ABSTRACT. Implantable loop recorders (ILRs) have evolved as an elegant means of establishing a correlation between symptoms and cardiac rhythm disturbances in patients suffering from recurrent and unexplained episodes of syncope. In this review, we focus on the currently available ILRs on the US market and our institution’s experience with a novel ILR implantation technique. We also review the currently available literature regarding the use of the ILR in various clinical settings and present our own experience with the utility of the ILR in diagnosis of recurrent and unexplained syncope. In addition, we explore potential uses in other conditions.

KEYWORDS. implantable loop recorder, syncope, bradycardia, asystole, tachycardia.

Introduction

Syncope, defined as the transient loss of consciousness with spontaneous recovery, is a common clinical complaint encountered in medical practice.

Current estimates show that syncope accounts for 3.5% of all emergency room visits and between 1% and 6% of all hospital admissions.\(^1\) Approximately 30% of people will experience syncope at least once during their lifetime. There are three periods of life when syncope is more common: the first of these is seen in toddlers where pallid breath-holding and reflex anoxic seizures are the principal causes. A second peak is seen during adolescence and young adulthood, when neurocardiogenic syncope is most common. The last peak occurs in the sixth and seventh decades of life, when arrhythmias (from organic or degenerative heart disease) and orthostasis predominate.\(^1\)–\(^3\)

Although clinical history and examination combined with laboratory testing are adequate in obtaining a diagnosis in many patients, there are nonetheless some who experience infrequent cardiac arrhythmias that are elusive in nature and difficult to detect. In these individuals, prolonged ambulatory monitoring with external (and more recently implanted) electrocardiographic recorders have been of great benefit.

Using a standardized, stepwise approach to patients with recurrent syncope admitted to the emergency department has been demonstrated to significantly increase diagnostic yields.\(^5\)–\(^8\) Interestingly, these studies showed that invasive testing measures added little to establishing a diagnosis. However, despite adequate clinical evaluation combined with non-invasive testing, the diagnosis of syncope may be unclear in a significant proportion of patients. By allowing for prolonged electrocardiographic monitoring, implantable loop recorders (ILRs) can provide a more certain correlation between a patient’s symptoms and documented abnormalities in heart rhythm. By comparison, traditional
methods of monitoring, such as Holter monitor or an external loop recorder, are rarely effective in capturing these fleeting arrhythmic events, because of either inadequate duration of monitoring or failure of the patient to appropriately activate the device. By contrast, the ILR not only allows for prolonged monitoring (up to 3 years) but it also has the ability to auto-activate when an arrhythmia is present, allowing episodes to be captured independent of patient activation of the device. The storage capability of ILRs is limited (e.g., 42 minutes per recording of a single lead bipolar electrogram, which can be downloaded via radiofrequency with a special programmer). The device is usually implanted into the subcutaneous tissue in the left pectoral area under local anesthesia. As noted before, current devices have an estimated battery life of 36 months. The Reveal XT includes an algorithm for atrial tachycardia and atrial fibrillation detection based on irregularities in RR intervals. The device operates by continuously recording electrocardiograms (ECGs) in “loops”, replacing prior ECG recordings with new ECG recordings.

The implantable loop recorders

There are two ILRs available on the market. These include the Reveal DX and XT by Medtronic (Minneapolis, MN) and the Confirm by St. Jude Medical (St. Paul, MN) (Figure 1). A third device, the sleuth by Transoma (St. Paul, MN), had been available but is now no longer made. The Reveal XT and DX are small, rectangular devices that measure 62 x 19 x 8 mm and weigh 17 g. A pair of built-in sensing leads located on the shell of the device allows for recording of a single lead bipolar electrogram, which can be downloaded via radiofrequency with a special programmer. The device is usually implanted into the subcutaneous tissue in the left pectoral area under local anesthesia. As noted before, current devices have an estimated battery life of 36 months. The Reveal XT includes an algorithm for atrial tachycardia and atrial fibrillation detection based on irregularities in RR intervals.

The device operates by continuously recording electrocardiograms (ECGs) in “loops”, replacing prior ECG recordings with new ECG recordings.

Figure 1: Two types of implantable loop recorders available on the US market today: the Medtronic Reveal and the St. Jude Medical Confirm.

Clinical trials

Krahn et al. were the first to report clinical experience with the use of ILRs in 16 patients with recurrent syncope. These patients had previously undergone a series of non-invasive and invasive studies that included electrophysiological testing, exercise testing, 48 h ambulatory ECG monitoring as well as head-up right tilt-table testing (HUTT). Despite this, no etiology for their syncope could be found. After implantation of an ILR, syncope occurred in 94% of the patients, of which 60% were found to have an arrhythmic cause. In each patient found to have an arrhythmic cause for their syncope, a therapy directed at treating the rhythm disturbance proved successful in preventing further syncopal events. The device provided an 85% success rate in correlating recorded rhythm and syncopal events. In another trial, the ILR provided a correlation between symptoms and recorded rhythm in 7 of 15 patients (47%) who had recurrent unexplained syncope despite an extensive evaluation (which included HUTT and electrophysiological studies). Additional studies have shown the usefulness of the ILR in patients who have not undergone extensive pre-implant testing. Reports by Krahn et al. and Nierop et al. have shown that ILR in this setting actually lowered the likelihood of syncope by 30% to 70%. The utility of using an ILR in providing a correlation between syncope and heart rhythm disturbances has also been confirmed in both pediatric and geriatric patients.

The ISSUE investigators (International Study on Syncope of Unknown Etiology) have published several landmark trials on the utility of the ILR in syncope. The first of these trials examined the use of ILR in three different groups of patients suffering from syncope who had undergone conventional testing. In the first trial, 111 patients with unexplained syncope underwent HUTT followed by ILR implantation (regardless of the HUTT results). Syncope occurred in 34% of patients in both HUTT-positive and HUTT-negative patients, with marked bradycardia and asystole being the most common recorded arrhythmia (46% of the HUTT-positive and 62% of the HUTT-negative patients). The heart rate responses seen during HUTT did not seem to predict the ILR recorded responses, with a much higher rate of asystole than was noted during HUTT. In the second ISSUE study, ILRs were placed in 52 patients with syncope and bundle branch block who had unremarkable electrophysiological studies. Syncope occurred in 22 of the 52 patients, with 17 patients exhibiting bradycardia due to complete heart block. The third part of the ISSUE study looked at 35 patients with syncope and structural heart disease who had negative electrophysiological testing. The underlying heart disease was principally ischemic heart disease or hypertrophic cardiomyopathy with only moderate left ventricular dysfunction. Syncope occurred in 19 of the 35 patients (54%), with bradycardia observed in four, supraventricular tachycardia in five, and ventricular tachycardia in only 1 patient. There were no cases of sudden cardiac death that occurred during the
16 ± 11 months of follow-up. The results of the study supported the use of ILR monitoring in syncope patients with moderate left ventricular dysfunction secondary to heart disease when electrophysiological testing is negative.

A single center, prospective, randomized trial compared traditional testing of syncope patients to prolonged monitoring with an ILR. Sixty patients (aged 64 ± 14 years, 33 men) were randomized to “conventional” testing, which employed external loop recorders, tilt-table testing and electrophysiological study versus immediate ILR placement with prolonged monitoring lasting up to 1 year. Patients could cross over from one arm to another if they remained undiagnosed following completion of the designed arm. Patients were excluded if they had a left ventricular ejection fraction of less than 35%. A diagnosis was obtained in 14 out of 30 patients randomized to prolonged monitoring compared with 6 of the 30 undergoing conventional testing (47% versus 20%, p=0.029).

Cross-over to the other arm led to the diagnosis of 6 patients who underwent initial ILR placement as opposed to 8 of 21 patients who began with conventional testing (17% versus 38%, p=0.44). Significant bradycardia was found in 14 patients who underwent ILR monitoring as compared with 3 patients who underwent conventional testing (40% versus 8%, p=0.005). These findings clearly illustrate the limitations of the conventional diagnostic modalities employed in the diagnosis of clinical arrhythmias. In particular they suggest that tilt table has only a modest yield when used as a screening test for all patients with syncope and demonstrates that electrophysiological testing has a very limited utility in patients with preserved left ventricular function. Although the ILR had an initial higher cost, it ultimately was 20% less expensive than employing traditional diagnostic approaches.

Shortly thereafter was the ISSUE-2 trial, a prospective, multicentric, observational study that aimed to assess the efficacy of specific therapies based on ILR results in patients with suspected recurrent neurally mediated syncope. Patients were enrolled if they had experienced more than three clinically severe syncopal episodes in the previous 2 years (in the absence of significant electrocardiographic or cardiac abnormalities). Patients suffering from orthostatic hypotension and carotid sinus hypersensitivity were excluded. Following ILR implantation, patients were followed until the first documented syncopal event (phase 1). Then characteristics of the ILR recording of this episode determined the subsequent therapy that was pursued during phase 2 of the study. Out of 392 patients, the recurring rate in the first year of the phase 1 study was 33%. One hundred = three patients had an ILR-documented syncopal event and were entered into phase 2 of the trial. Of these, 53 patients received specific therapy: 46 received permanent pacemakers because of documented asystole (median duration 11.5 s), 6 underwent therapy for tachyarrhythmias (catheter ablation in 4 patients, implantable cardioverter-defibrillator placement in 1, and antiarrhythmic drug therapy in another). The remaining 50 patients did not receive any specific therapy. The recurrence rate after 1 year in the ILR-guided therapy group was 10% (a syncope burden of 0.7 ± 0.2 episodes per patient per year) compared with 41% (burden 0.8 ± 1.57 episodes per patient per year) in patients who did not receive specific therapy. This represents an 80% relative risk reduction (p=0.002) as well as a 92% reduction in syncope burden (p=0.002) in the guided therapy group. The recurrence rate in the patients who received a pacemaker was 5% (burden 0.05 ± 0.15 episodes per patient year). Severe trauma secondary to the syncopal events was received in 2% of patients and mild traumas in 4% of patients. Thus, the study demonstrated that early use of an ILR in the evaluation of recurrent unexplained syncope, with application of therapy based on ILR results, allowed for a safe and effective means of diagnosis and management. In a subsequent study by Pezawas et al, an ILR was placed in 70 patients with recurrent unexplained syncpe following a negative evaluation that included carotid sinus massage, HUTT, echocardiography, and Holter monitoring. As opposed to the ISSUE-2 trial, almost half of the patients (47%) had documented structural heart disease. The rate of syncope recurrence was similar in patients with and without structural heart disease (approximately 85%), with arrhythmias documented in nearly half of the patients in both groups. Interestingly, while the presence of a major depressive disorder was predictive of an early recurrence of the syncope, the presence of the structural heart disease was not.

Loop recorders appear to be quite useful in helping differentiate between different causes of transient loss of consciousness. In some individuals, transient periods of global cerebral hypoxia may result in not only loss of consciousness, but also convulsive activity. In some patients, these episodes of “convulsive syncope” may be quite difficult to distinguish from true seizures due to epilepsy. Indeed, some studies have reported that up to 30–42% of patients are initially thought to have convulsive syncope due to a cardiovascular cause. Zaidi et al reported that close to 45% of patients with atypical “seizure” actually had a cardiac-related cause of those events, and only through prolonged monitoring with an ILR was this discovery made.

In a study of pediatric patients with a history of structural heart disease, a family history, exercise-associated symptoms, and palpitations, the early application of an ILR gave a diagnostic yield of close to 50%. Interestingly, the implantation of the ILR has been associated with decreased frequency of syncope. This placebo-like effect has been reported with other implanted cardiac devices as well. In one study, close to 17% of patients reported a resolution of their symptoms following ILR placement. Similar findings were observed in each of the ISSUE trials. This decrease in syncope frequency following ILR placement occurs in pediatric patients as well. Yeung et al reported resolution of syncope in close to 50% of pediatric patients who underwent ILR placement.

It is noteworthy that the vast majority of studies have shown a very low incidence of life-threatening arrhythmias or significant morbidity during follow-up after ILR.
implantation; however, this may reflect some degree of selection bias. Based on these observations, the overall prognosis of unexplained syncope in the absence of left ventricular dysfunction (or following an unremarkable electrophysiological study) is quite good and confirms the safety of the long-term monitoring strategy. As noted earlier, syncope resolves spontaneously in one-third of patients undergoing long-term ILR monitoring, despite having had frequent episodes prior to implantation.\textsuperscript{12,27} This suggests that syncope can be self-limited or represents a transient physiological abnormality. In addition, some form of placebo effect is undoubtedly present. Thus the literature clearly supports the use of ILRs in patients with recurrent unexplained syncope who have had unrewarding evaluation. This represents a select group of individuals in whom continuing symptoms are likely, where correlation of symptoms is a reasonable goal. The optimal patient for prolonged monitoring with an ILR has recurrent episodes of syncope that are suspicious for an arrhythmia, namely abrupt loss of consciousness with minimal prodrome, often a relatively brief loss of consciousness with complete resolution of symptoms afterwards.\textsuperscript{28}

The University of Toledo Medical Center experience with ILRs

The Syncope and Autonomic Disorder Clinic at the University of Toledo Medical Center (UTMC) is a tertiary care center that specializes in the evaluation and management of syncope. Early in our experience with ILRs, we realized that there was no real standard methodology for ILR placement, and all too often the electrocardiographic recordings were suboptimal, with very low voltage or unacceptable degree of artifact. We studied a variety of potential placement locations and determined that utilizing a modified ECG lead II axis would yield an adequate tracing in the majority of patients without the need for preoperative mapping. We evaluated this approach in 63 patients (40 women, 23 men, mean age 38 ± 15 years) using a Medtronic Reveal DX model 9528 in 32 patients and Reveal XT model 9529 in 31 patients.\textsuperscript{29} Placement was determined by drawing an imaginary line between the substernal notch and the approximate area of the left nipple (Figure 2). An area in the inferior middle segment of the line was prepped and draped and anesthetized with a 1% zylocaine solution. A 2-cm incision was made with a #15 scalpel along the lower one-third of the aforementioned line. Meticulous blunt dissection was used to create a subcutaneous pocket into which was inserted one of the aforementioned ILR devices. A telemetry wand (in a sterile cover) was then used to determine adequate signal size and strength. Very clearly visible P and QRS complexes were seen in all 63 patients at the time of initial placement. In none of the patients was it necessary to change the location or shape of the pocket. The average P-wave amplitude was 0.12 ± 0.02 mV and the mean peak-to-peak QRS amplitude was 0.48 ± 0.15 mV. Over a mean follow-up period of 10 ± 4 months, only 2 patients were noted to have a loss of P-wave amplitude (3.2%) while 1 patient had QRS undersensing (1.6%) and 1 patient had oversensing (1.6%). We did not stitch the ILR in place, as we found that this increases the amount of artifact present; rather, the subcutaneous pocket is made purposefully small so as to hold the device in place. (This also facilitates the later removal.) We have also developed a new wound closure technique that greatly reduces infection rates and enhances the cosmetic appearance of the scar. The interested reader can find more information on this technique elsewhere.\textsuperscript{30} Since the paper was published we have used this technique in more than 300 patients with identical results. We have used the technique in pediatric patients as young as 2 years of age with identical results. With the improved data collection, we were able to analyze our database to determine which clinical symptoms best predicted recording asystole or bradycardia on an ILR. Subsequently, we found that convulsive activity, prolonged loss of consciousness (>5 min), and absence of a prodrome or aura prior to syncope were the best predictors.\textsuperscript{31} We now incorporate these into our criteria for selecting patients for ILR placement. We later found that prolonged ILR monitoring could be useful in differentiating convulsive syncope from epilepsy in select patients.\textsuperscript{32} Later, we also showed that ILR could help identify an organic cause of syncope in patients thought to have psychogenic episodes\textsuperscript{33} (Figures 3 and 4). Although infrequent, ILR implantation can result in infection, bleeding complications as well as significant pain in some patients.

Future roles and directions for ILR monitoring

Recent improvements in the recognition capabilities of ILRs have allowed them to detect and record atrial fibrillation. Monteners et al\textsuperscript{34} monitored 9 patients with frequent episodes of atrial fibrillation, 6 of whom had the device both before and after catheter ablation. Although effective in recording atrial fibrillation, up to 30% of the
Figure 3: Download from an implantable loop recorder demonstrates an episode of prolonged asystole as a cause for the patient’s recurrent syncopal episodes (thought to be psychogenic). This patient received the permanent pacemaker and the episodes of syncope resolved thereafter.
recordings were triggered by frequent premature ventricular beats. In another study, 45 patients with drug-refractory atrial fibrillation received ILRs. The recorded rate of asymptomatic episodes of atrial fibrillation was only 3% before ILR placement but climbed to 42% after ILR placement, suggesting a much higher arrhythmic burden than expected based on standard recording methods. However, there was also a huge number of “false-positive” recordings, a fact that somewhat limits the utility of the device in accessing the arrhythmia burden following interventions such as catheter ablation. Nonetheless, further refinements in atrial fibrillation detection algorithms will greatly enhance the promising new application of the ILR.

Role of ILR in patients with palpitations

In patients suffering from recurrent intermittent symptomatic palpitations, the ILR offers a potential option for their evaluation. Giada et al. reported on 50 patients with infrequent (yet quite symptomatic) palpitations who were randomized to receive conventional monitoring on ILR placement. In patients who received an ILR, a definitive diagnosis was obtained in 73%, as opposed to only 21% who underwent conventional monitoring. Although the initial costs of ILR monitoring were higher, the cost per diagnosis was lower than conventional monitoring. Further studies will be needed to better define the role of ILR monitoring in patients with unexplained symptomatic palpitations.

Additional uses

In select patients with potentially life-threatening conditions such as long QT syndrome, Brugada syndrome, and hypertrophic cardiomyopathy who do not meet the criteria for implantable cardioverter-defibrillators but are felt to be at increased risk of arrhythmic events, the ILR offers a potentially attractive means of long-term arrhythmia monitoring. The possible role of the ILR in risk stratifying these patients requires further investigations. Also an ILR can play an important role in

Figure 4: The download from an implantable loop recorder in a patient with a presumed seizure disorder. The download during one of the patient’s typical convulsive episodes revealed a very prolonged asystole followed by the onset of convulsive activity. The patient received a permanent pacemaker, and all of the convulsive episodes were subsequently abolished.
ruling out an arrhythmic etiology for a patients symptoms (37). Current studies are underway which are evaluating the utility of ILRs in detecting atrial fibrillation recurrence after catheter ablation procedures, not only to evaluate the efficacy of the procedure but to also access the need for antiarrhythmic drug therapy and anticoagulation. In addition there are additional studies underway using the ILR to determine the frequency of atrial fibrillation in patients with cryptogenic stroke.

Future directions

The ILR represents the first step of what will be an emerging field of long-term physiologic monitoring devices. The development of new sensors that could allow for determination of blood pressure or blood flow would help provide information as to the mechanism of the syncope. Continued sensor development will potentially provide commercial products capable of monitoring blood pressure, glucose, oxygen saturation, and cerebral function, as well as other physiological parameters. These exciting possibilities would provide better tools for monitoring patients with a variety of conditions in an outpatient “real-world” setting. Also the fact that current external monitoring devices are capable of being triggered by the patients, all patients should be given the option of an auto-triggering event monitor for more frequent symptoms with ILR reserved for very infrequent symptoms.

Conclusion

The ILR has emerged as a safe and effective way of monitoring patients suffering from recurrent unexplained syncope. In addition, it shows promise in monitoring atrial fibrillation and identifying the etiology of palpitations.

References


