot places
- | Nausea, vomiting associated with syncope
- | During or in the absorptive state after a meal
- | With head rotation, pressure on carotid sinus(as in tumours, shaving, tight collars)
- | After exertion

#### Syncope due to orthostatic hypotension:

- | After standing up
- | Temporal relationship with start of medication leading to hypotension or changes of dosage
- | Prolonged standing especially in crowded, hot places
- | Presence of autonomic neuropathy or Parkinsonism
- | After exertion

#### Cardiac syncope:

- | Presence of electrical or structural heart disease
- | During exertion, or supine
- | Preceded by palpitation or accompanied by chest pain
- | Family history of sudden death

#### Cerebrovascular syncope:

- | With arm exercise
- | Differences in blood pressure or pulse in the two arms

### Cardiac diagnostic approach

#### Electrocardiography

Electrocardiography is essential in the work-up of patients with unexplained syncope but may reveal a direct cause in only 5 % of patients. Pre-excitation patterns, a long QT- interval, the recently reported Brugada syndrome and characteristic features in patients with arrhythmogenic right ventricular dysplasia should all be considered [5 -7]. **Table 3**

#### Echocardiography

No studies have been specifically designed to assess the usefulness of echocardiography in

syncope. However, in patients known to have or suspected of having heart disease, patients suspected of having arrhythmias, echocardiography is an important initial step in diagnostic testing. Unsuspected findings on echocardiography are reported in only 5% to 10% of unselected patients [8]. This yield is similar to that of 12-lead electrocardiography. The cost-effectiveness of echocardiography in diagnosing the cause of syncope has yet to be determined. In patients with exertional syncope, echocardiography should be done first to exclude hypertrophic cardiomyopathy.

**Table 3:** ECG abnormalities suggesting an arrhythmic syncope

- | Bifascicular block (defined as either left bundle branch block or right bundle branch block combined with left anterior or left posterior fascicular block)
- | Other intraventricular conduction abnormalities (QRS duration >0.12 s)
- | Mobitz I second degree atrioventricular block
- | Asymptomatic sinus bradycardia (<50 bpm), sinoatrial block or sinus pause in the absence of negatively chronotropic medications
- | Pre-excited QRS complexes
- | Prolonged QT interval
- | Right bundle branch block pattern with ST-elevation in leads V1–V3 (Brugada syndrome)
- | Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia
- | Q waves suggesting myocardial infarction

#### *Exercise Testing*

Exercise stress testing can be used for the evaluation of exertional syncope to diagnose ischemia or exercise-induced tachyarrhythmia's or to reproduce post exertional syncope. In one population study of patients with syncope, the yield of the exercise stress test was less than 1% [9]. Data is scarce to determine the yield for ischemia or exercise-induced tachyarrhythmia's or to define the test's usefulness in diagnosing exercise-associated syncope. Exercise stress testing is recommended if patients have exercise-associated syncope and if the results of clinical evaluation suggest ischemic heart disease.

#### *Tilt table testing*

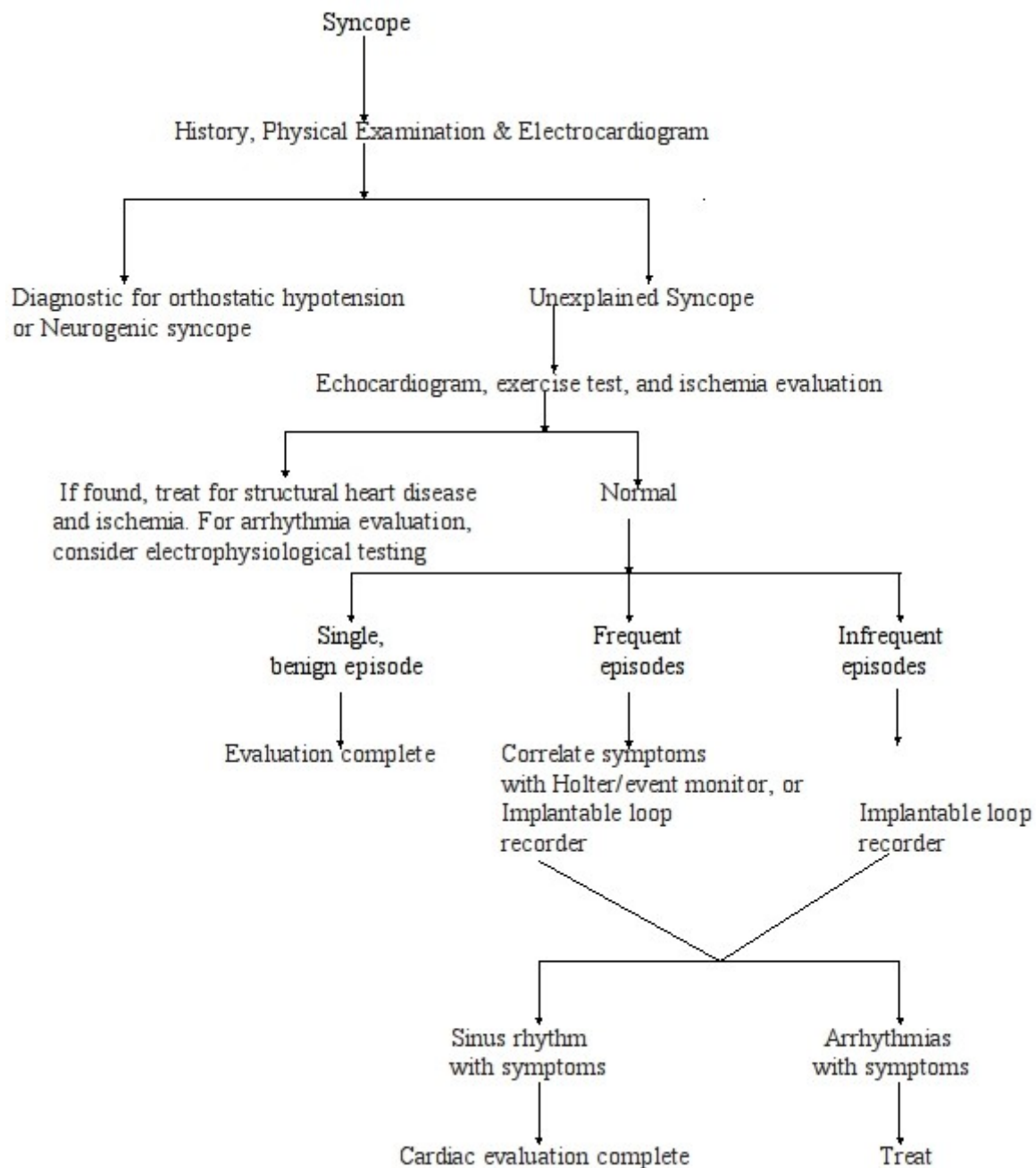
Tilt table testing has emerged as a safe and effective method of identifying individuals with a susceptibility to neurally mediated syncope [10]. Tilt table testing may be performed alone or with pharmacological provocation using isoprenaline or nitrate preparations. The tilt table test is best considered for patients with suspected neurally mediated syncope but in whom the cause is not obvious or in patients with syncope of otherwise unknown origin with no evidence of heart disease. The major problem with tilt table testing is quantifying the test's sensitivity. The sensitivity of the test has been calculated at between 20% and 75% [11]. In those known to have structural heart disease in which electrophysiological studies have not given a diagnostic clue, tilt table testing may prove cost-effective by avoiding expensive and unrewarding neurological investigations such as computed tomography or electroencephalography which might otherwise be requested. Interestingly, the frequency of syncope decreases following a positive test regardless of therapeutic intervention. The test may educate the patient to recognize the warning signs of syncope and to make appropriate changes in posture. [12, 13]

#### *Holter monitoring*

A 24-hour Holter monitor or inpatient telemetry is recommended when symptoms suggest arrhythmic syncope with brief loss of consciousness, no prodrome, palpitations with syncope and in patients who have syncope of unexplained cause, heart disease, or an abnormal electrocardiogram.

**Neurological diagnostic approach**

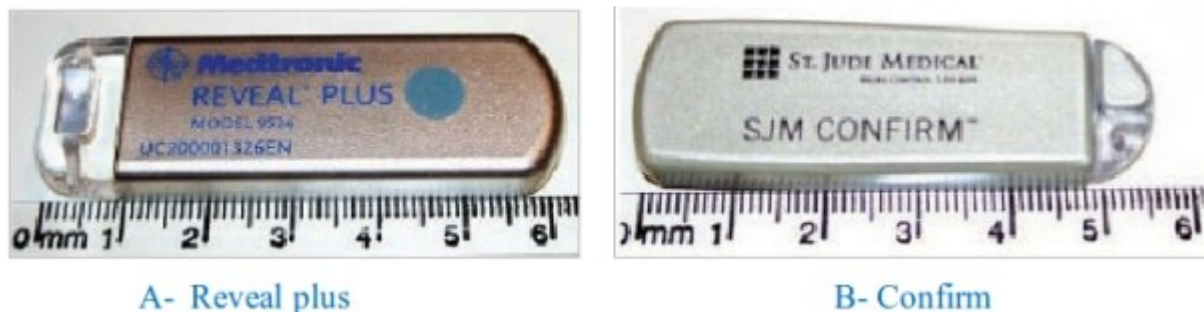
Neurologic tests used for patients with syncope include electroencephalography, brain imaging (computed tomography or magnetic resonance imaging), and neurovascular studies (carotid and transcranial doppler ultrasonographic studies). To determine which patients may benefit from neurologic testing, physicians should take a particularly careful neurologic history for example, patients should be asked about a history of seizure activity, prolonged loss of consciousness, diplopia, headache, and post ictal symptoms and perform a thorough, focused physical examination including a search for bruits or focal neurologic signs. A diagnostic algorithm and approach to a patient with syncope is suggested in **Figure 1**.



**Figure 1.** Flow chart for the diagnostic approach to the patient with syncope using an implantable loop recorder

**New method of monitoring to diagnose syncope: "Implantable loop recorder" (ILR)**

In spite of a detailed screening of patients and often multidisciplinary investigation, more than one third of the patients may remain undiagnosed [14]. Recently, an implantable loop recorder (ILR) has been developed for continuous monitoring of the cardiac rhythm to unravel the cause of unexplained syncope. The ILR is an implantable device that has a solid state loop memory capable of storing electrocardiographic events up to 40 minutes before and 1 to 2 minutes after activation. The ILR has built in electrodes on the back of the device to detect patients' cardiac rhythm and does not require any intra cardiac leads. This device is very small and is typically implanted subcutaneously in the left pectoral region as an out-patient procedure [15]. Currently, there are 2 FDA-approved ILRs available for clinical use as shown in **Figure 2**. The REVEAL PLUS device (MEDTRONIC, Minneapolis, USA) was the first approved device, it is about  $62 \times 19 \times 8$  mm in size and the battery of the device generally lasts 18 months. The CONFIRM device (ST JUDE, St Paul, USA), it is about  $56.3 \times 18.5 \times 8$  mm in size and its battery is expected to last up to 3 years. Data are retrieved and analyzed with a compatible programmer but this device also has a remote real-time monitoring capability that allows patients to send data directly to their health care providers.[16]



**Figure 2:** Two type of ILR, the REVEAL PLUS device (MEDTRONIC, Minneapolis, USA) is about  $62 \times 19 \times 8$  mm in size and the CONFIRM device (ST JUDE, St Paul, USA) , it is about  $56.3 \times 18.5 \times 8$  mm in size

**Method of Implantation**

After identification of the most appropriate pectoral position to record an electrocardiographic lead with a prominent QRS wave, the loop recorder is subcutaneously implanted snugly in a pocket similar to that of a pacemaker implantation, the size of a little finger. After suture of the skin, the quality of electrocardiographic recording is tested in supine and standing positions and during movements of both the arms. The device is explanted after a diagnosis is obtained or if syncope did not recur. The first experiences with the ILR have shown that the device was safe and was able to detect cardiac arrhythmias in about 23-42% of patients. The population in these studies was, however, not systematically evaluated prior to the ILR implantation to reach a diagnosis. [17]

**Clinical evaluation of the ILR**

In an initial study of 24 patients, 52% presented with an arrhythmic cause with the vast majority of patients having bradycardia. Treatment was directed at the underlying cause in the 18 patients who received a specific diagnosis. During follow up, syncope did not occur in 16 of the 18 treated patients. In 2 patients who underwent explantation of the device after the end of battery life, no recurrence was seen with a final analysis extending the follow-up to  $40 \pm 10$  months[18]. A larger series of 85 patients with recurrent undiagnosed syncope despite extensive evaluation had patients who were eligible if they had at least two syncopal episodes within the previous 2 months or if they had a single syncope with a history of presyncope. In all patients ILR was implanted which resulted in detection of abnormal rhythms in 21 patients, the vast majority having a bradycardia. Interestingly, in 29 patients no arrhythmia was detected

despite symptoms. Patients with syncope were more likely to record an arrhythmia during symptoms compared to patients with a history of presyncope (70 % vs 24 %  $p = 0.005$ )[19]. Recently another large and prospective study was carried out to collect information on the use of the REVEAL (MEDTRONIC, Minneapolis, USA) ILR in the patient care pathway and to investigate its effectiveness in the diagnosis of unexplained recurrent syncope in everyday clinical practice. Eligible patients had recurrent unexplained syncope or pre-syncope. Follow up was until the first recurrence of a syncopal event leading to a diagnosis or till the end of 1 year. In the course of the study, patients were evaluated by an average of three different specialists for management of their syncope and underwent a median of 13 tests. Average follow-up time after ILR implant was  $10 \pm 6$  months. The percentages of patients with recurrence of syncope were 19%, 26% and 36% after 3, 6 and 12 months respectively. Of 218 events within the study, ILR-guided diagnosis was obtained in 170 cases (78%), of which 128 (75%) were of cardiac origin.[20] The findings support the recommendation in current guidelines that an ILR should be implanted early rather than late in the evaluation of unexplained syncope.

Recently we conducted a similar work and enrolled 20 patients of unexplained syncope, out of which 11 patients completed a 12 month, follow up. The diagnostic yield was 100% in the 11 patients among which 7 patients got permanent pacemaker implantation and 4 patients having no arrhythmic event noted with symptoms and 9 patients continue in follow up. [21]

### Therapy Guided by ILR

Little is known about the outcome after ILR-guided specific therapy. In the East Bourne Syncope Assessment Study [22], performed in a typical unselected population, there was an increased diagnostic rate in the group of patients randomized to ILR management and ECG-directed treatments than in conventional investigation group. Despite that a specific ILR directed therapy could be applied to only a minority of patients, the long-term follow-up demonstrated a significant reduction in syncopal events with improved quality of life with ILR based treatment. Since prolonged asystole was the most frequent finding at the time of syncope, pacing was the specific therapy mostly used in the ILR population. In a pooled data of 720 ILR patients from 4 studies, a pacemaker was implanted in 17% of patients, with 45% of those having an ILR-documented event. In the ISSUE 2 study, the 1-year burden of syncope decreased from  $0.83 \pm 1.57$  episodes per patient per year in the control group of patients without any ILR-guided specific therapy to  $0.05 \pm 0.15$  episodes per patient per year in the patients treated with a ILR-guided specific therapy of pacemaker (87% relative risk reduction;  $P = .001$ ). [23] In another study, after the insertion of a cardiac pacemaker, syncope burden decreased from 2.17 per year to 0.45 per year in 1A or 1B group syncope patients ( $P = .02$ ) and from 4.57 per year to 0 per year in the type 1C syncope patients ( $P = .001$ ). Nevertheless, syncope still recurred in 12% (range, 3%–18%) of the patients during the long-term follow up (2.0–3.6 years), especially in those patients more likely to be affected by neurally mediated syncope, accounting for the coexistence of some vasodepressor reflex that cannot be overcome by pacing. Implantable cardioverter-defibrillator and radiofrequency catheter ablation were also consistently used in a few selected patients with ILR documented ventricular and atrial tachyarrhythmia's in 1.5% and 3.0% of the patients, respectively [23].

### Limitation of the device

Limitations of the device include the inability to monitor blood pressure changes, the necessity for surgical implant, cost of the device and a small risk of infection. Most patients in whom an arrhythmia is not documented during syncope have either hypotensive syndromes or psychogenic syncope. Hypotensive syndromes include vasovagal syncope, orthostatic hypotension, postprandial hypotension, and vasodepressor carotid sinus hypersensitivity. A facility to track blood pressure behavior in addition to heart rate during symptoms would undoubtedly advance real-time hemodynamic monitoring with implantable

devices. The inability of the present device to detect hypotension is a limitation and in the near future the devices capable of recording other physiological parameters may further increase the diagnostic yield [24]. With increasing healthcare costs, a proper selection of patients for implantation of an ILR is mandatory. Total costs of the investigation of patients with recurrent syncope are high because of extensive diagnostic testing [25]. However in a cost analysis study it was demonstrated that ILR implantation could reduce costs as was seen in a pilot study of 24 patients referred for recurrent syncope [26]. There may also be a small risk of interference from electronic article surveillance devices and found that interference may occur causing malfunction of this device [27].

## Conclusion

The prognosis of syncope ranges from benign to life threatening situations and risk stratification should be based on the result of history, physical examination, electrocardiography, and selected noninvasive test. ILR is a novel and useful diagnostic tool in patients with unexplained syncope. ILR is easy to implant and explant and is based on electrocardiography which is useful to establish if there is an arrhythmic cause of syncope, especially when symptoms are recurrent but too infrequent for conventional monitoring techniques.

**Table 4.** Summary of Recommendations

<p><b><u>Implantable loop recorders (ILRs) can be used:</u></b></p> <p>1) Patients with recurrent syncope of uncertain origin after the initial evaluation who have the following:</p> <ul style="list-style-type: none"> <li>• Clinical or electrocardiographic features suggesting an arrhythmic syncope</li> <li>• High probability of recurrence (ie, <math>\geq 3</math> episodes of syncope during the last 2 years)</li> <li>• Absence of high-risk criteria that require immediate hospitalization and intensive evaluation</li> </ul> <p>2) To assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain neurally mediated syncope presenting with frequent or traumatic syncopal episodes.</p> <p>3) Patients in whom the cause of syncope remains unexplained despite full evaluation and who have clinical or electrocardiographic features suggesting an arrhythmic syncope.</p> <p><b><u>Diagnosis:</u></b></p> <p>ILR findings are diagnostic when either of the following is true:</p> <p>1) A correlation between presyncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected.</p> <p>2) In the absence of such correlation, ventricular pauses <math>&gt;3</math> sec when awake or periods of periods of Mobitz II or III atrio-ventricular block when awake, or rapid paroxysmal ventricular tachycardia are detected.</p> <p>3) ILR findings exclude an arrhythmic cause when there is a correlation between syncope and no rhythm variation. Presyncope may not be an accurate surrogate for syncope in such circumstance, and therefore monitoring should be continued until syncope is documented.</p>
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