Randomized Assessment of Syncope Trial
Conventional Diagnostic Testing Versus a Prolonged Monitoring Strategy

Andrew D. Krahn, MD, FRCPC; George J. Klein, MD; Raymond Yee, MD; Allan C. Skanes, MD

Background—Establishing a diagnosis in patients with unexplained syncope is complicated by infrequent and unpredictable events. Prolonged monitoring may be an alternative strategy to conventional testing with short-term monitoring and provocative tilt and electrophysiological testing.

Methods and Results—Sixty patients (aged 66±14 years, 33 male) with unexplained syncope were randomized to “conventional” testing with an external loop recorder and tilt and electrophysiological testing or to prolonged monitoring with an implantable loop recorder with 1 year of monitoring. If patients remained undiagnosed after their assigned strategy, they were offered crossover to the alternate strategy. A diagnosis was obtained in 14 of 27 patients randomized to prolonged monitoring compared with 6 of 30 patients undergoing conventional testing (52% versus 20%, P=0.012). Crossover was associated with a diagnosis in 1 of 6 patients undergoing conventional testing compared with 8 of 13 patients who completed monitoring (17% versus 62%, P=0.069). Overall, prolonged monitoring was more likely to result in a diagnosis than was conventional testing (55% versus 19%, P=0.0014). Bradycardia was detected in 14 patients undergoing monitoring compared with 3 patients undergoing conventional testing (40% versus 8%, P=0.005).

Conclusions—A prolonged monitoring strategy is more likely to provide a diagnosis than conventional testing in patients with unexplained syncope. Consideration should be given to earlier implementation of a monitoring strategy. (Circulation. 2001;104:46-51.)

Key Words: syncope ■ diagnosis ■ electrophysiology ■ tests

The current approach to the investigation of patients with unexplained syncope involves short-term ECG monitoring or provocative testing with head-up tilt and electrophysiological testing.1–4 Provocative testing may be negative, or the results may be difficult to interpret. Difficulties may include the induction of abnormalities that do not reproduce the patients’ spontaneous symptoms or the need to infer a diagnosis based on limited observed abnormalities, such as nonsustained ventricular arrhythmias or ventricular fibrillation induced by multiple closely coupled extrastimuli.5,6

A prolonged monitoring strategy using an implantable loop recorder (ILR) has been reported to provide a symptom-rhythm correlation in a high proportion of patients with recurrent unexplained syncope and negative investigations.7,8 Use of prolonged monitoring may have merit as an initial strategy in many patients with problematic syncope. We report a prospective randomized comparison of these 2 diagnostic strategies in 60 patients with recurrent unexplained syncope.

Methods

Patients

Patients referred to the Arrhythmia Service at London Health Sciences Center for investigation of syncope were approached to participate in a prospective randomized trial comparing 2 diagnostic approaches to syncope. Consecutive patients were approached to participate in the trial if they had recurrent unexplained syncope or a single episode of syncope associated with injury that warranted cardiovascular investigation. Before enrollment, patients underwent a clinical assessment, including postural blood pressure testing, a minimum of 24 hours of baseline ambulatory monitoring or inpatient telemetry, and a transthoracic echocardiogram. The baseline Holter assessment was considered negative if the patient did not experience syncope or presyncope reminiscent of their referral symptoms during the recording and did not have evidence of asymptomatic second- or third-degree atrioventricular (AV) block, pauses >3 seconds, sustained supraventricular tachycardia, or >10 beats of wide QRS complex tachycardia likely to represent ventricular tachycardia. Additional neurological or cardiovascular testing before enrollment performed by the referring physician was recorded but was not mandated by the protocol. Patients were permitted to have a previous tilt test or loop recorder if symptoms suggested that repeat testing was indicated. Patients were excluded if the left ventricular ejection fraction was <35%, if they were unlikely to survive for 1 year, or if they were unable to provide follow-up or give informed consent. Patients with a presentation typical of neurally mediated syncope at baseline assessment were considered to have this diagnosis and were excluded. This included upright posture with a prodrome including warmth and diaphoresis, with postepisode fatigue. No patient refused enrollment.

Diagnostic Testing

Patients were randomized to a “conventional” investigation strategy or a prolonged monitoring strategy with use of an ILR. Conventional testing included a 2- to 4-week period of monitoring with an external
loop recorder, followed by tilt table, and electrophysiological testing. Tilt testing was performed with the use of 60° head-up tilt for 30 minutes with continuous ECG and noninvasive blood pressure monitoring. If no response occurred, intravenous isoproterenol was administered at 1 μg/min and titrated to a 25% increase in heart rate for an additional 15 minutes. A positive test was defined when syncope or presyncope occurred, accompanied by a >30 mm Hg fall in blood pressure, with or without a drop in heart rate. A protocol identical to this with 15 minutes of passive tilt has previously been shown to have a 61% sensitivity and 93% specificity in our laboratory. An additional 15 minutes of passive tilt was added before isoproterenol to enhance sensitivity.

Electrophysiological studies were performed in the postabsorptive unsedated state. Standard multipolar catheters were inserted into the right femoral vein and placed in the right atrium and right ventricle and near the His bundle. Sinus node recovery time, sinoatrial conduction time, and antegrade and retrograde AV node function were assessed by using atrial and ventricular pacing and extrastimuli. Programmed electrical stimulation was performed at the right ventricular apex at a drive cycle length of 600 and 400 ms for 8 beats, followed by up to 3 extrastimuli. This protocol has been found to be 90% sensitive for induction of ventricular tachycardia in patients with spontaneous ventricular tachycardia in our laboratory. A positive test was defined as induction of ventricular tachycardia >30 seconds in duration or requiring urgent intervention, sustained supraventricular tachycardia, a corrected sinus node recovery time >350 ms, or an HV interval >75 ms.

Patients randomized to a prolonged monitoring strategy underwent implantation of a Reveal ILR (Medtronic) under local anesthetic in the left chest region after administration of 1 g of intravenous cefazolin. Details of the ILR have been reported. The ILR is a continuous ECG monitor capable of recording up to 42 minutes of a single-lead ECG. After spontaneous symptoms, the patient uses an activator over the device to “freeze” the preceding ECG, which can be downloaded with a standard pacemaker programmer (Medtronic 9290C). After implantation, the patient, along with a spouse, family member, or friend, was instructed in the use of the activator. The patients randomized to the monitoring strategy underwent follow-up for 1 year. For the purpose of analysis in the monitoring strategy, a diagnosis was defined as obtaining a symptom-rhythm correlation in patients during spontaneous syncope or presyncope that resembled the symptoms before enrollment.

Crossover
If the assigned strategy did not provide a diagnosis, patients were offered crossover to the alternate strategy. An ILR was offered to all conventional patients immediately after tilt and electrophysiological testing was negative. Tilt and electrophysiological testing were offered to the patients subjected to monitoring if a diagnosis was not obtained after 1 year of follow-up. All patients provided informed consent. The protocol was approved by the University of Western Ontario Institutional Review Board.

The baseline ECG and echocardiogram were assessed to diagnose right and left bundle branch block (conduction disturbance), valvular heart disease (valve lesion graded moderate or greater), cardiomyopathy, ischemic heart disease, and left ventricular ejection fraction. The diagnosis of cardiomyopathy and ischemic heart disease also included available findings from cardiac catheterization, other noninvasive testing, and the clinical history. Dilated cardiomyopathy (cardiomyopathy, n=3) was defined as a global reduction in left ventricular function that was not explained on the basis of coronary artery disease (left ventricular ejection fraction <55%). Ischemic heart disease was diagnosed in the presence of previous coronary artery bypass surgery, documented myocardial infarction, or treated angina after clinical investigation, including stress testing, perfusion imaging, and/or cardiac catheterization. Structural heart disease was considered present when valvular heart disease, cardiomyopathy, or ischemic heart disease was diagnosed on the basis of the definitions above.

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<th>Clinical Characteristics of Conventional Group and Monitoring Group</th>
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<tr>
<td>Age, y</td>
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<td>Normal baseline ECG, n (%)</td>
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<td>Conduction disturbance, n (%)</td>
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<td>Sinus bradycardia, n (%)</td>
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<td>Atrial fibrillation, n (%)</td>
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<td>Structural heart disease, n (%)</td>
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<td>Valvular heart disease</td>
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<td>Cardiomyopathy</td>
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<td>LVEF, %</td>
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<tr>
<td>No. of syncopal episodes</td>
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<td>Last year</td>
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<tr>
<td>Lifetime</td>
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<td>Duration of syncope, y</td>
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LVEF indicates left ventricular ejection fraction. Values are mean±SD or number (percent).

Follow-Up
Patients were seen 1 week after loop recorder implantation for wound assessment and to reinforce patient understanding of the activation process. Subsequent follow-up occurred at 1, 2, 3, 6, 9, and 12 months. Patients were seen immediately after a symptomatic event.

Statistical Analysis
Continuous variables were compared by Student t test and ANOVA. Categorical variables were compared with a χ² test. A value of P<0.05 was considered significant.

Results
In the present study, 60 patients with unexplained syncope were randomized over a 30-month period. Syncope was recurrent in 53 patients. Seven patients had a single episode of syncope that was felt to warrant cardiovascular testing, 3 patients had valvular heart disease, and 2 patients had coronary artery disease. There was no difference in baseline variables between groups (Table). Structural heart disease was present in 23 patients (38%). Left ventricular function was well preserved in most patients, with an ejection fraction <50% in only 6 patients. Two patients had a previous negative tilt test. Before enrollment, neurological testing was performed in 36 patients (60%), with brain imaging in 25 (42%) and an electroencephalogram in 19 (32%).

Primary Strategy
In the 30 patients randomized to a monitoring strategy, a diagnosis was obtained in 14 (Figure 1). In 10 patients, bradycardia was noted during symptoms. In 1 patient, a regular narrow complex tachycardia at 240 bpm was noted. In 3 patients, heart rate fluctuation during symptoms along with clinical assessment led to the diagnosis of vasovagal syncope, with gradual slowing to 40 bpm in 1 patient and to 25 bpm in 1 patient. In the third patient with oscillation of heart rate
between 50 and 100 bpm, tilt testing at 80° reproduced spontaneous symptoms and confirmed the diagnosis. These 3 patients were advised to increase salt and water intake. In 12 patients, symptoms did not recur during the 12-month follow-up period. One patient failed to appropriately activate the loop recorder after an episode of syncope, and no further episodes occurred after the failure. Three patients remained in follow-up with a loop recorder implanted. In the 30 patients in the conventional arm, a diagnosis was obtained in 6 patients (20% for conventional treatment versus 52% for monitoring, P=0.012). One patient had symptomatic third-degree AV block while wearing an external loop recorder, and 2 patients had a positive tilt test. Electrophysiological testing demonstrated poor AV node function in 2 patients and inducible ventricular tachycardia in 1 patient.

Crossover
Six of the 13 patients who remained undiagnosed after 1 year of monitoring consented to crossover to conventional testing (Figure 2). Because of the previous monitoring, patients did not undergo short-term monitoring with an external loop recorder. Tilt testing was negative in all 6. Electrophysiological testing induced sustained AV node reentrant tachycardia associated with hypotension in 1 patient. This patient underwent slow pathway ablation.

Twenty-one of 24 patients with negative conventional testing underwent implantation of a loop recorder. During follow-up, a diagnosis was obtained in 8 patients, symptoms did not recur in 5 patients during 12 months of follow-up, and 8 patients remained in follow-up. Three of the latter 8 patients experienced a recurrent symptom but failed to activate the loop recorder; 1 event was attributed to activator failure. In the 8 patients that were diagnosed, bradycardia was noted in 4 (Figure 3), and tachycardia was noted in 2. Two patients had sinus rhythm recorded during syncope, with phasic motion artifact on the recorded signal suggestive of seizure activity. Both patients had a normal electroencephalogram before enrollment in the study. Neurological consultation led to empiric anticonvulsant therapy, with resolution of symptoms. In the 13 patients who completed a monitoring strategy in crossover, 5 achieved a diagnosis, compared with 1 of 6 patients who crossed over to provocative testing (62% versus 17%, respectively; P=0.069). Combining the primary strategy with crossover, the overall likelihood of being diagnosed was 55% with a monitoring strategy compared with 19% with conventional testing (P=0.0014). In the 51 patients that received an ILR, symptoms occurred in 3 patients within 1 month of implantation (6%). The mean time to recurrence was 117±106 days (median 93 days). No patient had infection at the site of implantation.

Diagnoses

Conventional Strategy
Conventional testing with an external loop recorder was associated with symptom recurrence in only 1 patient with third-degree AV block. Tilt testing was also of low yield, with a positive test in only 2 patients. Electrophysiological testing induced AV block with incremental pacing <100 bpm in 2 patients, leading to pacemaker implantation. One patient had inducible sustained monomorphic ventricular tachycardia associated with hypotension and was treated with an implantable defibrillator. A second patient had inducible sustained AV node reentrant tachycardia that was successfully ablated. Symptoms have resolved in all 7 patients diagnosed with a conventional strategy.

Monitoring Strategy
The monitoring strategy was more likely to detect arrhythmias, with symptomatic bradycardia detected in 14 patients. These subsequently underwent pacemaker implantation. As described above, 3 patients demonstrated heart rate fluctuation with a history in keeping with of vasovagal syncope. Tachycardia associated with presyncope was detected in 3 patients: a regular narrow complex tachycardia at 150 bpm felt to represent atrial flutter was present in 2 patients, and a narrow complex tachycardia at 240 bpm was detected in 1 patient. All 3 patients were treated with antiarrhythmic drug therapy after clinical assessment. Two patients were diagnosed with seizure disorder as indicated above. Neurological consultation led to empiric anticonvulsant therapy, with resolution of symptoms. One patient in the monitoring strategy died of a cerebrovascular accident 10 months after enrollment.

 Bradycardia
Bradycardia was detected in 14 patients undergoing monitoring compared with 3 patients undergoing conventional testing (40% versus 8%, respectively; P=0.005). In the 17 patients with bradycardia, AV block was detected in 8 patients, and sinus bradycardia or asystole was detected in 9. The mean age
of the bradycardia patients was 63±14 years compared with 66±14 years in patients with other diagnoses and 67±14 years in patients that were undiagnosed (P=0.66). Four of the 12 patients with baseline conduction system abnormalities on ECG developed subsequent complete AV block (33% in those with abnormalities versus 27% in those without baseline conduction disturbances). Three of these patients had left bundle branch block; incomplete right bundle branch block was present in the other patient. One patient was diagnosed with an external loop recorder, 1 patient had a negative electrophysiology study and was diagnosed after crossing over to monitoring strategy. The remaining 2 were identified during their primary strategy of monitoring. The remaining 4 patients with AV block had a normal baseline ECG. In those patients who experienced bradycardia during monitoring leading to pacemaker implantation, the bradycardia was associated with syncope in 10 patients and presyncope in 4.

Follow-Up
Syncope resolved in 27 of the 29 patients that were diagnosed during the 19.3±8.9 months of follow-up after a diagnosis was obtained. In 1 patient, negative conventional testing was followed by an ILR, which recorded a 38-second pause associated with syncope 7 months after implantation. A pacemaker was implanted. Eleven months later, the patient had an episode of syncope in the bathroom reminiscent of neurally mediated syncope, which has not recurred during the ensuing 12 months. The latter episode was not reminiscent of his index episodes. In the final patient, a primary monitoring strategy recorded an episode of marked sinus bradycardia followed by a 10-second pause associated with syncope 3 months after ILR implantation. Six months after pacemaker implantation, he began having episodes of confusion, disorientation, and transient unresponsiveness unlike his syncopal episodes before enrollment. Subsequent tilt testing was negative, and neurological assessment led to a diagnosis of partial complex seizures arising in the temporal lobe and anticonvulsant therapy.

Discussion
The etiology of syncope is often difficult to determine when initial investigations are negative. Referral for cardiovascular testing typically involves short-term monitoring, followed by
provocative tilt and electrophysiological testing. This prospective randomized trial suggests that an initial prolonged monitoring is associated with a considerably higher diagnostic yield than a conventional strategy and may be considered earlier in the approach to patients with unexplained syncope.

Tilt testing is reported to have a sensitivity of 67% to 83% and a specificity of ~90%.6,13–15 This estimate includes patients with a clinical presentation that is likely to represent neurally mediated syncope. The present study excluded younger patients whose history strongly suggested neurally mediated syncope, in whom tilt testing would be more likely to be positive.6 We excluded these patients because we felt that the diagnosis was clinically evident regardless of the result of tilt testing, and an invasive approach including electrophysiological testing and an ILR was not justified.

Electrophysiological testing is most likely to detect abnormalities in patients with structural heart disease.2,5,16–20 This is particularly the case in patients with previous myocardial infarction and reduced left ventricular function who are at risk for ventricular arrhythmias. Syncope in the presence of significant structural heart disease is a class I indication for electrophysiological testing.21 We excluded these patients because of concern that a monitoring strategy was unsafe, relying on recurrence of a potentially life-threatening ventricular arrhythmia. The low yield of electrophysiological testing in our patients is consistent with the reported yield in patients without structural heart disease.5,22 Nonetheless, electrophysiological testing does provide reassurance to the patient and physician that the risk of sudden death is low. The absence of recurrent ventricular arrhythmias during subsequent monitoring emphasizes the exclusion of patients with depressed left ventricular function at risk for sudden death.

The yield of a monitoring strategy in unexplained syncope is in keeping with previous reports, suggesting that an arrhythmia will be detected in 25% to 46% of patients and excluded in 34% to 42%.8,23 Monitoring was particularly useful for detection of intermittent bradycardia, which is frequently missed at electrophysiology study.24 Because of the relative infrequency of symptoms, short-term monitoring and electrophysiological testing have a low yield for detection of bradycardia.24–27 The present study suggests that prolonged monitoring has become the investigative tool of choice when this diagnosis is suspected.

When sinus rhythm was recorded during recurrent symptoms, an arrhythmia was excluded. A monitoring strategy may rule out an arrhythmia without necessarily providing a diagnosis. Exclusion of an arrhythmia often alleviates the concerns of both the patient and physician regarding the potential for life-threatening arrhythmias and allows the focus of further investigations to shift to other areas. Many of these patients are likely to have neurally mediated syncope. In the present study, clues to the diagnosis were obtained during symptom-rhythm correlation and repeat clinical assessment. Neurally mediated syncope was diagnosed in the context of a typical cardioinhibitory response in 2 patients, with heart rate fluctuation and symptoms in the third. Seizure activity was fortuitously detected as artifact during sinus rhythm in 2 patients. This finding directed the investigations and treatment and has previously been recognized.12 Although the current device monitors cardiac rhythm, expansion of monitoring capabilities to include other physiological parameters, including blood pressure and brain electrical function, would enhance the ability to correlate spontaneous symptoms with physiological status.

A monitoring strategy was more likely to provide a diagnosis as both a primary and a crossover approach. The latter is not surprising, given the proven efficacy of this approach in recurrent unexplained syncope with negative tilt and electrophysiological testing.2 The higher yield of the monitoring strategy compared with conventional testing suggests that a monitoring strategy with an ILR should be considered at an earlier stage in the diagnostic approach to patients with unexplained syncope.

Limitations of the Study
Diagnostic performance of investigative approaches is clearly influenced by patient selection. The low yield of the conventional approach probably reflects the population studied. We focused on patients with unexplained syncope after clinical assessment, excluding patients with a high pretest probability of neurally mediated syncope or ventricular arrhythmia. This selection bias led to assessment in an older population without serious structural heart disease. The role of a monitoring strategy in other patient groups is unproven. A more aggressive tilt protocol would have been more sensitive but would have reduced specificity. We used a widely accepted protocol with balanced sensitivity and specificity based on experience in our own tilt laboratory.25 Clearly, an implanted loop recorder is not meant to supplant tilt testing but rather to be considered earlier in the diagnostic cascade of patients with unexplained syncope. Less invasive testing is often preferable to both the patient and physician, even if diagnostic yield may be lower. Finally, patients were recruited at a single center in the present study. Nonetheless, the diagnostic yield of the prolonged monitoring strategy was comparable to that of larger studies from multiple centers.8

Conclusions
In patients with recurrent unexplained syncope without major structural heart disease, bradyarrhythmias are a frequent cause of syncope. In these patients, consideration should be given to earlier implementation of prolonged monitoring.

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