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Implantable rhythm devices in the management of vasovagal syncope

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ABSTRACT

The ECG registration during syncope allows physicians either to confirm or exclude an arrhythmia as the mechanism of syncope. Implantable loop recorders have an over-writeable memory buffer that continuously records and deletes the patient's ECG for up to three years. Many studies have analyzed the utility of implantable loop recorders in recurrent unexplained or high risk syncope. These studies suggest that early use of the ILR provides more and earlier diagnoses and could help in selecting patients with vasovagal syncope and prolonged asystolic pauses who might benefit from pacemaker therapy. However many questions remain, including its performance in the community by physicians with a range of experience in diagnosing syncope. Furthermore there is no evidence that the use of the ILR changes outcome.

Numerous attempts have been made to determine whether patients with predominantly cardioinhibitory syncope benefit from permanent pacemakers, especially if symptoms are frequent and debilitating. While the first open label trials of pacemakers in the treatment of vasovagal syncope showed promising results, this effect has not been confirmed by blinded randomized clinical trials. More recent data seem to suggest that patients over 40 years with severe asystolic vasovagal syncope might benefit from permanent pacemakers.

Syncope is a common symptom: observational studies have shown that about 40% of people faint at least once in their lifetime (Ganzeboom et al., 2003; Ganzeboom et al., 2006; Serletis et al., 2006). In the majority of cases, syncope is neurally-mediated, but the high mortality of cardiac (Kapoor et al., 1983) and high risk syncope (Baranchuk et al., 2011) triggers large resources that are deployed in attempts to exclude high risk etiologies. Nevertheless approximately 15 to 50% of syncopes remain unexplained after intensive diagnostic evaluation (Linzer et al., 1997; Sarasin et al., 2001). Despite its benign prognosis, even recurrent vasovagal syncope may lead to a significant decrease in the quality of life because of trauma and psychological, driving, employment, and financial implications (Moya et al., 2009). Therefore many low-risk syncope patients require extensive investigation or more aggressive treatments in selected cases.

In this chapter we will review the use of implantable cardiac rhythm devices, specifically implantable loop recorders and pacemakers, for the investigation and the treatment of vasovagal syncope.

1. Implantable electrocardiographic loop recorders

The electrocardiographic (ECG) registration during syncope allows physicians either to confirm or exclude an arrhythmia as the mechanism of syncope (Krahn et al., 2004). ECG monitoring is the most common procedure for diagnosing intermittent arrhythmias. Several systems of ECG ambulatory monitoring are currently available: in-hospital monitoring, conventional ambulatory Holter monitoring, event recorders, external or implantable loop recorders, and remote (at home) telemetry. The European Society of Cardiology guidelines (Moya et al., 2009) recommend the circumstances in which ECG findings can be considered as diagnostic (Table 1).

In patients with frequent symptoms, relatively short-term (one month) non-invasive ECG monitoring (for example with either event recorders or external loop recorders) may suffice. However syncopal episodes usually occur less frequently, and for this reason long term implantable loop recorders have been developed.

1.1. Technology

ECG loop recorders have an over-writeable memory buffer that continuously records and deletes the patient's ECG. The memory of specific epochs can be frozen by the patient, as a result of symptoms (using a handheld activator), and by an auto-activation feature (when heart rate exceeds or falls below pre-programmed parameters for tachy- or bradycardia) that allows the capture of arrhythmic events without relying on patient compliance or perception of symptoms (Brignole et al., 2009). Loop recorder devices can be either external or implantable (ILR). ILRs are typically implanted in the left parasternal pre-pectoral region under local anesthetic in a minor surgical procedure. They have no intravascular leads, recording a bipolar ECG signal from small electrodes

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Table 1
Diagnostic criteria for ECG monitoring.

	Class of recommendation	Level of evidence
ECG monitoring is diagnostic when a correlation between syncope and arrhythmia is detected.	I	B
In the absence of such correlation, ECG monitoring is diagnostic when periods of Mobitz II or III degree AV block or a ventricular pause >3 s, or rapid prolonged paroxysmal supraventricular or ventricular tachycardia are detected. The absence of an arrhythmia during syncope excludes arrhythmic syncope.	I	C
The ECG documentation of pre-syncope without any relevant arrhythmia is not an accurate surrogate for syncope.	III	C
Asymptomatic arrhythmias (other than those listed above) are not an accurate surrogate for syncope.	III	C
Sinus bradycardia (in the absence of syncope) is not an accurate surrogate for syncope.	III	C

on either end of the devices. Battery durations are now about 3 years (Brignole et al., 2009). Table 2 summarizes the characteristics of the most common ILRs. Recently, a much smaller ILR has been developed (Reveal LINQ(TM) ICM, Medtronic).

1.2. Diagnostic utility

A recent systematic review summarized the evidence for the clinical utility of ILRs in the investigation of unexplained syncope (Parry and Matthews, 2010). The initial clinical experience with the ILR was in a population of highly symptomatic patients with recurrent unexplained syncope (Krahn et al., 1995). Sixteen patients with a mean of 8.4 episodes of previous syncope and extensive negative investigation underwent ILR implantation. Fifteen patients had recurrent syncope during follow-up: a diagnosis was obtained in all of them with symptom–rhythm correlation in 9 (60%) patients. Since then, many studies have reported the use of ILR as part of the diagnostic strategy in recurrent unexplained syncope. However, almost all were small, observational, or retrospective. Of these, the ISSUE studies stand out.

The first International Study of Syncope of Uncertain Origin (ISSUE) was a multinational observational study to determine the etiology of syncope in 4 groups: recurrent syncope with a positive tilt test; recurrent syncope with a negative tilt test; recurrent syncope with bundle branch block at baseline and negative EP study; and recurrent syncope with structural heart disease and negative EP study (Moya et al., 2001). Syncope recurred in 34% of both tilt-positive and tilt-negative groups with an ECG correlation in 23% of the tilt-negative group and 28% of the tilt-positive group. The most frequent ECG finding was asystole, thought to be due to a vasovagal mechanism. The most frequent finding in pre-syncope was normal sinus rhythm. ISSUE also examined the mechanism of syncope in 52 patients with bundle branch block and a negative EP study (Brignole et al., 2001). Syncope recurred in 37% of patients and was due to sinus arrest or atrioventricular (AV) block in 89% of the events, demonstrating that bifascicular bundle branch block in syncope patients predicts a high likelihood of conducting system abnormalities as the cause of syncope. Finally, ISSUE examined the etiology of recurrent syncope in 35 patients with previous myocardial infarction or cardiomyopathy with a depressed ejection fraction or non-sustained ventricular tachycardia (NSVT) and a negative EP study (Menozzi et al., 2002). Unexpectedly, the outcome was favorable in most of the patients: during a follow-up of 3–15 months no patients died, only one patient developed ventricular tachycardia, and none suffered injury attributable to syncope.

The ISSUE group also analyzed the correlation between ILR documented spontaneous syncope and the results of tilt test and adenosine triphosphate (ATP) test (Brignole et al., 2006a, 2006b). They showed that clinical characteristics, outcome, and mechanism of syncope are poorly correlated and not predicted by the results of tilt test and ATP test.

Only three randomized trial studies involving ILRs have been reported. The Randomized Assessment of Syncope Trial (RAST) (Krahn et al., 2001) involved 60 consecutive patients with recurrent unexplained syncope or a single episode of syncope with injury warranting cardiovascular investigation. The purpose was to compare early use of the ILR to a strategy of extensive conventional investigations. The patients were randomized to a strategy of testing with an external loop recorder, tilt testing, and electrophysiological testing, or to prolonged monitoring with an implantable loop recorder with up to 1 year. If patients remained undiagnosed after their assigned strategy, they were offered crossover to the alternate strategy. A diagnosis was obtained in 52% of patients randomized to prolonged monitoring versus 20% of those undergoing conventional testing ($p = 0.012$). Overall, when combining the primary strategy with crossover, a diagnosis was established in 55% with a prolonged monitoring strategy compared to 19% with conventional testing. This forerunner Canadian study provided strong evidence, albeit with small patient numbers, for the efficiency of the early use of the ILR in the investigation of syncope.

In the similar Eastbourne Syncope Assessment Study (EaSyAS) (Farwell et al., 2004), 201 consecutive patients with recurrent syncope and no definite diagnosis following initial clinical workup (comprising history and a physical examination, 12-lead ECG, full blood count, urea and electrolytes, plasma glucose and Holter monitoring in the patients with suspected cardiac syncope) were randomly assigned to ILR implantation or conventional investigation and management. Fully 33% of ILR patients and only 4% of conventional patients had an ECG diagnosis of the cause of syncope. Interestingly there was no difference in the number of subsequent syncopal episodes, mortality, or quality of life between the two strategies.

Subsequently 246 patients with recurrent unexplained syncope were recruited in the Second Eastbourne Syncope Assessment Study (EaSyAS ll) (Sulke et al., 2010) and randomized in a factorial designed trial to four groups: a second-generation remotely monitored ILR alone, ILR plus syncope clinic, syncope clinic alone, or conventional management. Preliminary data show that ILR has comparable diagnostic efficacy to management in a syncope clinic but leads to superior outcomes in terms of long-term syncope prevention and, both were superior to conventional management.

Taken together these three studies suggest that early use of the ILR provides more diagnoses, and earlier diagnoses, than using a cascade of conventional investigations. However many questions remain, including its performance in the community by physicians with a range of experience in diagnosing syncope. Furthermore there is no evidence that the use of the ILR changes outcome. Finally, ILRs are not inexpensive, and whether they are cost-effective is an important issue.

1.3. Cost-effectiveness

Although no study specifically assessed the cost-effectiveness of ILR in the differential diagnosis of syncope, this has been addressed in two substudies. In the RAST study (Krahn et al., 2001) the prolonged monitoring strategy gave a diagnostic yield of 50% at a mean cost of $2937 per patient and a mean $5875 per diagnosis. Conventional testing (with subsequent ILR if necessary) gave a diagnostic yield of 47% at a greater cost of $3683 per patient and a greater mean cost ($7891) per diagnosis. In the EaSyAs study (Farwell et al., 2004) the ILR resulted in a cost saving: a mean of £406 with the ILR strategy compared to £1210 with the conventional strategy. The cost of the ILR itself, which was £1350 at the time of the study, was not included. Recently, data from the UK National Health Service have been used in a decision analytical model to assess the cost-effectiveness of ILRs and tilt testing to direct