

The Implantable Loop Recorder—An Important Addition to the Armentarium in the Management of Unexplained Syncope

Nesan Shanmugam,¹ BSc, MBBS, MRCP, Reginald Liew,^{1,2} MA, MRCP, PhD

Abstract

Introduction: Unexplained syncope is a common condition with a significant impact both on the patient and on healthcare expenditure. Often, the diagnosis is hampered due to the temporary sporadic nature of the symptoms. Conventional monitoring methods have a low yield for identifying an abnormality during a spontaneous event. The implantable loop recorder (ILR), often underutilised, is an important diagnostic device that may fill this void in the early assessment of patients presenting with syncope. **Materials and Methods:** This article begins with 2 case vignettes which highlight the clinical utility of ILRs in making a definitive diagnosis and guiding subsequent management. This is followed by a review of the existing evidence for ILRs, including the recent international guidelines, underpinning the role of ILRs in the present management algorithm of patients presenting with unexplained syncope. The technical aspects and cost implications will also be reviewed. **Results:** Present evidence-based international guidelines have recommended the early use of ILRs in the management of patients with unexplained syncope. Furthermore, there may also be an important role for ILR use in patients with presumed epilepsy refractory to treatment and in the neurally mediated syncope cohort with recurrent symptoms. Cost benefit analysis also demonstrates advantages with early ILR use. **Conclusion:** The early use of ILR in selected patients remains an accurate, cost-effective, high yield tool for diagnosis and management of patients with unexplained syncope. However, its use should not detract from the importance of taking a detailed medical history and physical examination in the initial assessment to facilitate identification of the aetiology and risk stratification of patients.

Ann Acad Med Singapore 2012;41:115-24

Key words: Electrophysiological study, Epilepsy, External loop recorder, Holter, Tilt testing

Introduction

Syncope is a clinical syndrome characterised by transient loss of consciousness and postural tone that is most often due to temporary and self terminating global cerebral hypoperfusion. It is a commonly encountered condition with up to 40% of selected populations having experienced an episode of syncope in their lifetime,¹ moreover 6% of all acute medical admissions can be attributed to a recurrent syncopal event.² Although a benign prognosis in the majority, syncope secondary to a cardiac cause can carry 18% to 33% of 1-year mortality.³

Establishing a diagnosis is often hampered due to the temporary sporadic nature of the symptoms, and as a consequence, syncope still remains undiagnosed in up to

30% of patients.⁴ Ideally, a diagnosis should be based upon documentation of an abnormality during a spontaneous event, although this is only rarely possible. Conventional detection methods such as 24-hour Holter monitoring, in-hospital monitoring, event recorders and external loop recorders are often ineffective at detecting the paroxysmal syncopal events due to their sporadic and infrequent occurrences. This often leaves patients with debilitating recurrent episodes which not only has a detrimental effect on the physical and emotional well-being of patients and their families⁵ but also a significant burden on healthcare expenditure.⁶

The logical target would be for a more prolonged cardiac

¹National Heart Centre Singapore

²Duke-NUS Graduate Medical School, Singapore

Address for Correspondence: Dr Reginald Liew, National Heart Centre Singapore, Mistri Wing, 17 Third Hospital Avenue, Singapore 168752.

Email: reginald.liew.k.c@nhcs.com.sg



Fig. 1. Implantable loop recorder trace from Case 1 showing a 5.6 seconds asystolic episode. Chart speed: 25mm/sec.

rhythm monitoring, which would not only assess the mechanism of syncope at the time of the event, but also provide valuable prognostic information which would guide appropriate therapy. The implantable loop recorder (ILR) was introduced for syncope assessment almost a decade ago and is widely acknowledged as an important diagnostic device that may fill this void in the early assessment of patients presenting with syncope.⁷ As a consequence, its utilisation has been predicted to significantly rise with estimates expected to increase to 135 ILRs per million population.⁸ However, despite its proposed advantages, it is an often underutilised tool in the management of patients with syncope.⁹

This article reviews the existing evidence underpinning the role of ILRs in the present management algorithm of patients presenting with unexplained syncope and highlights the diagnostic capabilities of ILRs through 2 interesting cases. The technical aspects and cost impact will also be discussed.

Case Vignettes

We present 2 interesting cases which highlight the valuable diagnostic capabilities of ILR in the setting of unexplained recurrent syncope.

Case 1

A 76-year-old hypertensive woman with a history of paroxysmal atrial fibrillation on warfarin and atenolol was admitted for evaluation for a 4-year history of recurrent syncope, often preceded by short lived palpitations and on occasions associated with head injury. The 12 lead electrocardiogram (ECG) confirmed sinus bradycardia at a rate 55 bpm and the transthoracic echocardiogram (TTE) was normal. Although the history and ECG findings were suggestive of a cardiac cause, the intermittent nature of her symptoms meant that standard investigations, with two 24 hour Holter monitors, a 2-week external loop recorder and a tilt test, failed to elucidate any significant arrhythmogenic

cause. Interestingly a subsequent electrophysiological study (EPS) was inconclusive with evidence to suggest normal sino-atrial conduction.

An ILR was subsequently inserted in order to increase the chances of making a definitive diagnosis. Following a symptomatic episode a month later, the device was interrogated (Fig. 1). Frequent episodes of asystole, the longest lasting up to 9.3 seconds, was detected with and without associated symptoms. A dual chamber pacemaker was implanted with reversal of her debilitating symptoms, thereby allowing appropriate treatment with warfarin and rate therapy for her paroxysmal atrial fibrillation.

Case 2

A 44-year-old hypertensive lady was referred by our Neurology colleagues, having been diagnosed with presumed epilepsy since 2006. However, despite optimal anti-convulsant therapy she was still experiencing periods of transient loss of consciousness. Accordingly, she had evidence of a normal 12 lead ECG and TTE. Previously, over a 4-year period, the lady had undergone 2 tilt tests, four 24-hour Holters and 2 external loop recorders to no avail. In view of the patient's strong family history for coronary heart disease, exercise treadmill testing was performed. This showed a short run of non-sustained ventricular tachycardia. Subsequent coronary angiography revealed a significant mid left anterior descending artery lesion which was duly stented. However, following successful revascularisation the patient continued to experience syncopal episodes, despite the subsequent demonstration of a normal myocardial perfusion scan (2-methoxy isobutyl isonitrile (MIBI) scan).

Implantation of an ILR was therefore recommended. The patient initially refused but finally agreed 10 months later after further syncopal events. Six weeks following implantation, interrogation of the ILR revealed multiple episodes of significant nocturnal asystole, the longest lasting 72 seconds (Fig. 2A) and frequent premature ventricular complexes, with further disturbing evidence of a short run of non-sustained ventricular fibrillation at

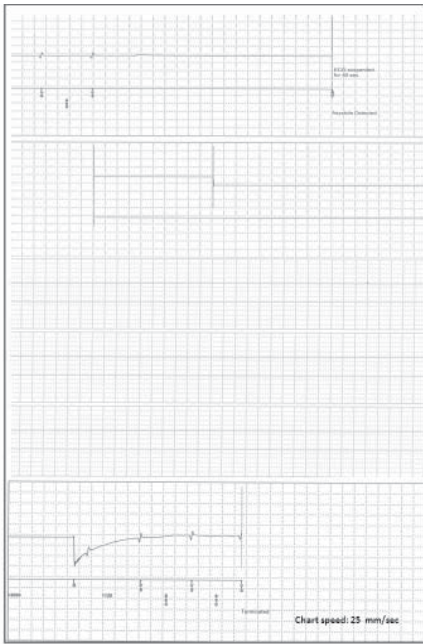


Fig. 2A

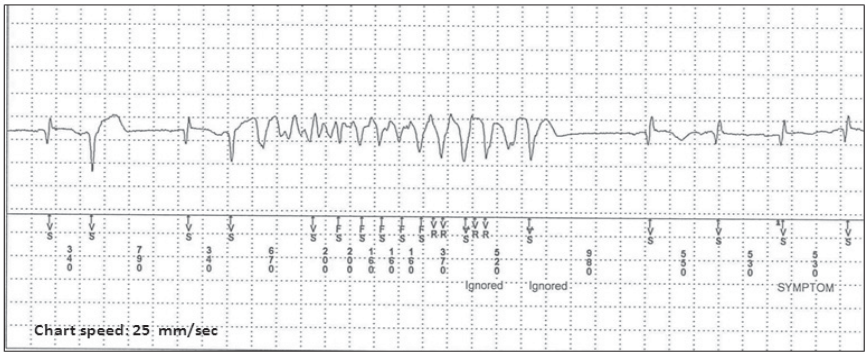


Fig. 2B

Fig. 2. Implantable loop recorder traces from Case 2. (A) Shows 2 sinus beats (top left corner) that are followed by a prolonged period of asystole lasting 72 seconds, followed by the return of 4 sinus beats (bottom left caption). This occurred at 6 am in the morning, whilst the patient was asleep and so was not noted by the patient. (B) ILR trace from the same patient showing a short run of non-sustained ventricular fibrillation. Chart speed: 25mm/sec

8.30 am (Fig. 2B). The patient was aware of palpitations and dizziness during this period. An urgent implantable cardiac defibrillator (ICD) was inserted with resolution of her syncope. Interestingly, 2 months later the patient was admitted with multiple appropriate ICD shocks for ventricular tachycardia, suggesting that the tachyarrhythmia may have been an important contributing cause for her recurrent syncope. Eighteen months post-ICD insertion and optimisation of her antiarrhythmic therapy, the patient has been syncope free and, more importantly, is now off anticonvulsant therapy.

Initial Standard Evaluation in Patients with Suspected Syncope

With regard to the initial assessment of a patient presenting with transient loss of consciousness, it is important to distinguish syncope with other forms of non-syncope causes, which are generally characterised by a lack of global cerebral hypoperfusion. These include epilepsy, hypoglycaemia, hypoxia, hyperventilation, vertebrobasilar transient ischaemic attack and intoxication.

Once syncope has been elucidated, the diagnostic approach should be focused on identifying the aetiology (Table 1) and also risk stratification of the patient as a consequence of the potential cause (Fig. 3). With regard to risk, there are 2 elements that need to be assessed—risk of death- and life-threatening events and secondly, the risk of recurrence and subsequent physical injury. Central to this initial evaluation is obtaining a thorough detailed medical history of the symptomatic event, including the

Table 1. Causes of Syncope

Reflex (neurally mediated)	Orthostatic hypotension	Cardiac syncope
Vasovagal	1° Autonomic Failure Pure Autonomic Failure Multiple system atrophy Parkinson’s Disease Lewy Body Dementia	Bradyarrhythmia sinus node dysfunction AV conduction disease Drug induced
Situational Cough, sneeze GI - swallow, defaecation Micturition Post exercise Post prandial Others- weight lifting, laughter	2° Autonomic Failure Diabetes Amyloidosis Renal failure Spinal cord injuries	Tachyarrhythmia SVT Ventricular- Idiopathic SHD related Channelopathies Drug induced
Carotid Sinus Syncope	Drug Induced Vasodilators Diuretics Antidepressants Alcohol phenothiazines	Structural Heart Disease Valvular Ischaemic Hypertrophic cardiomyopathy Cardiac masses-myxoma tumours Pericardial- effusion/ tamponade Congenital coronary anomalies
Atypical Without obvious triggers/ atypical presentation	Volume depletion	Others Pulmonary embolus Acute aortic dissection Pulmonary hypertension

GI: gastrointestinal; AV: atrioventricular; SVT: supraventricular tachycardia; SHD: structural heart disease

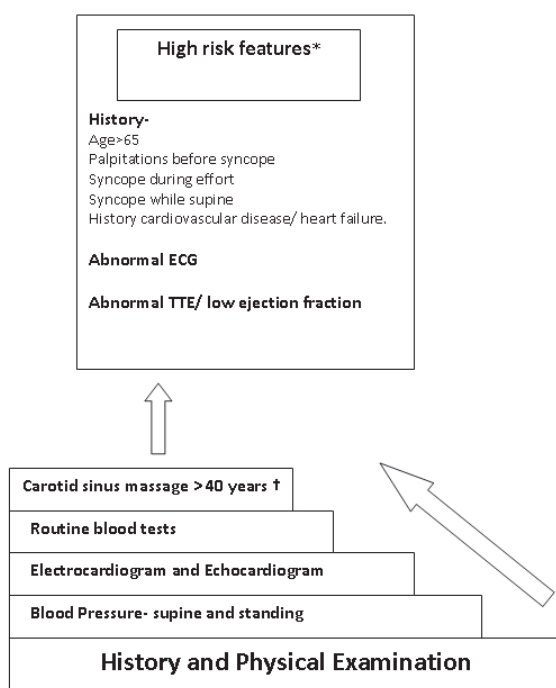


Fig. 3. Stepwise approach to the initial diagnostic evaluation and risk stratification of patients presenting with syncope.

ECG: electrocardiogram; TTE: transthoracic echocardiogram

*High-risk features¹⁰⁻¹²

†Carotid sinus massage should only be performed by experienced physicians and if no audible murmurs are heard over the carotid arteries. Adequate haemodynamic monitoring facilities should be available.

interviewing of a witness of the event and a subsequent physical examination. This initial important evaluation is thought to correctly identify the aetiology or preselect patients for appropriate investigations in the majority.¹³

If the diagnosis is unclear or a cardiac reason is suspected, then it is critical that the subsequent management algorithm is focused on excluding a treatable cardiac cause. An ECG and a TTE analysis should be undertaken to ascertain whether there is evidence of underlying structural heart disease (SHD). The presence of SHD increases the likelihood of documentation of an arrhythmia which will guide further management. Furthermore, if the left ventricular (LV) ejection fraction (EF) is less than 35% on TTE, the likelihood that potentially life-threatening ventricular arrhythmias were responsible for the syncopal episode increases. Consequently, work up for an implantable cardiac defibrillator (ICD) should be considered even without definite documentation of ventricular arrhythmias, based on current guidelines.¹⁴

In current practice, ECG monitoring is indicated when there is suspicion based on clinical, ECG or TTE evidence of SHD or in patients with uncertain diagnosis. In patients over 40 years of age with a history of recurrent syncope

without evidence of SHD or ECG abnormalities, asystole can still be present in up to 50% of patients.¹⁵ Standard ECG monitoring is usually undertaken with conventional 24 to 48 hours or 7-day Holter recorders or external loop recorders. The external loop recorder is connected to the patient via cutaneous patch electrodes and has loop memory capabilities that continuously records and deletes ECG data. If activated by the patient after a symptom, 5 to 15 minutes of pre-activation ECG is stored and can be retrieved. However, the low probability of recording a spontaneous event and its correlation with a cardiac arrhythmia leads to a poor diagnostic yield for present conventional ECG monitoring in syncopal patients with the true yield for Holter in syncope estimated to be as low as 1% to 2% in an unselected population.¹⁶ In addition, there is contradicting data for external loop recorders, with 1 study reporting a 25% detection rate after 1-month monitoring¹⁷ and another showing no significant benefit.¹⁸ Moreover, patients often do not comply for more than a few weeks if an external loop recorder is used. As a consequence, to increase the pre-test probability, these conventional monitoring strategies should be reserved for patients whom symptoms are more frequent.

Invasive EPS is often employed for patients with high likelihood for development of a cardiac arrhythmia and demonstratable high prognostic risk features for a cardiac aetiology, but whom non-invasive ECG testing have not been fruitful. The diagnostic efficacy of EPS will depend on the pretest probability, which is particularly high in syncopal patients with asymptomatic sinus bradycardia (<50 bpm) or sinoatrial block, bundle branch block (BBB) or suspected tachycardia including patients with syncope preceded by acute non-sustained palpitations.¹⁶ However, caution should be noted with an EPS, since it is an invasive procedure and carries no guarantees that an induced arrhythmia will replicate the specific cause of the spontaneous syncope.

Tilt testing is often utilised to confirm a diagnosis where neurally mediated syncope is suspected but not confirmed by medical history or in patients whom the diagnosis is unclear, recurrent or associated with physical injury or with occupation implications. In addition, tilt testing may have a role in patients with known organic heart disease after a cardiac cause has been excluded. Despite these recommendations, the specificity and sensitivity of tilt testing have been brought into question. Those undergoing upright tilt testing with isoproterenol, a positive response is observed in up to 65% of those without a history of syncope.¹⁹ Due to this low specificity (increased false positives), it is difficult to interpret and guide clinical decision-making based on the results obtained from tilt testing. Furthermore, neurally mediated syncope cannot be excluded by a negative tilt test, with the false negative rate as high as 29% in certain populations.^{15,20}

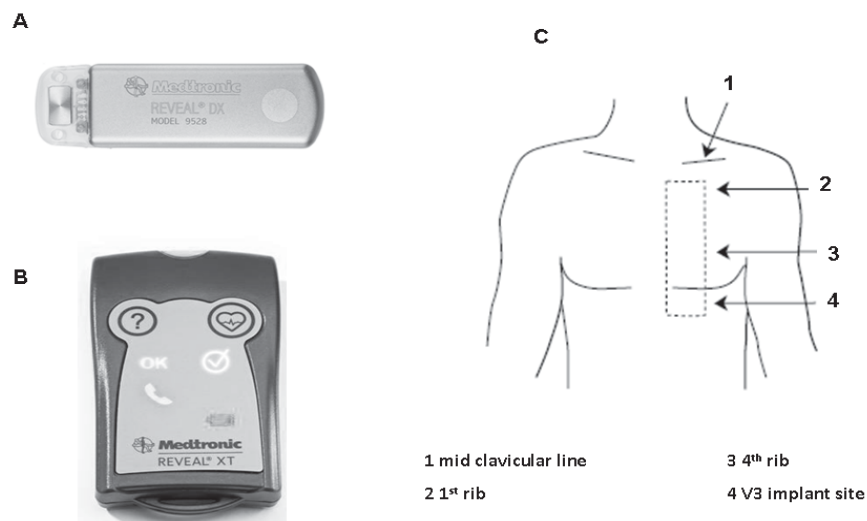


Fig. 4. A Medtronic REVEAL DX implantable loop recorder. (A) An implantable loop recorder. (B) Patient manual activator. (C) The vector check and recommended implant zone. (Images reproduced with permission from Medtronic Inc.)

Implantable Loop Recorders (ILRs)

The ILR is a small device, roughly the size of a memory stick, which is implanted subcutaneously in the patient's anterior chest wall. (Fig. 4A). It weighs approximately 17 grams and can continuously record a patient's single-channel ECG onto a memory loop for about 49.5 minutes. Detection can be automatically or manually activated and the battery lifespan is up to 3 years. If activated by the patient following an episode, the preceding 6 minutes and 1.5 minutes after activation for the last 3 events of ECG recordings are preserved for later assessment to search for correlates between the syncopal event and arrhythmia. Automatic activation is normally programmed for a ventricular pause of more than 3 seconds, a ventricular rate of less than 40 bpm or ventricular rate above 165 bpm for more than 16 beats. Data retrieval is performed with a programmer header (Fig. 4B). Prior to implantation, a vector check, in relation to the axis of the heart, is performed to determine the optimal implant site and device position, and to confirm reliable sensing (Fig. 4C). Implantation of the ILR is subcutaneous and normally in the left pectoral region following an incision of 2 cm incision under local anesthetic and formation of a 6 cm pocket. As the procedure does not require lead placement, no vascular access is required, making the process much simpler, safer and faster compared with insertion of a permanent pacemaker.

Recent Guidelines for the Diagnosis and Management of Syncope—with Specific Mention of the Role of ILRs

In 2009, international guidelines were eagerly reported at the European Society of Cardiology (ESC) in relation to the specific role of ILRs in the management of syncope in collaboration with the European (EHRA) and United States Heart Rhythm Associations and Heart Failure Association¹⁶ with subsequent clarification by an EHRA task force.⁸ The evidence-based guidelines cite Class 1 (Level of evidence B) indication for ILRs in assessing syncope:

- With particular mention of the early implementation of ILRs in the early phase of evaluating patients with recurrent syncope of uncertain origin who lack high risk criteria but have a high likelihood of recurrent episodes during the battery life of the ILR (up to 3 years);
- in high-risk patients whose initial evaluation including electrophysiological evaluation did not identify a cause of syncope (refer to Case 1) and
- a class 2A (Level of evidence B) or more equivocal indication of ILR use to assess the role of bradycardia in patients with known or suspected reflex syncope prior to considering cardiac pacing.

Interestingly, there was also specific mention of the potential valuable role of ILRs in 2 difficult diagnostic cohorts: patients in whom epilepsy was suspected but the treatment had proven ineffective (refer to Case 2) and in

elderly patients presenting with unexplained falls.

If an early approach is adopted, then careful prescreening is required during the initial evaluation, particularly regarding appropriate risk stratification of patients with potential life-threatening conditions that would require immediate evaluation and treatment, i.e. those with a clear indication for ICD, pacemaker or other treatments independent of a definitive diagnosis of syncope.

The ILR Evidence

So what is the evidence that underpins these recent guidelines? The best way to approach this question is to review the literature within the specific patient cohorts investigated which include the recurrent unexplained group, the neural mediated group, in patient groups whom a diagnosis of syncope is not established but suspected and finally, the evidence underlying the early use of ILRs.

Recurrent Unexplained Syncope Group

In 1995, a novel approach to the monitoring and diagnosis of unexplained syncope was reported in 16 patients using an implantable subcutaneous monitoring device capable of storing electrograms after patient activation for up to 2 years.²¹ Using this technique, a mechanism for syncope was established in 94% of patients, with a bradyarrhythmia being the commonest cause. Successful therapy was implemented in all the patients without recurrence of syncope during the 13 ± 8.4 months follow-up. A subsequent multicentre study confirmed a high symptom-rhythm correlation, however concerns regarding postoperative wound infections (4%) and technical issues related to 16% of patients being unable to activate the device, led to cautious optimism.²²

In the first prospective randomised study in this field, Krahn et al²³ compared standard assessment with prolonged monitoring strategy with an ILR. In 60 patients presenting with recurrent unexplained syncope or a single event associated with injury who warranted cardiovascular work-up. Interestingly, initial evaluation yielded no positive results in all 60 patients. Subsequently, 30 patients were randomised to receive an ILR, whilst the remainder went down the route of standard investigations. Those in the standard arm underwent a 2- to 4-week period of monitoring with an external loop recorder, followed by Tilt test and EPS. If no diagnosis was established during one particular strategy, then patients were offered crossover to the alternative arm. A diagnosis was achieved in 52% of patients in the ILR arm compared to 20% in the standard arm ($P = 0.012$).

In their randomised larger study, Farwell et al,²⁴ in 198 unselected patients presenting with recurrent syncope with no definitive diagnosis and no evidence of structural HD

were randomised to either ILR or standard investigations. The patients randomised to ILR management demonstrated an increase in diagnostic yield and subsequent ECG directed therapy compared to the conventional group. Thirty-three patients in the ILR group and 4 in the conventional arm received an ECG diagnosis (33% vs 4%, HR 8.93, 95% CI, 3.17 to 25.2, $P < 0.0001$). Subsequent 17-month follow-up data showed a similar significant trend favouring ILR assessment, with almost half the ILR group receiving an ECG diagnosis compared to 6% in the conventional testing strategy (HR 6.53, 95% CI, 3.73 to 11.4, $P < 0.0001$).²⁵

Subsequent observational studies, particularly The International Study of Syncope of Uncertain Origin (ISSUE) study^{15,26,27} have been fundamental in establishing a role for ILRs in the investigation of patients with syncope. The chief objectives of this international multicentre observational study were to elucidate the diagnostic contribution of ILRs in patients with recurrent syncope in 4 important clinical groups:

1. those with a negative tilt result;
2. those with a positive tilt result;
3. those with bundle branch block and negative EP study; and
4. those with structural heart disease and negative EP study.

Recurrent syncope was defined as >3 syncopal episodes in the previous 2 years with an interval between the first and last episode of more than 6 months.

In their first publication, 111 patients were split into those who developed a positive ($n = 29$) or negative response ($n = 89$) to Tilt testing.¹⁵ The primary endpoint was the analysis of ILR ECG tracing during their first syncopal episode. Similar results were observed in both groups with 34% of patients experiencing a further syncopal recurrence, with ECG correlation in 23% in the tilt negative group and 28% in the tilt positive group. The predominant rhythm identified was asystolic pauses with 46% in the tilt negative group and 62% in the positive group. Furthermore, a frequent finding observed during syncope in both groups was sinus rhythm, thereby also highlighting the importance of ILRs in excluding an arrhythmic cause for syncope in some individuals.

The next cohort investigated, by the ISSUE investigators, represented a difficult diagnostic group, that is those patients presenting with recurrent syncope of unknown origin and high-risk features during their initial clinical evaluation. The subsequent 2 studies from the ISSUE investigators aimed to address this in patients with ECG evidence of BBB and those with evidence of SHD. In 52 patients with BBB (QRS >100 ms) and a negative EPS and negative conventional work-up, an ILR was implanted and followed up for 15

months.²⁶ Syncope occurred in 22 patients (42%) with 19 of these patients having ILR documentation. The remaining 2 demonstrated normal sinus rhythm during syncope. Again the most frequent finding in 77% of patients was one or more prolonged asystolic pauses, most likely attributable to paroxysmal atrioventricular block; thereby reinforcing the importance of performing further investigations in patients with abnormal ECG findings and syncope.

Prior to the advent of the primary prevention ICD guidelines, the final ISSUE study studied 35 patients with documented SHD (previous MI or cardiomyopathy with LV dysfunction (mean EF $47 \pm 17\%$, and 6% EF $<30\%$ or evidence NSVT in 46%) in whom a EP study did not induce sustained monomorphic VT. An ILR documented syncopal event recurred in 17% patients after a mean of 6 ± 5 months. Reassuringly, no patients died.²⁷ Interestingly, the mechanism of syncope was heterogeneous, and not as expected, purely related to ventricular arrhythmias, a finding also demonstrated by Solano et al.²⁸

In summary, a total of 198 patients were studied in the ISSUE study with 57 (29%) presenting with syncopal recurrence. The majority had a bradycardia related syncope (68%). A further 4% developed a tachycardia of atrial or ventricular origin and importantly 28% demonstrated a non arrhythmic aetiology thereby providing reassurance for both the physician and patient.

Neurally Mediated Syncope Group

As already mentioned, analysis of ISSUE study patients who demonstrated non-arrhythmic syncope accounted for 28% of the patient cohort and represented the first study to assess the potential role of ILR in this specific cohort. Subanalysis of this group, led the authors to conclude that ILR observed heart rate changes at the time of syncope may be related to a reflex activation of the cardiovascular system and the diagnosis of possible hypotensive related syncope such as neurally mediated syncope or autonomic failure.²⁹

The subsequent prospective observational ISSUE 2 study sort to recruit patients diagnosed with suspected neurally mediated syncope.³⁰ All patients had a history of recurrent syncope and showed no high-risk features suggestive of a cardiac cause accounting for their symptoms. Those with orthostatic hypotension and carotid sinus syncope were also excluded from the study. After the ILR was implanted in 392 patients, 33% developed recurrence of their syncope with the mechanism of syncope being documented in 103 (26%) patients after a mean time of 12 months. As a result, a pacemaker was inserted in 47 patients because of asystole, 6 patients were treated with antiarrhythmic therapy, 4 underwent catheter ablation and 1 patient received an ICD. The remaining 50 patients did not receive specific therapy.

Subsequent follow-up showed that patients assigned to a mechanism-guided therapy, had a significantly reduced syncope burden over a year compared to those without a specific therapy (92% relative risk reduction, $P = 0.002$). The therapeutic application of pacing in patients with asystolic neurally mediated syncope is presently being investigated in the prospective, randomised controlled double-blind study, ISSUE 3 study and the results are eagerly awaited.³¹

Spurred on by the positive results in ISSUE 2, the same authors explored the potential superiority of ILR monitoring over tilt testing in patients with suspected vasovagal syncope. Interestingly, the results suggested that tilt testing had no correlation with the rate of recurrence or mechanism of syncope, while further supporting the use of ILRs to not only identify the mechanism of syncope but also guide therapy.³²

Role for Early Use

Despite the non-randomised observational nature of the study, the ISSUE 2 study and a subsequent study by Brignole et al⁷ led many to consider a policy of early ILR implantation in the management of patients with syncope. Furthermore, the ISSUE study clearly demonstrated that when the pretest conditions pointed in one direction, especially towards a tachyarrhythmia aetiology, ILRs often revealed an alternative diagnosis, with predominantly a bradycardia, providing further evidence for an early ILR strategy compared to a conventional strategy with or without EPS assessment.

Bajpai et al,³³ in their single centre study, retrospectively compared, in an unselected population, early ILR implementation compared to a delayed standard protocol with ambulatory ECG recordings, Tilt testing, and EPS. They were able to show a high diagnostic yield of early ILR therapy earlier in the management algorithm for syncope and hence reduce the number of investigations required and time to diagnosis. Moreover, they confirmed previous findings that the diagnostic yield of tilt testing and EPS were non-contributory in the majority of patients.

Recent registry data from The Place of Reveal in the Care Pathway and Treatment of Patients with Unexplained Recurrent Syncope (PICTURE) registry further supports this strategy and supports the current ESC guideline recommendations that these patients should be considered for an early ILR implantation in their evaluation.³⁴ The registry included 650 patients with unexplained syncope, all implanted with ILR. Patients were followed up until the first recurrence of the syncopal event. Of the 218 syncopal events during the study, ILR-guided diagnosis was obtained in 78%, of which 75% were shown to have a cardiac aetiology. Again the study highlighted the large number of diagnostic tests that patients underwent prior to getting an ILR implant (median of 13 tests per patient) and the

subsequent high diagnostic yield of ILR in the study cohort.

Syncope Diagnosis not Established

Epilepsy group

The misdiagnosis of epilepsy, estimated in the region of 20% of patients,³⁵ not only has a major impact on healthcare expenditure, but more importantly significant emotional costs to the patient. The common alternative diagnosis in patients with a misdiagnosis of epilepsy is convulsive syncope.³⁶ In the recent Reveal in the Investigation of Syncope and Epilepsy (REVISE) study, Petkar et al,³⁷ were able to demonstrate that 1 in 8 patients with a previous diagnosis of epilepsy or in whom the diagnosis was in doubt, actually showed evidence of cardiac syncope as established by ILR therapy. ECG-symptom correlation was achieved in 29 (71%) patients with the majority of patients showing normal sinus rhythm, however more importantly, 7 (24%) patients showed evidence of asystole and as a consequence, 6 out of the 7 underwent permanent pacing with resolution of symptoms in 5 (80%) patients over a 9-month follow-up period. Interestingly, the ILR was also able to confirm the diagnosis of epilepsy in 4 of the patients, by depicting a specific myopotential pattern suggestive of tonic clonic seizures, which also enables the neurologist to differentiate between convulsive syncope or non-generalised seizures with generalised seizures.³⁸

Furthermore, the European Heart Rhythm Association (EHRA) task force extended the use of ILRs in patients with an established diagnosis of epilepsy in order to detect treatable neurogenic cardiac arrhythmias in the periictal period.⁸

Elderly Patients with Recurrent Non-accidental Falls

As in the epilepsy group, syncope in the elderly population also has major healthcare implications. Significant comorbidity and atypical presentations render diagnosis difficult to achieve, and hence leads to extensive non-invasive testing.³⁹ In their small group study, Armstrong et al⁴⁰ were able to demonstrate a diagnostic yield of nearly 50% with ILR in older people with unexplained falls and syncope, comparable to studies involving younger patients.²² It can be argued, however, that in some cases, elderly patients with recurrent syncope and ECG evidence of conducting tissue disease (e.g. bifascicular block) or sinus node disease and preserved LV function, may be considered for insertion of a permanent pacemaker without necessarily requiring an ILR to be inserted beforehand, since the diagnosis is very likely to be related to bradyarrhythmias. Insertion of an ILR would necessitate an additional procedure, with associated costs, and may delay treatment in some cases.

Recurrent Unexplained TLOC to Exclude an Arrhythmic Cause of Syncope

The exclusion of cardiac syncope, particularly, in patients with recurrent infrequent unexplained TLOC, is prognostically reassuring for both the patient and the referring physician and cost saving with regard to termination of ongoing unnecessary investigations. This was observed in a study by Pezawas et al⁴¹ in which 70 consecutive patients with and without SHD, who had recurrent unexplained syncope were implanted with an ILR. The investigators found an almost 50% diagnostic yield for arrhythmia detection with an ILR, while most of the remaining patients had normal sinus rhythm. Interestingly, 57% of patients with major depressive disorder had sinus rhythm during recurrence compared with 31% of patients without the disorder ($P = 0.01$).

Cost Implications

The cost implications of the ILR compared to conventional strategies has been assessed in the two randomised controlled trials.^{25,42} Using Canadian health costings, Krahn et al⁴² concluded that the cost per diagnosis using ILR prolonged monitoring was significantly less than the cost of conventional testing (\$5852 vs \$8414, [SG\$6554 vs SG\$9423] $P = 0.002$) despite a higher initial cost with ILR approach versus a conventional strategy (\$2713 vs \$1683, [SG\$3038 vs SG\$1884]). Furthermore, the performance of conventional testing leads to a high incidence of crossover to the monitored approach, thereby increasing cost.

The EaSyAs study²⁵ ILR, resulted in a cost saving of £406 versus £1210 [SG\$1259 vs SG\$3751] (mean difference £809 [SG\$2508], 95% CI, £123 to £2730 [SG\$381 to SG\$8463]) resulting in a 60% recovery of the initial cost of the ILR.

Therefore the common principle underlying both cost analyses was that the higher initial costs of monitoring by an ILR strategy was justified by its greater diagnostic yield and decreased hospitalisation rates compared to conventional management. However, it is important to emphasise that cost advantages of prolonged monitoring can only be effective if patients are carefully selected for ILR implantation.

Limitations

There are some limitations associated with ILRs. Owing to the fact that it is a minor surgical procedure, there is a reported 1% risk of pocket infection with 4 patients out of 392, in ISSUE 2, developing an infection complication. There have also been some reports of over and under detection of arrhythmias in the automatic activation mode as a result of device sensing issues.⁴³

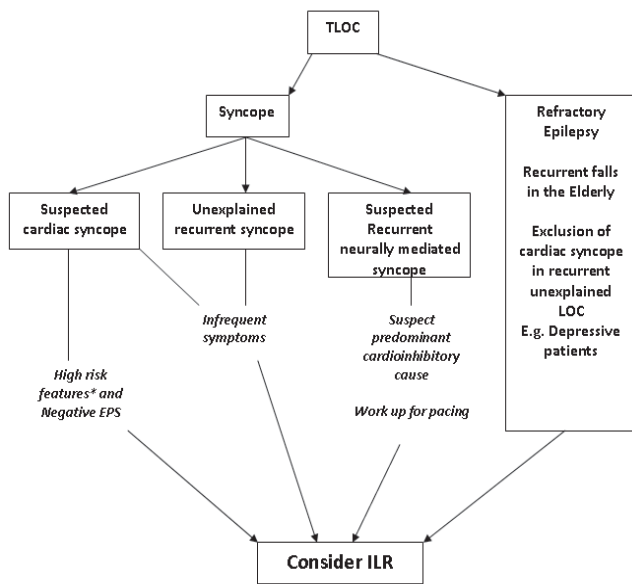


Fig. 5. Algorithm incorporating the implantable loop recorder in the work-up of transient loss of consciousness (T-LOC) based on 2009 European Society of Cardiology Guidelines¹⁶

EPS: electrophysiological study

*High-risk features: bundle branch block; definitive structural heart disease

Conclusion

Figure 5 shows a summary algorithm, highlighting the stages at which an ILR may be considered during the work-up of a patient presenting with transient loss of consciousness based on the recent ESC guidelines.^{8,16} The use of ILR in selected patients remains an accurate, cost effective and valuable tool for diagnosis and management of patients with unexplained syncope. Unlike most conventional monitoring methods available, the use of ILR provides both high yield diagnostic and risk stratification information in one single test. Based on current evidence-based guidelines, an ILR strategy should be considered in the forefront of the investigations available to the physician for the management of patients with syncope. However, it is imperative that the ILR should not substitute a detailed initial evaluation with a careful history and physical examination.

REFERENCES

1. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. *Am J Cardiol* 2003;91:1006-8.
2. Kapoor WN. Evaluation and outcome of patients with syncope. *Medicine (Baltimore)* 1990;69:160-75.
3. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med* 1982 ;73:15-23.
4. Iglesias JF, Graf D, Forclaz A, Schlaepfer J, Fromer M, Pruvot E. Stepwise evaluation of unexplained syncope in a large ambulatory population. *Pacing Clin Electrophysiol* 2009;32:S202-6.
5. Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, Brooks WB. Impairment of physical and psychosocial function in recurrent syncope. *J Clin Epidemiol* 1991;44:1037-43.
6. Ammirati F, Colaceci R, Cesario A, Strano S, Della Scala A, Colangelo I, et al. Management of syncope: clinical and economic impact of a Syncope Unit. *Europace* 2008;10:471-6.
7. Brignole M, Menozzi C, Moya A, Garcia-Civera R. International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Implantable loop recorder: towards a gold standard for the diagnosis of syncope? *Heart* 2001 ;85:610-2.
8. Task Force Members, Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W; EHRA Scientific Documents Committee, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F; Document Reviewers, Lip GY, Almendral J, Kirchhof P, Botto GL; EHRA Scientific Documents Committee. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;11:671-87.
9. Kulakowski P, Lelonek M, Krynski T, Bacior B, Kowalczyk J, Malkowska B, et al. Prospective evaluation of diagnostic work-up in syncope patients: results of the PL-US registry. *Europace* 2010;12:230-9.
10. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;29:459-466.
11. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M; OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J* 2003;24:811-9.
12. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart* 2008;94:1620-6.
13. Alboni P, Brignole M, Menozzi C, Raviele A, Del Rosso A, Dinelli M, et al. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol* 2001;37:1921-8.
14. Epstein AE, DiMarco JP, Ellenbogen KA, Mark Estes III NA, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). *J Am Coll Cardiol* 2008;51:e1-e62.
15. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, et al. International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261-7.
16. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS),

- Eur Heart J 2009;30:2631-71.
17. Linzer M, Pritchett EL, Pontinen M, McCarthy E, Divine GW. Incremental diagnostic yield of loop electrocardiographic recorders in unexplained syncope. *Am J Cardiol* 1990;66:214-9.
 18. Schuchert A, Maas R, Kretschmar C, Behrens G, Kratzmann I, Meinertz T. Diagnostic yield of external electrocardiographic loop recorders in patients with recurrent syncope and negative tilt table test. *Pacing Clin Electrophysiol* 2003 ;26:1837-40.
 19. Kapoor WN, Brant N. Evaluation of syncope by upright tilt testing with isoproterenol. A nonspecific test. *Ann Intern Med* 1992;116:358-63.
 20. Sumiyoshi M, Nakata Y, Mineda Y, Shimamoto T, Yasuda M, Nakazato et al. Response to head-up tilt testing in patients with situational syncope. *Am J Cardiol* 1998;82:1117-8, A9.
 21. Krahn AD, Klein GJ, Norris C, Yee R. The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation* 1995;92:1819-24.
 22. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. *Reveal Investigators. Circulation* 1999;99:406-10.
 23. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;104:46-51.
 24. Farwell DJ, Sulke AN. A randomised prospective comparison of three protocols for head-up tilt testing and carotid sinus massage. *Int J Cardiol* 2005;105:241-9. Epub 2005 Jul 12.
 25. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J* 2006;27:351-6. Epub 2005 Nov 28.
 26. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, et al. International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with bundle branch block and negative electrophysiologic test. *Circulation* 2001;104:2045-50.
 27. Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, et al. International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation* 2002;105:2741-5.
 28. Solano A, Menozzi C, Maggi R, Donato P, Bottoni N, Lolli G, et al. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. *Eur Heart J* 2004;25:1116-9.
 29. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Donato P, Puggioni E, et al. International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Nonarrhythmic syncope documented by an implantable loop recorder (an ISSUE substudy). *Am J Cardiol* 2002;90:654-7.
 30. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. *Eur Heart J* 2006;27:2232-9.
 31. Brignole M. International study on syncope of uncertain aetiology 3 (ISSUE 3): pacemaker therapy for patients with asystolic neurally-mediated syncope: rationale and study design. *Europace* 2007;9:25-30.
 32. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;27:1085-92.
 33. Bajpai A, Eruchie D, Asrress KN, Yavari A, Cotterill D, Dickinson K, et al. Early use of implantable loop recorders in the assessment of patients presenting to secondary care with syncope or severe palpitations with pre-syncope. *Eur Heart J* 2009;30(Abstract Supplement):16.
 34. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL, et al. PICTURE Study Investigators. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;13:262-9.
 35. McDade G, Brown SW. Non-epileptic seizures: management and predictive factors of outcome. *Seizure* 1992;1:7-10.
 36. Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000;36:181-4.
 37. Petkar S, Iddon P, Bell W, Rice N, McKee D, Curtis N, et al. EVISE (Reveal in the Investigation of Syncope and Epilepsy) study. *Eur Heart J* 2009;30(Abstract Supplement):15.
 38. Ho RT, Wicks T, Wyeth D, Nei M. Generalized tonic-clonic seizures detected by implantable loop recorder devices: diagnosing more than cardiac arrhythmias. *Heart Rhythm* 2006;3:857-61. Epub 2006 Mar 27.
 39. Kapoor W, Snustad D, Peterson J. Syncope in the elderly. *Am J Med* 1986;88: 419-28.
 40. Armstrong VL, Lawson J, Kamper AM, Newton J, Kenny RA. The use of an implantable loop recorder in the investigation of unexplained syncope in older people. *Age Ageing* 2003;32:185-8.
 41. Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M, Schmidinger H. Implantable loop recorder in unexplained syncope: classification, mechanism, transient loss of consciousness and role of major depressive disorder in patients with and without structural heart disease. *Heart* 2008;94:e17.
 42. Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. *J Am Coll Cardiol* 2003;42:495-501.
 43. Ng E, Stafford PJ, Ng GA. Arrhythmia detection by patient and auto-activation in implantable loop recorders. *J Interv Card Electrophysiol* 2004;10:147-52.