Use of an Extended Monitoring Strategy in Patients With Problematic Syncope

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Background—The conventional investigation of patients who present with syncope involves short-term ECG monitoring or provocative testing with head-up tilt and electrophysiological testing. A symptom-rhythm correlation is often difficult to obtain during spontaneous syncope because of its sporadic, infrequent, and unpredictable nature.

Methods and Results—We used a prolonged monitoring strategy to determine the cause of syncope in 85 patients (age, 59±18 years; 44 men) with recurrent undiagnosed syncope with an implantable loop recorder capable of cardiac monitoring for up to 18 months. During a mean of 10.5±4.0 months of follow-up, symptoms recurred in 58 patients (68%) 71±79 days (2.3±2.6 months) after implantable loop recorder insertion. An arrhythmia was detected in 42% of patients who recorded a rhythm during recurrent symptoms, with bradycardia present in 18 and tachycardia in 3. Five of the 18 bradycardic patients and 2 additional sinus rhythm patients received a clinical diagnosis of neurally mediated syncope. Patients who experienced presyncope were much less likely to record an arrhythmia during symptoms compared with recurrence of syncope (24% versus 70%, \( P = 0.0005 \)). There were no adverse events associated with recurrent symptoms, and there were no sudden deaths. Inability to freeze after an event occurred in 8 patients, and pocket infection occurred in 3.

Conclusions—The strategy of prolonged monitoring is effective and safe in patients with problematic syncope.

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Key Words: syncope ■ arrhythmia ■ diagnosis

Current investigation of patients who present with syncope involves short-term ECG monitoring or provocative testing with head-up tilt and electrophysiological testing.\(^1\)\(^-\)\(^4\) The diagnostic yield of Holter monitoring in syncope is disappointing,\(^5\)\(^-\)\(^7\) and provocative test results may be negative or difficult to interpret.\(^8\)\(^,\)\(^9\) A prolonged monitoring strategy has previously been difficult to use because of waning patient compliance and motivation with external loop recorder technology and the relatively short memory capabilities of these devices.\(^7\)\(^-\)\(^10\)\(^,\)\(^12\) Prolonged monitoring is also reliant on the spontaneous recurrence of symptoms, with attendant risk of injury, concern regarding life-threatening arrhythmias, and ongoing diagnostic uncertainty.

A symptom-rhythm correlation is often difficult to obtain during spontaneous episodes because of the sporadic, infrequent, and unpredictable nature of syncope. Despite a wide array of diagnostic tools, the cause of syncope is not determined after initial investigations in 38% to 47% of patients.\(^6\)\(^,\)\(^13\)\(^,\)\(^14\) Even after referral for tilt-table and electrophysiological testing, 10% to 26% of patients will remain undiagnosed.\(^2\)\(^,\)\(^15\)\(^,\)\(^16\)

Recent advances in loop recorder technology have permitted a longer duration of external ECG monitoring than conventional Holter monitoring, improving the overall diagnostic yield.\(^7\)\(^,\)\(^10\)\(^-\)\(^12\) We used a new insertable loop recorder (ILR) that can provide monitoring for 14 months to assess the utility and safety of a prolonged monitoring strategy in a multicenter study of 85 syncopal patients without a diagnosis after initial assessment.

Methods

Patient Population

Patients with undiagnosed syncope after initial assessment that included a history, physical examination, ECG, and at least 24 hours of ambulatory or in-hospital monitoring were approached to participate in a study using an ILR (Reveal ILR, Medtronic USA Inc) to determine the cardiac rhythm during spontaneous syncope. Patients were eligible for the study if they had had 2 syncopal episodes within the previous 12 months or a single episode with a history of presyncope as well. Patients were excluded if they were unlikely to survive 1 year, were unable to give informed consent, had a previously implanted programmable medical device, were pregnant, or were women of childbearing potential not on a reliable form of contraception. Eighty-five patients with unexplained syncope underwent insertion of the ILR (Table 1). The mean number of syncopal episodes in the previous 12 months was 5.1±5.5 (median, 3). The majority of patients had suffered from recurrent syncope for >2
TABLE 1. Clinical Characteristics of the 85 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±18</td>
</tr>
<tr>
<td>Concomitant cardiovascular disease,*</td>
<td>% 62</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>52</td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>No. of syncope spells in previous 12 months</td>
<td>5.1±5.5</td>
</tr>
<tr>
<td>Duration of symptoms, y</td>
<td>5.5±8.9</td>
</tr>
<tr>
<td>Symptoms &gt;2 years, %</td>
<td>71</td>
</tr>
<tr>
<td>Symptoms &gt;4 years, %</td>
<td>37</td>
</tr>
<tr>
<td>Investigations before enrollment</td>
<td></td>
</tr>
<tr>
<td>Holter monitor, %</td>
<td>100</td>
</tr>
<tr>
<td>Echocardiography, %</td>
<td>70</td>
</tr>
<tr>
<td>Head-up tilt test, %</td>
<td>49</td>
</tr>
<tr>
<td>Electrophysiological study, %</td>
<td>43</td>
</tr>
<tr>
<td>External loop recorder, %</td>
<td>24</td>
</tr>
</tbody>
</table>

*Includes angina, prior myocardial infarction, previous cardiac arrest, cardiomyopathy, cardiomegaly, congestive heart failure, and valvular, congenital, or pericardial heart disease.

years. The study was approved by the institutional review board or medical ethics committee at each study center.

Previous Investigations

Testing before patient enrollment in the study was performed at the discretion of the investigator (Table 1). All patients underwent clinical assessment, including ambulatory or in-hospital monitoring. Of the 85 patients, 21 had been referred to an internist and 73 had been referred to another cardiologist before assessment by the study investigator. Most patients had several investigations for syncope before ILR insertion, the most common of which were echocardiography, head-up tilt testing, and electrophysiological testing. One patient had experienced a previous cardiac arrest and underwent extensive investigation, including electrophysiological testing, before enrollment in the study.

Device

The ILR is a 61×19×8-mm recording device with 2 sensing bipoles 37 mm apart within its shell. It weighs 17 g and has a volume of 8 cm³, slightly smaller than a standard VVI pacemaker. The recorded ECG signal is stored in a circular buffer capable of retaining 21 minutes of uncompressed signal or 42 minutes of compressed signal in 1 or 3 divided parts. The memory buffer is frozen with a hand-held activator provided to the patient at the time of device implantation. The resultant programming can store a single episode of 21 minutes (20 minutes before and 1 minute after “freeze”), a 42-minute compressed episode (40 minutes before, 2 minutes after), three 7-minute episodes (6 minutes before, 1 minute after), or three 14-minute compressed episodes (12 minutes before, 2 minutes after). The episodes are then downloaded after interrogation with a standard pacemaker programmer (Medtronic 9790C).

Investigators performed device implantation in an operating room, cardiac catheterization laboratory, electrophysiology laboratory, or specialized procedure room at their discretion. The site of the implant was generally in the left infraclavicular region but was determined in each circumstance by patient and physician preference. Use of prophylactic antibiotics was left to the discretion of the implanting physician. After the skin was infiltrated with local anesthesia, a 2-cm incision was made. A pocket was fashioned, and the device was inserted and anchored with a nonabsorbable suture. The skin was closed with absorbable sutures, and a satisfactory R-wave signal was verified with the programming head applied over the implanted device. The patient, along with a spouse, family member, or friend, was instructed in the use of the activator at the time of implantation. Patients were instructed to activate the device in the event of syncope or presyncope. Follow-up was performed after each event. The device remained implanted until syncope or presyncope recurred unless the patient or investigator chose to remove it sooner. Devices were removed after 18 months of follow-up or at end of battery life.

Analysis

Continuous variables were compared by Student’s t tests, and categorical variables were compared by a χ² test. A value of P<0.05 was considered significant.

Results

Recurrent Symptoms

During a mean of 10.5±4.0 months of follow-up, symptoms recurred in 58 patients (68%) 71±79 days (2.3±2.6 months) after ILR insertion (median, 51 days, or 1.7 months). One patient had recurrence within a week of the implantation, and 3 patients had recurrence within the first month. Forty-nine of 85 patients (58%) had recurrence of symptoms within 6 months of implantation. Follow-up was >9 months in 68 of 85 patients. Failure to appropriately “freeze” after symptoms occurred 24 times in 14 patients. No instance was attributed to device failure. Six of these patients had an appropriate freeze after spontaneous symptoms on a different occasion. A total of 128 events were frozen by the remaining 50 patients during the course of follow-up. The remaining 27 patients have not had recurrence and continue to be followed up.

Symptom-Rhythm Correlation

An arrhythmia was detected in 21 of the 50 patients (42%) who recorded a rhythm during recurrent symptoms, with bradycardia being the most frequent (Figure 1). Of the 18 patients with bradycardia (heart rate <50 bpm), 12 underwent device removal and pacemaker implantation. Five of the 18 patients had heart rate slowing, which the investigator interpreted as the cardioinhibitory component of neurally mediated syncope. Two additional patients had relative slowing, with a heart rate >50 bpm, and also received a clinical diagnosis of neurally mediated syncope (Figure 2). Three patients had tachyarrhythmias associated with recurrent symptoms: sustained supraventricular tachycardia in 2 patients, who subsequently underwent catheter ablation, and atrial flutter with a rapid ventricular response in 1 patient, who received pharmacological therapy. The remaining 29 patients had sinus rhythm during symptomatic recurrence and continue to be followed up. Devices remained implanted in these patients to monitor subsequent episodes.
Syncope Versus Presyncope

Of the 50 patients with a symptom-rhythm correlation, 13 had syncope, 10 had recurrence of syncope and presyncope, and 27 had presyncope alone. When patients experienced presyncope, they were much less likely to record an arrhythmia during symptoms compared with recurrence of syncope (24% versus 70%, \( P=0.0005 \), Figure 3). When those patients with a clinical diagnosis of neurally mediated syncope (n=4) or presyncope (n=4) were excluded, the difference remained significant (24% versus 63%, \( P=0.006 \)). Arrhythmias were seen in 9 of the 13 patients (69%) who had recurrence of syncope alone (without other presyncopal events), with bradycardia recorded in all 9 patients during syncope. In the 10 patients with both syncope and presyncope, syncope was associated with an arrhythmia in 7 (bradycardia in 5, tachycardia in 2), whereas presyncope documented an arrhythmia in only 4 patients (bradycardia in 2, tachycardia in 2). The 3 patients with an arrhythmia during presyncope had the same arrhythmia during syncope.

Device

The majority of devices were implanted outside of an operating room setting (Table 2). The device was inserted in the left pectoral region near a traditional pacemaker implant site in 64% of patients. Of the remaining 31 devices, 27 were implanted in the left inframammary region. The mean implant voltage was 481±279 \( \mu \text{V} \) for all 85 patients. An adequate electrogram was obtained in all 85 patients (range, 58 to 1300 \( \mu \text{V} \)). The signal-to-noise ratio was 19:1. P waves were seen in 37% of vertical implants, compared with 14% of horizontal ones. The sensed amplitude was 831±343 \( \mu \text{V} \) at the single center at which systematic surface mapping was performed before implantation to optimize the sensed signal amplitude.

Two patients who did not receive prophylactic antibiotics developed local infection requiring treatment with oral antibiotics after device removal. A second device was reimplanted in another site in 1 of these patients. A third patient had persistent pain at a left inframammary implant site, which resolved when the device was moved to the left pectoral region. A fourth patient developed local erosion with infection 13 weeks after implantation. The device was explanted without incident. No patient requested removal of the device before recurrence of symptoms. The devices were removed at the end of follow-up without complications.

Outcome

During the study, 1 patient died of myocardial infarction that was not complicated by arrhythmias. A second patient died of cancer of the lung, and a third patient suffered a cerebrovascular accident and withdrew from the study.

Discussion

The cause of syncope can be difficult to determine if it is not obvious after initial assessment.\(^6,13,14\) Despite the good prognosis of patients whose investigations are negative, syncope may recur, with attendant morbidity and even mortality.\(^2,8,17–21\) The current approach to the syncopal patient involves a mixture of passive monitoring, which samples a relatively small time frame, and provocative testing aimed at actively reproducing the clinical situation. Both tilt-table and electrophysiological testing are negative in as many as 70% of cases\(^8,9\) and represent an artificial environment, making interpretation of results particularly difficult. The reference standard for establishing a diagnosis is the recording of physiological parameters during a clinical episode. This obviates the interpretation difficulties of extrapolating the results of provocative testing to the clinical situation.

In a previous pilot study of 24 patients with syncope, a prototype implantable loop recorder established the cardiac rhythm in all 21 patients who had recurrent syncope after the device was implanted.\(^15\) This population represented a difficult subgroup with refractory but infrequent syncope that was not diagnosed after extensive testing. The present study examined the utility of the ILR in a multicenter study. The patient population was selected to be more representative of those referred to cardiologists or electrophysiologists for investigation of syncope after a workup that varied according to physician preference.

The strategy of prolonged monitoring was successful in establishing a symptom-rhythm correlation in 86% of the 58 patients who had recurrence during the follow-up period. The
rhythm profile of patients during recurrent syncope reflected
an arrhythmic cause in 42% of patients, in keeping with the
findings of the pilot study (48%). In the remaining patients,
an arrhythmia was eliminated as a potential cause of symp-
toms, alleviating concerns of a life-threatening arrhythmia.

The absence of sudden death or significant morbidity
suggests that this observational approach was safe in the
population studied and did not place patients at risk during
spontaneous recurrence. This is of particular interest given
the prevalence of significant structural heart disease, the
major determinant of prognosis in syncopal patients.3 Sixty-
two percent of patients had some structural heart disease, with
19% having documented coronary artery disease, previous
cardiac arrest, or left ventricular dysfunction. Investigator
selection and preceding negative investigations, including
electrophysiological testing in some patients, may have
screened out those patients at higher risk of life-threatening
arrhythmias. This does not necessarily imply that a monitor-
ing strategy is safe in all patients. For example, patients with
poor left ventricular function and inducible ventricular
tachycardia at electrophysiological testing have been shown
to receive appropriate shocks when managed with an implan-
table defibrillator.22 A proactive approach using electrophys-
iological testing in this population seems reasonable.

Symptoms did not recur in 32% of patients over 10 months
of follow-up. This spontaneous resolution is in keeping with
other series, which have noted a 57% to 85% resolution
during 10 to 40 months of follow-up after negative initial
investigations.1,2,21,23,24 This finding may relate to the spon-
taneous periodicity of syncope, a self-limited cause, or a
screening effect of the completed investigations, which have
identified the causes of syncope that are most likely to recur.

The occurrence of presyncope is often clinically inter-
preted as “imminent” syncope. It is tempting to use presyn-
cope as a surrogate for syncope. The predictive value of
presyncope in establishing an arrhythmic cause for symptoms
was low. Excluding patients with a diagnosis of neurally
mediated syncope, only 24% of patients with presyncope
were found to have an arrhythmia (versus 63% for syncope).
The majority of patients (76%) reporting presyncope were in
sinus rhythm. In those patients with both presyncope and
syncpe, presyncope was misleading in 3 of the 6 patients
with sinus rhythm during presyncope who subsequently had
an arrhythmia documented in conjunction with frank syn-
cpe. Others have similarly reported a low yield for external
monitoring in patients with presyncope,25 although data on
the relationship between presyncope and syncope in the same
patients remain scant.

Individual investigators each implanted 1 to 4 devices,
with the exception of a single site, at which 11 devices
were implanted. Despite the absence of a learning period
with respect to implantation technique, the relatively low
complication rate suggests that the procedure is readily
adopted by operators experienced with implantable de-
vices. The unexpected infection rate may reflect the need
for routine antibiotic prophylaxis, which was not required
in the study. Programming and interrogation were per-
formed with a pacemaker programmer, which is accessible
to most pacing centers. Patient-related difficulties with
freezing after events occurred in 16% of patients. Of these
patients, ≈50% subsequently froze appropriately. This
problem may be minimized in the future by development of
autodetection functions, improved patient education,
and expanded memory capacity. Similar difficulties with
freezing have been reported in 32% of patients using an
external loop recorder,7,10 in whom device malfunction,
patient noncompliance, or inability to activate the recorder
was responsible for the lack of success. External devices
suffer from insufficient memory for many patients who are
unable to activate the device within 4 to 6 minutes of
syncope, as well as waning patient compliance with
external electrodes in the absence of a diagnosis.

Limitations
The population under study represents a spectrum of individ-
uals referred to a cardiologist or electrophysiologist for
evaluation. Although they may not represent a primary
syncpe population, they served to test the utility of a
prolonged monitoring strategy in patients with recurrent
syncpe. Second, obtaining a symptom-rhythm correlation
does not necessarily lead to a diagnosis. Nonetheless, exclu-
sion of 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 (if necessary) to shift to other areas. Finally,
a small proportion of patients were unable to activate the
device after a spontaneous event. Future iterations should
include programmable automatic detection algorithms and
longer memory loops. In addition, monitoring of other phys-
iological parameters, such as blood pressure and oxygen
saturation, is a feasible goal. Current development suggests
that device size may decrease by 30% to 60%, facilitating
implantation in an office setting by operators with less
surgical experience.

Conclusions
The strategy of prolonged monitoring is effective in estab-
lishing a symptom-rhythm correlation in the majority of
patients with problematic syncope. It obviates the need for
difficult interpretation of provocative testing. Presyncope is
much less likely to be associated with an arrhythmia than
syncpe and did not prove to be an accurate surrogate for
syncpe in establishing a diagnosis.

Appendix

Investigators
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Acknowledgments

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