

Tilt Table Testing and Implantable Loop Recorders for Syncope

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KEYWORDS

• Tilt table tests • Implantable loop recorders • Syncope • Randomized studies • Diagnosis

KEY POINTS

- Tilt table tests have provided important benefits in the field of neurally mediated syncope; however, they have significant limitations.
- Tilt table tests have many significant methodological variables, have not been validated against gold standard populations, are only moderately reproducible, do not provide prognostic predictive power, and have not been shown useful in selecting effective therapies.
- Implantable loop recorders (ILRs) are small, subcutaneous digital recording devices with a lifespan of 2 to 3 years. Randomized studies have established the safety and efficacy of their early application in the diagnosis of syncope.
- About 40% of patients have syncope and a diagnosis its cause while bearing ILRs.
- ILRs have identified 2 populations of older patients with syncope who may benefit from permanent pacing.

INTRODUCTION

Neurally mediated syncope is a common problem. Numerous epidemiologic studies have shown that the lifetime prevalence is over 40%, and many people faint recurrently.¹⁻³ Not surprisingly, many people who faint seek help. Syncope is responsible for 1% to 6% of emergency room visits and 1% to 3% of hospital admissions, and it is a frequent reason for referral to internists, cardiologists, and neurologists.^{4,5} Some causes of syncope are potentially fatal, and, coupled with a limited insight into the symptoms that surround syncope, many physicians are uncertain about how to approach the diagnostic process with both accuracy and efficiency.

The European Society of Cardiology guidelines⁴ provide streamlined guidance for the diagnosis of syncope. They are written generally from the perspective of consulting cardiologists and

advocate the use of a detailed history early in the diagnostic process. A comprehensive history can provide a wealth of useful information, and structured histories and point scores are useful for the initial, rapid diagnosis of syncope versus epileptic seizures,⁶ syncope with a structurally normal heart,⁷ and syncope with structural heart disease.⁸ They also are useful in risk stratification in the emergency room,⁹ and in predicting the likelihood of syncope recurrences.⁵

Many patients, however, continue to provide diagnostic challenges after the initial assessment. Most of these patients require further investigation. An electrocardiogram (ECG) is warranted in all patients, and following this, the 2 most useful diagnostic tools are the tilt table test and the implantable loop recorder (ILR). This article will review both these tools and provide some suggestions on deciding when and which of them to use.

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TILT TABLE TESTS

History of Tilt Table Tests

Tilt table tests were initially used as tools to study compensatory responses to orthostatic stress, and their ability to induce syncope was recognized in the middle of the 20th century by US Air Force clinical investigators. This was prompted by studies that showed that 25% of US Air Force personnel had a history of syncope.⁴ Somewhat later, civilian physicians, faced with the diagnostic challenge of syncope and the ability of tilt table tests to induce vasovagal syncope, developed them as clinical tools. Tilt table tests now are widely used for diagnosing syncope, and have also been used as tools for physiologic studies, predicting outcome, and selecting therapies.

Types of Tilt Table Tests

The core of tilt table testing is passive head-upright tilt for 20 to 60 minutes, until hypotension, bradycardia, presyncope, or syncope ensues, or until the test ends (**Box 1**). Prolonged orthostatic stress may be coupled with intravenous isoproterenol, sublingual nitrates, or intravenous clomipramine¹⁰ to induce an endpoint. Nitrates are given to increase venodilation; isoproterenol is given to mimic the catecholamine response to stress, and clomipramine is given to increase intracranial serotonin, which is postulated to be a neurotransmitter central to the reflex. Combinations of these variables led to a large number of individual tilt table test protocols, each with its own reported accuracy.¹¹ On average, positive response in patients with prior syncope occurs in 49% of passive tests and 66% of tests with an additional provocative factor. They have been used in diagnostic studies in populations such as those with neurally mediated syncope, syncope in the setting of structural heart disease, loss of consciousness that might be due to syncope or epilepsy, postural orthostatic tachycardia, and autonomic neuropathy.⁴ They have been used as

Box 1

How are tilt table tests performed?

Patients are awake and alert and gently restrained on a table capable of head-up tilt

Table pivoted upwards at 60° to 80°

Intravenous isoproterenol or clomipramine or sublingual nitrates may be included

Generally last up to 45 minutes

End points: presyncope or syncope, and hypotension and/or bradycardia

entry criteria in observational studies and clinical trials, mechanistic studies of the vasovagal reflex, and in drug studies, and they have been proposed to be useful for selecting efficacious treatment. However, their true usefulness has not been validated.

Tilt table tests have made several significant contributions. They have made the informed care of syncope patients more accessible and less daunting, and by their ability to induce syncope under controlled conditions have reassured many patients about the diagnosis and provided a measure of comfort to physicians. They have provided the inclusion criteria for diagnostic and long-term observational studies and randomized clinical trials. Tilt table tests have been used as platforms for physiologic studies and pilot treatment studies. However, there are limitations to the use and interpretation of studies based on or including tilt table tests.

Test Accuracy

The central problem is that there is not a good evidence-based clinical definition of a syndrome of neurally mediated syncope. In essence, it is a syndrome defined by a test, rather than a test that diagnoses a syndrome. There is a lack of the validation of tilt table testing against populations with defined causes of syncope.¹² This causes problems with defining or knowing the sensitivity of tilt table tests, raising the issue of whether patients with negative tests have a different syndrome. This is a genuine concern. Patients with negative and positive tests have similar symptoms,⁷ similar symptom burdens,⁷ similar clinical outcomes in the 3 years following the tilt table test,¹³ and have ties between symptoms and outcomes.¹³⁻¹⁵ These results suggest that a significant number of patients with neurally mediated syncope may have falsely negative tilt table tests. Therefore, a positive tilt table test may be an epiphenomenon associated with neurally mediated syncope, rather than a core feature. Lelonek and colleagues¹⁶ reported that a single nucleotide polymorphism in a G protein is associated with negative tilt table tests in syncope patients.

Studies of the specificity of tilt table tests are equally difficult to interpret. Numerous studies have reported that the first lifetime syncopal spell can occur at any age, and the lifetime prevalence is at least 20% to 40%.¹⁻³ It is not known how many control subjects are simply people who have not yet fainted but will at some later time. If tilt table tests identify people predisposed to fainting, then populations of younger control subjects will appear to have more falsely positive tilt table

tests. This will confound studies of aging and the autonomic nervous system. Finally, the specificity of a tilt table test protocol seems to be inversely related to its positive yield, and there may be no ideal protocol.

Robustness of Methodology

A robust test is a test whose outcome does not vary markedly on the specific local methodological details that are used. However, the likelihood of positive tests depends on whether intravenous cannulation is used,¹⁷ the angle and duration of head-up tilt,^{18,19} whether and how a drug challenge is used, the number of head-up iterations during the test,^{20,21} the volume status of the subject,^{22–24} and the subject's age.^{25–27} Outcomes can be quite sensitive to subtle changes in tilt conditions. For example, tilts with isoproterenol at 5 µg/min at 80° head-up tilt for less than 10 minutes are quite specific, while those lasting more than 10 minutes are much less specific.¹⁹ Protocols that use a longer observation period, a steeper tilt angle, and drug interventions have higher diagnostic yield and lower specificity. Similarly, younger subjects are more sensitive to tilt testing, regardless of whether isoproterenol is used. Finally, tilt tests using either isoproterenol or nitroglycerin as provocative factors were compared directly in a cross-over study by Delepine and colleagues.¹¹ The drugs increased the diagnostic yield by the same proportion, but not always in the same patient. That is, some patients respond to 1 drug but not the other. This poses a significant interpretative problem: which test result is correct?

In summary, the apparent simplicity of tilt tests is deceptive. Their diagnostic performance depends significantly on several patient and methodological factors, making comparisons difficult and diagnostic conclusions insecure.

Reproducibility

Tilt table tests are 70% to 87% reproducible over periods of days to months.^{4,28} Do patients who have a negative first test followed by a positive second test have neurally mediated syncope? If so, this suggests that a moderate minority of patients has either a falsely negative or falsely positive diagnostic test. The degree of bradycardia and hypotension during tilt table tests is only modestly reproducible, suggesting that patients cannot be classified based on the hemodynamic changes seen on a single positive tilt table test. Therefore, the modest reproducibility of tilt table test symptomatic and hemodynamic outcomes moderates confidence in its usefulness.

Clinical Outcomes

Tilt table test outcomes do not predict clinical outcome. Patients have similar likelihoods of syncope recurrence after tilt table testing whether the test outcome was positive or negative.^{13–15} Similarly, International Study on Syncope of Uncertain Etiology (ISSUE) investigators concluded that the degree of bradycardia during a positive tilt table test does not correlate with the degree of bradycardia recorded in an ILR during a subsequent syncopal spell in the community.¹⁵ Thus the findings of tilt table testing do not predict either the clinical or hemodynamic outcome of the patient.

Similar conclusions have been drawn about the role of tilt table testing in selecting efficacious therapy. The need for isoproterenol to induce syncope does not predict a clinical response to beta-blockers,²⁹ and asystole induced during tilt table testing does not predict a clinical response to pacemakers. Two observational, historically controlled studies of pacing and syncope^{30,31} and a meta-analysis of pacemakers for treating vasovagal syncope³² concluded that the degree of bradycardia on baseline tilt table tests did not predict the subsequent likelihood of syncope in paced patients. Therefore baseline tilt table test conditions and outcomes do not predict eventual improvement with either beta-blockers or pacemakers.

In summary, tilt table tests have improved care of syncope patients and revived interest in the field. The role of tilt table tests for neurally mediated syncope is summarized in **Box 2**.

Box 2 Contributions and limitations of tilt table tests for neurally mediated syncope

Tilt tests have provided the inclusion criteria for study populations for diagnostic studies, long-term observational studies, and randomized clinical trials.

Tilt tests have been used as platforms for physiologic studies and pilot treatment studies.

The usefulness of tilt tests is limited by uncertain diagnostic test performance and a complex mix of significant methodological variables, modest reproducibility, lack of prognostic power, and inability to select efficacious therapies.

Tilt tests should be used judiciously and with the intent to act on the test outcome whether positive or negative.

IMPLANTABLE LOOP RECORDER

ILRs were developed in the early 1990s to provide a means of documenting the ECG findings of events that occur sporadically and infrequently, such as syncope. Other technologies such as ambulatory electrocardiography and external event recorders had a low rate of diagnosis due to the infrequent nature of the events, and syncope was one of among the first targets. The ILR is described in **Box 3**. A review³³ and European position paper³⁴ were published recently and provide more details. This section will provide a broad overview of the ILR.

Early Observational Studies

Nearly 30 case series appeared³³ following the initial report in 1995 by Krahn and colleagues.³⁵ Although there is substantial variation among studies, the ILR appears to provide an ECG-syncope correlation in about 35% of patients during the lifetime of the device.³⁴ Of these, 56% had asystole or severe bradycardia; 11% had a tachycardia, and 33% had no arrhythmia. Pre-syncope is much less likely to have ECG correlates, suggesting that much of it is due to either hypotension or a noncardiovascular cause. Up to 16% of events are not captured, because patients fail to activate the device with a magnet. The ISSUE investigators also concluded that that the ECG findings during syncopal spells within each patient were highly reproducible,^{15,36,37} indicating that a single syncopal spell suffices to provide useable diagnostic information.

The place of reveal in the care pathway and treatment of patients with unexplained recurrent syncope (PICTURE) study³⁸ was the largest observational report. It was a multinational European and Israeli registry that included 570 analyzable syncope patients who received an ILR either early or late in their assessment. Fully 38% of patients had a syncopal spell that was documented during a mean follow-up of 10 months. After 2 years, the

probability of a diagnosis was about 50%, and 75% of the diagnoses were cardiac-related. Although the precise diagnoses were not stated, most of the therapies were directed toward bradycardias.

The overall likelihood of establishing a diagnosis within the 2- to 3-year lifetime of an ILR is therefore in the range of 40%, which agrees well with the likelihood of at least 1 syncope recurrence in numerous observational and randomized clinical trials.³⁴

ISSUE 1

Some of the most important insights into the mechanisms, diagnosis, prognosis, and treatment of syncope have come from the ISSUE studies.^{15,36,37,39,40} ISSUE 1 studied 4 groups^{15,37,40}: syncope with a positive tilt table test, syncope with a negative tilt table test, syncope with bundle branch block, and syncope with structural heart disease with a moderate reduction in ejection fraction and a negative electrophysiologic study.

There were 111 patients in the tilt table test subgroups, with a mean age of 64 years. Syncope recurred in 34% of patients, and there were ECG correlates in about 75% of these. Asystole occurred in about half the ECG findings, with a smattering of other arrhythmias also detected. Whether this high proportion of asystole also occurs in younger patients is unknown. Nonetheless, the high numbers of patients with asystole did lead to ISSUE 2 and 3.

The ISSUE investigators implanted loop recorders in 52 patients with syncope and bundle branch block and negative electrophysiologic testing and moderate or no structural heart disease.⁴⁰ All patients had had an electrophysiologic (EP) study that showed a normal sinus node recovery time (SNRT), no inducible tachyarrhythmias, a His-to-ventricle (HV) interval less than 70 milliseconds, and an left ventricular ejection fraction (LVEF) greater than 35%. There was no ventricular tachycardia (VT) in follow-up, but over a follow-up of 3 to 15 months, syncope recurred in 22 patients (42%), the event being documented in 19 patients after a median of only 48 days. These included complete heart block in 24% of patients, sinus arrest in 8% of patients, and asystole undefined in 2% of patients, for a total of 34% of patients. Another 6% of patients developed stable complete heart block, and 4% of patients had pre-syncope due to transient complete heart block. Syncope without a rhythm disturbance occurred in 4% of patients. This substudy highlighted the high risk of this group, and led directly to the Prevention of Syncope Study 3 (SPRITELY; Syncope: Pacing or Recording In The Later

Box 3

Description of ILRs

Are small devices implanted subcutaneously in the left hemithorax

Have no intravascular leads, thereby avoiding most complications caused by pacemakers

Detect a bipolar ECG signal from small leads on either end, and the event can be detected either automatically with rate algorithms, or manually with magnet application

Now last about 3 years

Years),⁴¹ which directly tests whether empirical pacing or therapy targeted by ILR findings provides the best overall outcome in these patients.

The final subgroup of 35 patients had syncope and structural heart disease due to either coronary artery disease or idiopathic dilated cardiomyopathy.³⁷ The mean LVEF was 47%, and only 6% of patients had an LVEF less than 30%. All had had a negative conventional invasive electrophysiologic study. The patients had a mean follow-up of only 6 months, with a maximum of 19 months. During this time, 6 patients had syncope, and none was due to a VT. Another 6 patients had presyncope, and again none was due to a VT.

Finally, the results of ISSUE 1 led to a proposed scheme for classifying ILR findings during syncope. The intent was to help guide future therapy by diagnosing the cause of syncope from ECG findings alone.⁴² The ISSUE 1 reports provided fundamental insights into the mechanism of syncope in a variety of settings, and laid the groundwork for further studies by the ISSUE group. Generally, the investigators proposed that syncope due to cardiac arrhythmias could be diagnosed when there was a symptom-rhythm correlation with tachyarrhythmias, or with abrupt atrioventricular block. Gradually progressive sinus bradycardia that might end with asystole or atrioventricular block was deemed to be due to reflex syncope, such as vasovagal syncope. Lesser changes in heart rate, or sinus tachycardia, were defined as uncertain. This classification resonates with what is known about the vasovagal reflex, but the classification would benefit from outcomes validation.

ISSUE 2 and Guided Therapy

The ISSUE 2 study extended the findings of ISSUE 1 and addressed whether the ILR could be used safely to guide therapy.³⁶ Three hundred ninety-two subjects with recurrent syncope in the preceding 2 years were enrolled, and all received an ILR. The patients had a mean age of 67 years and were included if other causes of syncope were reasonably excluded and if neurally mediated syncope was suspected. After a median follow-up of 9 months, 103 patients had syncope recurrences. A total of 53 had asystole during syncope, and most subsequently received a dual chamber. Their subsequent course was compared with patients who did not receive pacemaker therapy. Pacing was associated with a relative risk reduction of 80%, and from this it seemed likely that a strategy of pacing guided by ILR findings was both safe and efficacious.

There were residual concerns among the ISSUE investigators and others. The patients were selected

as much by excluding other causes as by definite diagnosis of neurally mediated syncope, and other causes of bradycardic syncope exist in older patients.^{41,43} The patients were much older than those seen in North America. Finally, comparison of the Vasovagal Pacemaker Studies demonstrated the potential for a very large placebo effect in open-label syncope studies.^{32,44,45} To address the latter concern, the investigators undertook ISSUE 3.⁴⁶

ISSUE 3 and Guided Therapy

The structure of ISSUE 3⁴⁶ was generally like ISSUE 2, but the final phase involved a double-blind trial of permanent pacing in eligible patients. In this international study, 511 patients with a mean age 63 years and recent frequently recurrent syncope received an ILR.³⁹ Of these, 89 patients had syncope associated with a prolonged pause, or a long nonsyncopal pause. Subsequently, 77 were randomized to a pacemaker either activated or not, and pacing caused a 32% absolute reduction in the likelihood of a patient having a first faint, and 25% of patients continued to faint despite pacing. For every 100 patients who embarked on an ILR-directed strategy, 17 received pacemakers. Of the paced patients, over the first 2 years, 7 patients would not have fainted without pacing; 6 patients were prevented from fainting, and 4 patients continued to faint. Although an ILR-guided approach does have a statistically significant benefit, only 6 in 100 patients will benefit.

Health Economics and the ILR

There is good evidence that that the ILR provides a diagnosis in a large minority of patients during the lifetime of single ILR. Health care administrators, however, are very interested in the cost utility of ILRs, and whether this information comes at a tolerable cost. The cost was addressed by 2 small randomized trials.

The RAST (Randomized Assessment of Syncope Trial) was reported by Krahn and colleagues⁴⁷ in 2003.⁴⁸ Sixty patients (mean age 66 years) with syncope and preserved left ventricular function were randomized evenly to early use of an ILR or to conventional assessment with tilt table testing, external loop recorders, and invasive electrophysiologic study. The ILR strategy was diagnostically superior; 14 of 30 ILR subjects received a diagnosis compared with only 6 of 30 subjects with a conventional approach. Overall, a strategy of monitoring followed by tilt table testing and EP testing was associated with a diagnostic yield of 50%, at a cost of \$2937 per patient and \$5875 per diagnosis. Conventional testing followed by monitoring was associated with an eventual diagnostic yield of

Table 1
EHRA indications for ILRs in patients with syncope

Recommendation	Strength of Recommendation and Level of Evidence
In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have absence of high-risk criteria that require immediate hospitalization or intensive evaluation, and a likely recurrence within battery longevity of the device	Class 1, level A
In high-risk patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to specific treatment	Class 1, level B
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	Class 2A, level B
In patients with T-LOC of uncertain syncopal origin to definitely exclude an arrhythmic mechanism	Class 2B, level C

47%, at a greater costs of \$3683 per patient and \$7891 per diagnosis.

The Eastbourne Syncope Assessment Study (EASYAS) randomized 201 older syncope patients with mean age 74 years to receive an ILR or undergo conventional investigation after early assessment.⁴⁹ They were followed for a minimum of 6 months and up to 18 months; as with RAST, the ILR strategy was diagnostically superior. Thirty-four of 103 ILR subjects received a diagnosis compared with only 4 of 98 subjects with a conventional approach. Of the 34 diagnoses made by ILR, 16 were vasovagal syncope, and 3 were hyperventilation. ILR patients had fewer postrandomization investigations and fewer hospital days, resulting in a saving of costs, £406 versus £1210 (mean difference £809). This meant that 60% of the price of the device was recovered. There was no difference in the number of subsequent syncopal spells, mortality, or quality of life.

Although early use of the ILR appears to provide a diagnosis at a reasonable cost, there is as yet no evidence that on an intent-to-insert basis it improves outcome. Much of this is may be due to the lack of effective treatments for most patients with neurally mediated syncope. Nonetheless there is now compelling evidence that early use of ILRs provides more and earlier diagnoses than conventional investigations.

European Heart Rhythm Association Guidelines

The European Heart Rhythm Association (EHRA) issued guidelines for the indications for ILRs in the assessment of syncope.³⁴ These were informed by the efficacy, safety, and cost utility demonstrated in studies of ILRs for syncope, particularly the EASYAS⁴⁹ and RAST⁴⁷ studies.

Essentially, the guidelines recommend the early use of ILRs in patients in the middle zone of diagnosis and risk (**Table 1**). They should not be used in low-risk patients, unless they are diagnostic or therapeutic conundrums. Similarly, they should not be used in patients who otherwise have a high risk of adverse outcomes, such as patients with syncope and an indication for implantable cardioverter-defibrillator insertion.

SUMMARY

There now is ample evidence for the roles of tilt table tests and ILRs in the evaluation of syncope.^{4,34} The following is a very simplistic approach, but it should suffice in busy cardiology and internal medicine clinics.

Age is the first consideration. Almost all young patients who faint have vasovagal syncope, and this can be teased out and confirmed in most cases with a careful history. Diagnostic scores can serve as memory aids for the main criteria, and as rapid screening tools. The most satisfying approach is to combine knowledge of the physiology of vasovagal syncope with its diagnostic points. Tilt table tests and ILRs should be used with great caution. The concerns are that with a very high probability of vasovagal syncope, negative tilt table tests are likely to be falsely negative,⁵⁰ and most vasovagal syncope in younger patients may not be associated with bradycardia. Therefore in younger patients, both tests may be misleading: tilt table tests because of false negatives, and ILRs because only sinus rhythm may be seen.

In older patients (age 50 is a reasonable definition of older), the situation is quite different for several reasons. The history is less sensitive for vasovagal syncope for older patients,^{51,52} and tilt table tests are less sensitive but probably more specific. There

are numerous competing diagnoses; the risk of potentially fatal causes and comorbidities rises,⁵³ and at least 2 types of recently understood bradycardias (neurally mediated syncope and adenosine triphosphate-sensitive heart block) exist. These bradycardias can be treated with permanent pacing.^{39,43,54} In older patients (and if the history fails to provide a diagnosis with a high degree of comfort) both options are reasonable. Tilt table tests can be used to establish a diagnosis of vasovagal syncope, and ILRs are a reasonable first investigation. They will detect asymptomatic but relevant arrhythmias, and establish whether patients with vasovagal syncope are candidates for permanent pacing. They should not be used if patients are at high risk of life-threatening arrhythmias, because empirical treatment with defibrillators is proven therapy. The implantable cardioverter-defibrillators may not prevent vasodepressor syncope, but they do prevent death.

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