Clinical Experience of Two Israeli Medical Centers with the Implantable Loop Recorder in Patients with Syncope: From Diagnosis to Treatment

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ABSTRACT: Background: The implantable loop recorder (ILR) is an important tool for the evaluation of unexplained syncope, particularly in cases of rarely occurring arrhythmia. Objectives: To review the clinical experience of two Israeli medical centers with the ILR. Methods: We reviewed the medical records of patients with unexplained syncope evaluated with the ILR at Rabin Medical Center (2006–2010) and Wolfson Medical Center (2000–2009). Results: The study group included 75 patients (44 males) followed for 11.9 ± 9.5 months after ILR implantation. Patients’ mean age was 64 ± 20 years. The ILR identified an arrhythmic mechanism of syncope in 20 patients (17 bradyarrhythmias, 3 tachyarrhythmias) and excluded arrhythmias in 12, for a diagnostic yield of 42.7%. It was not diagnostic in 17 patients (22.7%) at the time of explant; 26 patients (34.7%) were still in follow-up. In two patients ILR results that were initially negative were reversed by later ILR tracings. The patients with bradyarrhythmias included 9 of 16 (56.3%) with surface electrocardiogram conduction disturbances and 2 of 12 (16.7%) with negative findings on carotid sinus massage. All bradyarrhythmic patients received pacemakers; the seven patients for whom post-intervention data were available had no or mild symptoms. Conclusions: The ILR has a high diagnostic yield. Pre-ILR findings correlating with the ILR results are conduction disturbances (positive predictor of arrhythmia) and negative carotid sinus massage results (negative predictor of arrhythmia). Proper patient instruction is necessary to obtain accurate results. Caution is advised when excluding an arrhythmia on the basis of ILR tracings, and long-term follow-up is warranted.

KEY WORDS: syncope, implantable loop recorder (ILR), arrhythmias, pacemakers, conduction disturbances

The cause of syncope is often difficult to determine, even after comprehensive investigation. Suspected arrhythmia may be confirmed by a Holter monitor worn for 24–48 hours or an external loop recorder worn for 14–28 days. However, if the syncope occurs infrequently, the physician needs a tool that can monitor and record the heart rhythm over long periods, up to years. The implantable loop recorder was designed for this purpose [1-3]. The ILR has a diagnostic yield of approximately 60%, with considerable variation among studies [4,5]. It has been shown to be not only efficacious, but also more cost-effective than conventional diagnostic studies (including external loop recorders, tilt-table test, and electrophysiologic study) [6]. The European Society of Cardiology guidelines for the diagnosis and management of syncope included the ILR in the class I recommendations for the evaluation of recurrent unexplained syncope, either in the early phase in non-high risk patients or after comprehensive workup in high risk patients [7,8]. The usefulness of the ILR in this setting was reconfirmed on a large scale in a recent prospective observational study (PICTURE) conducted in Europe and Israel [9]. The aim of the present study was to review the clinical experience of two Israeli medical centers with the ILR. Since abundant information on the efficacy and diagnostic yield of the ILR is already available, we focused on pre-implantation factors that may be predictive of the ILR results and on the clinical response to ILR-guided therapeutic interventions.

PATIENTS AND METHODS

The study group consisted of 75 patients who were evaluated with the ILR: 71 with the Medtronic Reveal® (Minneapolis, MN, USA) and 4 with the St. Jude Confirmer® (St. Paul, MN), at Rabin Medical Center (2006–2010) or Wolfson Medical Center (2000–2009), both in central Israel. Their medical records were reviewed for baseline clinical characteristics, features of the syncopal episodes, diagnostic workup prior
to ILR implantation, diagnosis derived from the ILR trac-
ings, resulting intervention, and clinical response to the ILR-
guided intervention.

ILR findings were considered positive for arrhythmias when
the rhythm disorders identified were severe enough to result in
hemodynamic instability, manifesting as syncope. The findings
were considered negative (excluding an arrhythmic etiology for
the syncope) if patient-triggered events did not correlate with
a concurrent finding of arrhythmia. ILR studies were consid-
ered diagnostic if they identified or excluded an arrhythmia
as the cause of the syncope, and non-diagnostic if they were
not diagnostic at the time of explant or if the patient was still
in follow-up. The diagnostic yield was defined as the ratio of
diagnostic ILR studies to all ILR studies. Follow-up time was
calculated from implantation of the loop recorder to its explant
(due to battery depletion or permanent pacemaker implanta-
tion) or until data collection for the present study (in patients
still being followed). The study protocol was approved by the
institutional review board of Rabin Medical Center.

The data were summarized with descriptive statistics. Differ-
ences in diagnostic yield between the two medical
centers were assessed by chi-square test.

RESULTS

PATIENT CHARACTERISTICS AND DIAGNOSTIC YIELD OF THE ILR

The study sample comprised 75 patients with a mean (± SD)
age of 64 ± 20 years. Patients were followed for a mean dura-
tion of 11.9 ± 9.5 months from ILR implantation [Table 1]. The
overall diagnostic yield of the ILR was 42.7% [Figure 1]. The
difference in diagnostic yield between the two centers was
statistically significant (52% at Rabin Medical Center, 24% at
Wolfson Medical Center, P = 0.02). Tracings from two patients
are shown in Figure 2.

MAIN ILR RESULTS BY INDICATION FOR ILR EVALUATION

The most common indication for ILR evaluation was syn-
cope (66 patients). Other indications were pre-syncope (four
patients) and recurrent falls (two patients). In three patients,
the ILR was used off-label for follow-up of dual atrioven-
tricular nodal physiology, status/post AV nodal ablation, or
a long QT interval (one patient each).

Arrhythmia was diagnosed in 20 patients (26.7%) on
the basis of the ILR data: bradyarrhythmia in 17 (22.7%; 15
with syncope, 1 with pre-syncope, and 1 with dual AV nodal
physiology) and tachyarrhythmia in 3 (4.0%; 1 with syncope,
2 with pre-syncope). The bradyarrhythmias were typically
“pauses” (absence of QRS complexes for 3 seconds or longer);
most were due to AV block and some to sinus node dysfunc-
tion. The tachyarrhythmias were all supraventricular.

The ILR tracings excluded an arrhythmic etiology of the

Table 1. Main clinical characteristics and ILR findings in 75 patients with unexplained
syncope, by medical center and combined

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Rabin Medical Center</th>
<th>Wolfson Medical Center</th>
<th>Pooled data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>25</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>Age (yrs) mean ± SD (range)</td>
<td>69 ± 16 (27–96)</td>
<td>53 ± 24 (17–90)</td>
<td>64 ± 20 (17–96)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Follow-up (mos), mean ± SD</td>
<td>10.0 ± 8.1</td>
<td>15.7 ± 11.0</td>
<td>11.9 ± 9.5</td>
</tr>
<tr>
<td>ILR findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis obtained, n</td>
<td>26 (52%)*</td>
<td>6 (24%)*</td>
<td>32 (42.7%)*</td>
</tr>
<tr>
<td>Arrhythmia detected, n</td>
<td>16</td>
<td>4</td>
<td>20 (26.7%)*</td>
</tr>
<tr>
<td>Bradycardia, n</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Tachycardia, n</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Arrhythmia excluded, n</td>
<td>10</td>
<td>2</td>
<td>12 (16%)*</td>
</tr>
<tr>
<td>No diagnosis, n</td>
<td>6</td>
<td>11</td>
<td>17 (22.7%)*</td>
</tr>
<tr>
<td>Ongoing follow-up, n</td>
<td>18</td>
<td>8</td>
<td>26 (34.7%)*</td>
</tr>
</tbody>
</table>

* P = 0.02

Figure 1. Diagnostic yield of ILR after a mean period of 11.9 months
in 75 patients referred for unexplained syncope

Figure 2. ILR tracings in Patient # 41, with paroxysmal atrioventricular block lasting
more than 6 sec, Patient # 22, with supraventricular tachycardia at
cycle length of 350 msec (rate 170 beats/min)
syncope in 12 patients (16%). In another two patients, the ILR excluded an arrhythmia early in the course of follow-up, but these results were reversed in later tracings in which a significant arrhythmia was detected. Both these patients had bradyarrhythmia.

**ILR-GUIDED INTERVENTION AND ILR EXPLANT**

Patients with bradyarrhythmia were treated by implantation of a permanent pacemaker, and patients with tachyarrhythmia were referred for ablation. The mean (± SD) interval from ILR implantation to pacemaker implantation was 4.0 ± 4.3 months. The seven patients for whom clinical post-intervention follow-up information was available at the time of data collection (mean follow-up time 4.8 ± 7.5 months) were either asymptomatic or had only mild symptoms.

The mean (± SD) time from ILR implantation to ILR explant was 5.4 ± 7.1 months for patients with diagnostic findings and 9.9 ± 10.4 months for all patients, including those with non-diagnostic findings at the time of explant.

**ASSOCIATION OF PATIENT AND SYNCOPAL CHARACTERISTICS WITH DIAGNOSIS OF ARRHYTHMIA**

There was no association of patient demographic characteristics (age, gender) with the diagnosis of arrhythmia by the ILR. Among the 18 patients who had syncopal episodes with features suggestive of an arrhythmic etiology (injury or palpitations), 3 (16.7%) were diagnosed with an arrhythmia [Table 2]; whereas among the 14 patients with features suggestive of a non-arrhythmic etiology (warning symptoms or posture related episodes), 6 (42.9%) were eventually diagnosed with arrhythmia [Table 2]. Interestingly, palpitations were associated with a diagnosis of arrhythmia (bradyarrhythmia) in only one patient.

Data on medications were available for 25 patients of whom 17 (68%) were treated with beta-blockers. Four of the 25 patients had bradyarrhythmia requiring pacemaker implantation; 3 of the 4 (75%) were receiving beta-blockers.

Three patients were treated with anti-arrhythmic drugs; none had clinically significant tachyarrhythmia. One of the three who was concomitantly treated with a beta-blocker had clinically significant bradyarrhythmia.

**COMPARISON OF PRE-ILR WORKUP AND ILR RESULTS**

Most patients underwent basic cardiac workup including an electrocardiogram (100%), echocardiogram (90%), and Holter study (80%). Eighty-five percent of patients also had up to four additional tests from the core batteries of cardiac tests (tilt-table test, carotid sinus massage, electrophysiologic study) and neurologic tests (brain computed tomography, carotid artery Doppler study, electroencephalography). The average number of total additional tests was 2.18 per patient: 0.72 cardiac tests per patient and 1.46 neurologic tests (mainly brain CT) per patient.

The results of most studies performed prior to ILR implantation (e.g., Holter monitor, tilt-table test, electrophysiologic study) were poor predictors of the final diagnosis based on the ILR tracings [Table 2]. Those with the highest yield were the surface ECG and carotid sinus massage. Among the 16 patients with ECG evidence of a conduction disturbance (long PR interval or bundle branch block), 10 were found to have an arrhythmia, mainly bradyarrhythmia (9 patients). Among the 12 patients with negative results on carotid sinus massage, 10 were not documented as having an arrhythmia; the sole patient with positive findings on carotid sinus massage had bradyarrhythmia (carotid sinus hypersensitivity) according to the ILR tracings.

Seventy-five percent of patients had normal cardiac structure and function on the echocardiogram. None had more than a moderate degree of left ventricular dysfunction, and there was no association between left ventricular function and an ILR diagnosis of arrhythmia. No aortic stenosis or other hemodynamically significant valvular disease was noted. Hypertrophy up to 15 mm was found in three patients, none with outflow tract obstruction; one was later diagnosed with bradyarrhythmia. The presence of coronary artery disease by history, non-invasive study or angiography was not associated with the detection of an arrhythmia.

The results of one electrophysiologic study were inconclusive (HV interval 64 msec); the patient was later diagnosed with a bradyarrhythmia (paroxysmal AV block). Seventeen of the 24 hour Holter studies were inconclusive as well, demonstrating pauses shorter than 3 seconds, bradycardia, atrial fibrillation, or non-sustained ventricular tachycardia. They were not more predictive of arrhythmia than normal Holter studies.
Among the patients who underwent neurological workup and were found to have arrhythmia by ILR, all but two were characterized by an absence of a history of neurological disease and normal findings on electroencephalography, brain CT and carotid duplex study. The two exceptions had a history of stroke, which was not considered clinically relevant to the syncope. Among the patients in whom no arrhythmia was detected, 12 had a history of neurovascular disease, 6 had abnormalities on brain CT scan (which was normal in 24), 1 had an abnormal carotid artery Doppler study (normal in 23), and 1 had an abnormality on the electroencephalogram (normal in 17).

SAFETY
Adverse events after ILR implantation occurred in two patients. They included a local pocket infection in one patient (which appeared after a significant clinical arrhythmia was already recorded) and local pain. The ILR was explanted in both. The pain in the second patient did not resolve after explant, and it was retrospectively assumed to have been unrelated to the device.

DISCUSSION
We present the experience of two Israeli medical centers with the ILR over several years in 75 patients, most of whom were referred for investigation of unexplained syncope. In 42.7% of patients the ILR tracings either identified an arrhythmia that was considered responsible for the syncope or excluded arrhythmia. This rate is well within the range of diagnostic yield reported in previous studies [4,5]. The majority of arrhythmias were bradyarrhythmias requiring implantation of a permanent pacemaker. The average interval from ILR implantation to the main intervention (pacemaker implantation) was 4 months, which is long enough to justify the use of an ILR.

Unexpectedly, there was a significant difference in the diagnostic yield of the ILR between the two centers (52% vs. 24%, P = 0.02), despite their similar practice protocols. Several factors may cause variations in diagnostic yield. First, differences in clinical approach may affect patient selection for ILR implantation. In patients with borderline findings on cardiac workup, some clinicians favor the more conservative approach of ILR implantation, whereas others are more proactive and opt for a pacemaker. With the referral of more borderline patients for an ILR, we may expect a higher rate of detected arrhythmias and a lower rate of excluded arrhythmias. Second, the exclusion of arrhythmia based on ILR studies relies heavily on proper patient education in the use of the device during clinically relevant events and keeping a corresponding log book. Third, the cutoff used to define ILR results as positive (i.e., sufficiently abnormal to account for syncope) may differ among clinicians. According to our data, the higher diagnostic yield in one medical center was related less to a higher rate of arrhythmia detection than to a higher rate of arrhythmia exclusion. This may suggest that patient cooperation accounts for most of the differences among centers relative to patient selection and is the more important factor in obtaining accurate results.

In our study, beta-blockers were being used by 68% of all patients and by 75% of the patients with bradyarrhythmia requiring a pacemaker. The similarity of these rates suggests that the bradyarrhythmias could not be attributed to the beta-blocker therapy.

We extracted information on clinical features and diagnostic studies prior to ILR in order to search for factors that might help clinicians in decision making. We found that the ILR results were not associated with patient age or gender or with the clinical characteristics of the syncopal episodes that are generally considered suggestive of arrhythmia or of a non-arrhythmic mechanism. Indeed, not a single patient with palpitations was found by the ILR to have a tachyarrhythmia.

The diagnostic workup included various tests. Brain CT was commonly performed, not necessarily to identify the reason for the syncope but to rule out intracranial bleeding resulting from the syncope. Conduction abnormalities on the surface electrocardiogram had a fairly high positive predictive value (56.3%) for bradyarrhythmia. This high rate is consistent with the ISSUE study where the presence of bundle branch block reliably predicted the diagnosis of bradyarrhythmia (mainly paroxysmal high degree atrioventricular block), even in patients with no conduction disorders on electrophysiologic study [10]. Carotid sinus massage had high negative predictive value (83.3%). The actual negative predictive value, however, may be lower, because we defined cases in which arrhythmia was not detected as negative and not only cases in which arrhythmia was excluded. Nevertheless, this approximation is reasonable, because when an arrhythmia was detected, it occurred early – within the first 4 months of follow-up.

Holter studies demonstrating arrhythmia that was not clearly responsible for the syncope were defined as inconclusive. There was no difference in the association of pre-ILR normal (negative) and inconclusive Holter studies with arrhythmias detected by ILR, probably because any patient with a clearly abnormal Holter study suggestive of arrhythmia would have undergone intervention such as pacemaker implantation, obviating the need for an ILR.

Follow-up information was available for only seven of the patients who underwent ILR-guided pacemaker implantation. None had a significant recurrence of syncope. Although the follow-up period was short (4.8 months), it was longer than the time needed to obtain the diagnosis and implant a pacemaker (4.0 months). Therefore, the absence of a recurrence during this time period is encouraging.

A troubling finding was the apparent early ILR-based exclusion of an arrhythmic mechanism for the syncope in two patients, who were eventually diagnosed with arrhythmia by
CONCLUSIONS
In our experience, ILR is a safe and effective instrument for confirming and excluding arrhythmias in patients with unexplained syncope. For cases in which the indication for ILR implantation seems borderline, conduction abnormalities on the surface electrocardiogram and a negative finding on carotid sinus massage may assist in patient management. Educating patients on the proper use of the ILR is necessary to obtain reliable results. Our study also emphasizes the importance of long-term follow-up of ILR data, even after the diagnosis seems to be established.

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References

Capsule
Potential therapeutic target for the treatment of bone-destructive diseases and malignancies
Osteoclasts are cells that promote bone remodeling, and their hyperactivity is linked to bone-destructive disorders, including osteoporosis. Activated osteoclast precursors develop columnar actin structures, known as podosomes, which are similar to the invadopodia observed in invasive cancer cells. During osteoclast differentiation, cells can fuse with one another to create multinucleate cells. Oikawa et al. found that in osteoclastic cell cultures, a protein known to be involved in Src-induced cancer cell invadopodia production, Tks5, was also induced during osteoclastogenesis. Tyrosine phosphorylation of Tks5 by Src was required for the generation of circumferential podosomes in osteoclasts and for their fusion. Knockdown of Tks5 in osteoclasts interfered with circumferential podosome formation and cell-cell fusion, whereas polarized membrane extensions seemed to be unaffected. Tks5-expressing osteoclasts were also able to fuse with melanoma cells. Similar osteoclast-cancer cell hybrid cells have been detected in bone lesions in myeloma patients. Thus, Src-Tks5 signaling may represent a potential therapeutic target for the treatment of bone-destructive diseases and malignancies.

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A hidden connexion is stronger than an obvious one
Heraclitus (535-475 BCE), pre-Socratic Greek philosopher. From the lonely life he led, and still more from the riddling nature of his philosophy and his contempt for humankind in general, he was called “The Obscure” and the “Weeping Philosopher.” Heraclitus is famous for his insistence on ever-present change in the universe, as stated in the famous saying, “No man ever steps in the same river twice.” He believed in the unity of opposites, stating that “the path up and down are one and the same,” all existing entities being characterized by pairs of contrary properties.

While marriage is conservative, lovemaking is radical
Eric Hoffer (1902-1931), American philosopher and social writer