CLINICAL RESEARCH

Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: A randomized multicentre prospective study

Place du moniteur ECG implantable chez les patients avec première syncope, bloc de branche complet et bilan électrophysiologique négatif : étude prospective randomisée multicentrique

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Abbreviations: AV, atrioventricular; BBB, bundle branch block; EPS, electrophysiological study; HV, His to ventricular; ILR, implantable loop recorder; LV EF, left ventricular ejection fraction; RTE, R. Test Evolution.

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KEYWORDS
Syncope; Arrhythmia; Diagnosis; Implantable loop recorder

Summary
Background. — Few studies have compared conventional testing with prolonged monitoring using an implantable loop recorder (ILR) following the first syncpe episode in patients with bundle branch block (BBB) and negative workup.
Objectives. — To compare two syncpe evaluation strategies—primary use of an ILR (Group 1) versus conventional testing (Group 2)—and to estimate the prevalence of significant arrhythmias in the ILR patient subset.
Methods. — From January 2005 to December 2010, 78 patients admitted after one syncpe episode were randomized to ILR (n = 41) or conventional follow-up (n = 37). Mean follow-up was 27 ± 12 months.
Results. — Mean age was 76 ± 8 years and 30 patients were women (38.5%); 18 presented cardiomyopathy (23%) and 12 had a history of atrial fibrillation (15.4%). Mean left ventricular ejection fraction was 56.5 ± 11% and mean His-to-ventricle interval was 55 ± 6 ms based on negative electrophysiological study (EPS). Electrocardiogram abnormalities involved: 34 left bundle branch blocks (BBBs); 11 right BBBs; and 33 bifascicular blocks. Overall, 21 patients (27%) developed significant arrhythmic events: ventricular tachycardia (n = 1; 1.3%); sudden death (n = 2; 2.6%); third-degree atrioventricular (AV) block (n = 14; 18%); sick sinus syndrome (n = 4; 5.1%). In 19 (24.4%) patients, relevant arrhythmias were detected, with a significant difference between the ILR group (n = 15/41; 36.6%) and the conventional follow-up group (n = 4/37; 10.8%) (P = 0.02). Eighteen patients were implanted with pacemakers; one received an implantable defibrillator. No predictors of AV block were identified in the ILR group.
Conclusions. — In this randomized prospective study, the ILR strategy proved largely superior to conventional follow-up in detecting recurrent events, with a potential impact on therapeutic management. This observation highlights the usefulness of early monitoring in patients with BBB and negative EPS even after the first syncpe episode but an empiric pacemaker strategy remains to be validated in this selected population.
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MOTS CLÉS
Syncope ; Arthymies ; Diagnostic ; Moniteur ECG implantable

Résumé
Contexte. — Les données publiées sur le mécanisme des syncopes isolées chez les patients avec bloc de branche complet (BBC) et bilan électrophysiologique négatif sont peu nombreuses.
Objectifs. — De comparer pour les patients avec première syncope et BBC une stratégie avec mise en place d’un moniteur ECG implantable (MEI) (Group I) versus un suivi conventionnel clinique et holter (Group II).
Méthodes. — De janvier 2005 à décembre 2010, 78 patients (76 ± 8 ans) ont été randomisés, 41 patients dans le groupe MEI et 37 patients dans le groupe suivi conventionnel. Le suivi moyen était de 27 ± 12 mois.
Résultats. — Les troubles de conduite étaient les suivants : 34 BBC gauche, 11 BBC droit et 33 blocs bifasciculaires. Dans l’ensemble de la population, 21 patients (27%) ont développé un événement rythmique : une TV dans un cas (1,3%), une mort subite dans deux cas (2,6%), un BAV du 3e degré chez 14 patients (18%) et une dysfonction sinusale dans quatre cas (5,1%). Pour 19 patients (24,4%), la détection dun événement rythmique a été possible, avec une différence significative entre les deux groupes de suivi : MEI (n = 15/41; 36,6%) versus suivi conventionnel (n = 4/37; 10,8%) (P = 0.02). Par conséquent, 18 patients ont bénéficié de l’implantation d’un pacemaker et un patient de la mise en place d’un défibrillateur.
Conclusions. — Cette étude prospective randomisée multicentrique chez des patients avec un épisode de syncpe associé à un BBC et une exploration électrophysiologique négative montre que la stratégie du MEI est très largement supérieure au suivi conventionnel. Dans le groupe avec MEI, la prévalence des événements rythmiques était de 36,6% à 2,5 ans (14,6% par an) versus 10,8% (4,3% par an) dans le groupe de suivi conventionnel.
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Background
Cardiac syncpe doubles the risk of all-cause death, while increasing the risk of fatal and non-fatal cardiovascular events [1]. Soteriades et al. demonstrated that subjects with syncpe of unknown aetioloype comprise a heterogeneous patient group with an increased risk of death [1]. The current approach to investigating patients with unexplained syncpe involves short-term electrocardiographic monitoring or tests such as head-up tilt testing and electrophysiological study (EPS) [2–6]. Recent advances in long-term monitoring with an implantable loop recorder

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(ILR) have enabled clinicians to obtain a correlation between symptoms and rhythm in the majority of patients [7–14]. Despite the number of published reports on ILRs, only a few randomized studies are available, with their major limitations being small sample size and short-term follow-up [11]. Furthermore, most published trials included patients with recurrent syncope, with three to seven syncope episodes [8–14].

In patients with both syncope and bundle branch block (BBB), syncope is suspected to be attributed to atrioventricular (AV) block, with EPS being able to predict the development of AV block in 87% of patients [15]. In patients with BBB and negative EPS, the risk of developing a stable AV block was shown to be close to 20% after 4 years, with the risk of syncope recurrence being close to 40% at 3 years [16–18]. Given this clinical setting, Brignole et al. found that syncope recurrences were mainly accounted for by paroxysmal AV block, with the risk estimated at 34% at 15 months (27% incidence/year), suggesting that some EPS results were, in fact, false negatives [16]. Accordingly, an ILR was shown to be able to establish a symptom-rhythm correlation in most patients with recurrent syncope [11,16,19]. To date, there are little data available regarding patients with a first syncope episode, BBB and negative workup, including EPS. Moreover, in this subset of patients with initial negative EPS results, no randomized studies have compared a conventional monitoring strategy (clinical, electrocardiogram and standard Holter monitoring) with ILR following a first syncope episode, despite the European Society of Cardiology guidelines of 2009 [19]. In these guidelines, patients with left BBB are considered at high risk and syncope in these patients should lead to an ILR (class I, level B) [19]. The recommendation for patients with syncope and left BBB could lead to pacemaker implantation but the level of proof is considered as class IIa, level C [19]. A recent paper underlined the role of ILRs in a subset of patients despite negative EPS but patients could have had more than one syncope episode [20].

The aim of this multicentre prospective study was to compare two syncope evaluation strategies—namely, the use of an ILR (Group 1) versus conventional follow-up (Group 2)—in a population of patients with BBB and negative EPS following a first syncope episode, in addition to assessing the prevalence of significant arrhythmic events in the ILR patient subset.

**Methods**

**Study population**

The study protocol was approved by the Institutional Research Board of the Saint-Étienne Hospital and the Ethics Committee in October 2004. The study was supported by the Ministère Français de la Santé (Projet Hospitalier de Recherche Clinique, 2003) and Saint-Étienne University Hospital.

**Inclusion criteria**

Patients admitted after one syncope episode were invited to participate in this prospective randomized trial comparing two diagnostic approaches to syncope. Consecutive patients were included in the trial if they met the following inclusion criteria: single syncopeal episode associated with any type of BBB with QRS greater or equal to 120 ms; no evidence of second- or third-degree AV block; and negative workup including EPS. Prior to enrolment, patients underwent clinical assessment, involving postural blood pressure testing, baseline ambulatory monitoring or inpatient telemetry for at least 24 hours and transthoracic echocardiogram. Baseline Holter assessment was considered negative if patients did not experience syncope or presyncope reminiscent of their referral symptoms during the recording and if there was no evidence of the following: asymptomatic second- or third-degree AV block; pauses of at least 3 seconds; sustained supraventricular tachycardia or greater or equal to 10 heartbeats of wide QRS complex tachycardia likely to represent ventricular tachycardia. Before enrolment, additional neurological or cardiovascular testing was performed by the referring physician, although this was not mandatory according to the protocol. Patients were excluded if one of the following conditions was found: left ventricular ejection fraction (LVEF) less or equal to 35%; likelihood of surviving 1 year; or inability to attend follow-up or give informed consent. Patients with LVEF less than 60% were considered as having cardiomyopathy and thus were included. The difference between ischaemic cardiomyopathy and dilated cardiomyopathy was based on the coronary angiography values. Patients with a typical presentation of neurally mediated syncope at baseline were diagnosed as such and excluded from participating in the study. The clinical symptoms of neurally mediated syncope were induced by upright posture, with a prodromal phase, including the feeling of warmth and excessive sweating, followed by postepisode complaints of fatigue. The EPS included the measurement of the sinus node recovery time in addition to the measurement of the His to ventricle (HV) interval at baseline and under stress during incremental atrial pacing, although if the baseline assessment was inconclusive, the EPS was continued with pharmacological provocation using a slow infusion of ajmaline (1 mg/kg intravenously). Furthermore, the EPS involved the assessment of the inducibility of ventricular arrhythmia by programmed ventricular stimulation and supraventricular arrhythmia by any atrial stimulation protocol.

**Exclusion criteria**

In line with the published literature, the EPS was considered diagnostic and resulted in patients being excluded from the study if one of the following criteria was met: sinus bradycardia and abnormal sinus node recovery time; baseline HV interval greater or equal to 70 ms, second- or third-degree His-Purkinje block shown during incremental atrial pacing or high-degree His-Purkinje block provoked by intravenous administration of ajmaline; induction of sustained monomorphic ventricular tachycardia; induction of rapid supraventricular arrhythmia associated with hypotensive or spontaneous symptoms; carotid sinus hypersensitivity; symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; subclavian steal syndrome.
Implantable loop recorder in isolated syncope, BBB and negative workup

ILR group

Patients randomly assigned to the prolonged monitoring strategy were implanted with the Reveal ILR (Medtronic model 9526 Reveal Plus, replaced by model 9528 Reveal DX after 2008 and, more recently, by model XT Reveal; Minneapolis, MN, USA) in the left upper chest region under local anaesthesia following intravenous administration of 1 g of cefazolin. The ILR was a continuous electrocardiogram monitor capable of providing spontaneous automatic single-lead electrocardiogram recordings for up to 42 minutes. If patients experienced spontaneous symptoms, they were invited to press the button in order to “freeze” the prior electrocardiogram recording, which was downloaded using a standard pacemaker programmer (Medtronic 9290C). After implantation, the patients, along with their family members or friends, were instructed in how to use the activator. The recommended programme mode involved one manual event and 13 automatic events for 42 minutes of storage. The resulting memory configuration meant that the automated backup activation was able to detect bradycardia or pauses in addition to prespecified extreme rates or pauses (typically < 30 beats/min, > 160 beats/min and pauses > 3 s). Patients were told to activate the device after each syncope episode. In the absence of recurrent symptoms, the device detected any asymptomatic heart rate changes that were likely to provide clinical insights into the potential causes of the syncope [21,22]. After ILR implantation, patients had follow-up visits every 3 months until the first symptomatic or asymptomatic episode documented by electrocardiogram or until 36 months. The mechanism of syncope was designated by the endpoints as defined by the committee members, who analysed the full set of all episodes. In the case of battery depletion prior to the study end, a second ILR was implanted.

Conventional strategy group

Patients randomly assigned to conventional follow-up were seen in the outpatient department at 3, 6, 12, 15, 18, 21, 24, 27, 30 and 33 months after randomization and at the study end (36 months). At each visit, arrhythmic or cardiovascular events were recorded and a 12-lead electrocardiogram was obtained, with follow-up continued in order to record any additional endpoints other than the initial endpoint. At each visit, a Holter monitor was used for 7 days, with analyses performed using the R.Test Evolution (RTE) event recorder (Novacor, Rueil Malmaison, France) and two electrodes placed on the patient’s body [23,24]. The RTE event recorder ensured continuous electrocardiogram analysis, with any abnormal events being automatically stored in a 20-minute solid-state memory, which was autonomous for up to 7 days. Additionally, the patient was able to trigger the Holter manually [23]. The RTE was programmed to recognize 10 types of arrhythmic events and one category of ischaemic event [23,24]. The patients were instructed to report any clinical abnormality that occurred during the recording, by providing a detailed description and precise frequency of clinical symptoms. All recordings were analysed by two independent observers, with a third being used in case of discrepancies.

Endpoints

Clinically significant symptomatic and asymptomatic arrhythmias were defined as follows: pause more than 5 seconds; third-degree AV block; heart rate less than 30 beats/min for more than 10 seconds while awake; more than 10 beats of wide complex tachycardia consistent with ventricular tachycardia; and more than 30 beats of narrow complex tachycardia more than 165 beats/min. Borderline asymptomatic arrhythmias were defined as follows: less than 10 seconds of second- or third-degree AV block (Mobitz II); or heart rate less than 30 beats/min for less than 10 seconds while asleep. These endpoints were based on the guidelines from the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the North American Society of Pacing and Electrophysiology regarding the implantation of cardiac pacemakers and antiarrhythmia devices [25,26]. The primary study endpoint was reached when a symptom-rhythm correlation was obtained by manual activation of the device after spontaneous symptoms or when a prespecified significant asymptomatic arrhythmia was observed. Patients with borderline arrhythmias continued to be monitored without intervention. The primary endpoint was the time to the occurrence of significant symptomatic or asymptomatic events such as those defined above, thus requiring the implantation of a pacing or antiarrhythmic device based on the aforementioned guidelines [25,26].

Statistical analysis

Baseline patient characteristics were compared between the ILR group and the conventional group using Fisher’s exact test for categorical variables and the two-sample t-test for continuous variables, as appropriate. Summary values were reported as proportions and means ± standard deviations. For all time-to-event analyses, rates were estimated using the Kaplan-Meier method and compared by the log-rank test. Cox regression was used to calculate the hazard ratio and 95% confidence interval of risk of events in a first model and risk of AV block III in a second model between the ILR group and conventional group. Crude and adjusted hazard ratios were presented. Patient data were censored at the time of last follow-up, withdrawal from the study or non-rhythmic death. Symptomatic and asymptomatic events episodes were recorded, with a safety monitoring board reviewing the recordings. All reported levels of significance were two-sided. A probability value of P < 0.05 was considered statistically significant. It was estimated that 80 patients would need to be enrolled to detect a 20% event-difference at 2 years in favour of the ILR group, with 80% power, a two-sided 0.05α level and a two-sided 0.20β level, assuming that 5% of patients would be lost to follow-up in this elderly population. Statistical procedures were performed using SPSS for Windows (version 15.0) and Statview. All authors had full access to the data, take responsibility for its integrity and have read and approved the final manuscript.
Results

Study population

Patient characteristics are summarized in Table 1. From January 2005 to December 2010, 78 patients were included in the study. Population characteristics were as follows: mean age 76 ± 8 years; 30 women (38.5%); 18 presented cardiomyopathy (23%); and 12 had a history of atrial fibrillation (15.4%). Among the 18 cardiomyopathy patients included in our study, 12 had documented ischaemic cardiomyopathy, while six had left ventricular dysfunction without coronary disease. The mean LVEF of the patients presenting cardiomyopathy was 48 ± 11% versus 56.5 ± 11% in the overall population. The mean HV interval was 55 ± 6 ms, while electrocardiogram abnormalities were as follows: 34 left BBBS; 11 right BBBS; and 33 bifascicular blocks. Subsequently, 41 patients were randomly assigned to the ILR group and 37 to conventional follow-up. There were no clinical, electrocardiographic or echocardiographic differences between the two groups (Table 2).

Follow-up

In the overall population, 21 patients (27%) experienced significant symptomatic arrhythmic events: ventricular tachycardia (n = 1; 1.3%); sudden death (n = 2; 2.6%); third-degree AV block (n = 14; 18%); and sick sinus syndrome (n = 4; 5.1%). Events were detectable in 19 patients, with a statistically significant difference found between the ILR and conventional follow-up groups (n = 15/41, 36.6% vs n = 4/37, 10.8%; P = 0.01) (Table 2; Fig. 1). ILR-documented events occurred in 15 out of 41 patients after a median of 6 months (interquartile range, 1 to 23 months): 11 (26.8%) patients presented third-degree AV block; three (7.3%) presented sick sinus syndrome (sinus arrest); and one (2.4%) presented ventricular tachycardia. In the conventional group, three (8.1%) patients presented third-degree AV block and one (2.7%) presented sick sinus syndrome, after a median of 9 months (interquartile range, 3 to 12 months) (Fig. 1).

In line with the final diagnosis, 18 patients were implanted with a pacemaker, while one received an implantable defibrillator. During follow-up, there were no significant differences observed between ILR and conventional groups with regard to the number of presyncopes and syncopes (0.7 ± 0.7 vs 0.5 ± 0.9; P = 0.3). No variables were identified to predict the occurrence of AV block, including BBB (hazard ratios, Table 3). The Kaplan-Meier curve showed that patients in the ILR group had lower survival rates concerning AV block III (P = 0.01) (Fig. 2).

Table 1 Baseline population characteristics (n = 78).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 41)</th>
<th>Group 2 (n = 37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76 ± 8</td>
<td>74 ± 8</td>
<td>0.6</td>
</tr>
<tr>
<td>Women</td>
<td>15 (36.6)</td>
<td>15 (40.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>10 (24.5)</td>
<td>8 (22)</td>
<td>0.9</td>
</tr>
<tr>
<td>Arterial pressure (mmHg)</td>
<td>140 ± 15</td>
<td>140 ± 20</td>
<td>0.6</td>
</tr>
<tr>
<td>Prodomes</td>
<td>7 (17.1)</td>
<td>8 (21.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Prior atrial fibrillation</td>
<td>7 (17.1)</td>
<td>5 (13.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Standard electrocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left BBB</td>
<td>18 (43.9)</td>
<td>14 (37.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Right BBB</td>
<td>6 (14.6)</td>
<td>5 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Bifascicular block</td>
<td>17 (41.5)</td>
<td>18 (48.6)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.5 ± 11</td>
<td>57 ± 11</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean AH interval (ms)</td>
<td>127 ± 65</td>
<td>108 ± 35</td>
<td>0.2</td>
</tr>
<tr>
<td>Sinus recovery time (%)</td>
<td>124 ± 21</td>
<td>118 ± 12</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean HV interval (ms)</td>
<td>54.5 ± 6</td>
<td>55 ± 6</td>
<td>0.8</td>
</tr>
<tr>
<td>Maximal HV after ajmaline (ms)</td>
<td>72 ± 6</td>
<td>77 ± 4</td>
<td>0.8</td>
</tr>
<tr>
<td>Tilt testing, positive response</td>
<td>14 (34.2)</td>
<td>11 (29.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Events</td>
<td>15 (36.6)</td>
<td>4 (10.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>AV block III</td>
<td>11 (26.8)</td>
<td>3 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>3 (7.3)</td>
<td>1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%). AV: atrioventricular; BBB: bundle branch block; HV: His to ventricular; ILR: implantable loop recorder; LVEF: left ventricular ejection fraction.

Table 2 Comparison between the ILR and conventional groups.

(2.4%) presented ventricular tachycardia. In the conventional group, three (8.1%) patients presented third-degree AV block and one (2.7%) presented sick sinus syndrome, after a median of 9 months (interquartile range, 3 to 12 months) (Fig. 1). In line with the final diagnosis, 18 patients were implanted with a pacemaker, while one received an implantable defibrillator. During follow-up, there were no significant differences observed between ILR and conventional groups with regard to the number of presyncopes and syncopes (0.7 ± 0.7 vs 0.5 ± 0.9; P = 0.3). No variables were identified to predict the occurrence of AV block, including BBB (hazard ratios, Table 3). The Kaplan-Meier curve showed that patients in the ILR group had lower survival rates concerning AV block III (P = 0.01) (Fig. 2).
Figure 1. Kaplan-Meier estimates of the percentage of patients remaining free of arrhythmia recurrence in the implantable loop recorder (ILR) (green line) and conventional (blue line) groups. The Kaplan-Meier curve shows that patients in the ILR group have lower event-free survival rates; the log-rank test gave \( P = 0.01 \).

Figure 2. Kaplan-Meier estimates of the percentage of patients remaining free of atrioventricular (AV) block III in the implantable loop recorder (ILR) (green line) and conventional (blue line) groups. The Kaplan-Meier curve shows that patients in the ILR group have lower AV block III-free survival rates; the log-rank test gave \( P = 0.012 \).

Discussion

Major findings

This randomized, prospective study demonstrated and confirmed that the ILR strategy was largely superior to the conventional strategy in detecting recurrent significant events in patients with isolated syncope, BBB and negative EPS; accordingly, this approach was shown to be a favourable early therapeutic strategy. In addition, the study showed that the true prevalence of arrhythmic events detected using ILR was 36.6% at 2.5 years (14.6% incidence/year) in the same patient population.

Table 3. Hazard ratios for the ILR group compared with the conventional group for risk of events and risk of AV block III.

<table>
<thead>
<tr>
<th></th>
<th>Crude hazard ratio (95% CI)</th>
<th>( P )</th>
<th>Adjusted hazard ratio(^c) (95% CI)</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td>Prior atrial fibrillation</td>
<td></td>
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<tr>
<td>Standard electrocardiogram</td>
<td></td>
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</tr>
<tr>
<td>Left BBB</td>
<td>0.7 (0.2—3.6)</td>
<td>0.8</td>
<td>1.0 (0.3—3.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Right BBB</td>
<td>0.6 (0.08—5.4)</td>
<td>0.7</td>
<td>1.1 (0.2—5.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Bifascicular block</td>
<td>0.9 (0.3—2.6)</td>
<td>0.8</td>
<td>0.9 (0.3—2.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Events(^a)</td>
<td>3.4 (1.2—9.5)</td>
<td>0.02</td>
<td>3.4 (1.2—9.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>AV block III(^b)</td>
<td>4.4 (1.2—15.8)</td>
<td>0.02</td>
<td>4.3 (1.2—15.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

AV: atrioventricular; BBB: bundle branch block; CI: confidence interval; ILR: implantable loop recorder.

Prognosis of patients with syncope, BBB and negative EPS results

Syncope is a frequent reason for emergency consultations, accounting for more than 1.3% of all adult admissions [1,27]. However, the percentage of patients leaving hospital with a definite diagnosis is variable, ranging from 52.5 to 87% depending on the study [25,27—29]. Furthermore, Soteriades et al. showed that subjects with syncope of unknown aetiology formed a mixed group of patients at high risk for death [1]. However, to our knowledge, no study to date has investigated syncopal patients with negative workup following the first syncopal episode [9—12,19,20,22]. For
patients with BBB and negative EPS, the risk of recurrent syncope was estimated to be 20% at 2.5 years and 40% at 3 years, according to the studies by Click et al. and Link et al., respectively [18,30]. In general, the patients investigated in these studies presented more than one single syncope episode and, in most cases, syncope was suspected to be due to paroxysmal AV block. Given this context, the risk of developing a permanent AV block was estimated to be 5%/year and 18% after 2.5 years, which suggested that some EPS results were, in fact, false negatives [17,18,30]. In a prospective study, McAnulty et al. established that patients with symptomatic BBB, with or without associated cardiomyopathy, had an estimated 17% risk of developing AV block versus 2% for asymptomatic patients [31]. In the 2009 European Society of Cardiology guidelines [19], patients with LBB are considered at high risk and syncope in this patient group should lead to ILR (class I, level B) but no differentiation was made between patients with one or more syncope episodes and no prospective comparison strategy has been done to date [19]. The recommendation for patients with syncope and LBB could also lead to pacemaker implantation but the level of proof is considered as class IIa, level C [19]. Lastly, a recent paper underlined the role of ILR in a subset of patients despite negative EPS but the patients could have had more than one syncope episode and the study was not a comparative strategy [20]. In our study involving a population with isolated syncope, BBB and negative workup including EPS, the risk of arrhythmic events was found to be 36.6% at 2.5 years (14.6% incidence/year), with 75% of arrhythmic events being third-degree AV block III (10.7% incidence/year). No variables were identified to predict the risk of AV block, including the BBB type (left versus others; not significant).

Previous ILR studies in syncopal patients

While previous studies largely validated the utility of ILR in patients with unexplained syncope, patients experiencing a first syncyne episode along with BBB and negative EPS were not included in the majority of published reports [9–12,16,19,20,22]. Initially, ILR was used to diagnose patients with unexplained syncope in the case of a completed negative workup. In a small series of highly selected patients, symptom-electrocardiogram correlation was achieved in 88% of patients within a mean time of 5 months following implantation [9,10,12]. In the guidelines for the diagnosis and management of syncope, pooled data from nine studies involving 506 patients with unexplained syncope showed that after a complete conventional investigation, a correlation between syncope and electrocardiogram was found in 176 patients (35%). Among these patients, 56% exhibited a systole (or bradycardia in a few cases) at the time of the recorded event and 11% exhibited tachycardia, while 33% of patients had no arrhythmia [26]. The ISSUE study demonstrated that the risk of developing paroxysmal AV block was not negligible, with the incidence estimated to be about 35% at 15 months [2,3,6,16]. This last study involved patients with recurrent syncope (median number, 3) in the presence of BBB, although no comparison was made with standard conventional testing at diagnosis [16]. In our study, the prevalence of AV block was close to 27% at 2.5 years (10.7%/year) in the ILR group compared with 8.13% (3.3%/year) in the conventional group. The incidence was almost three times lower than the data reported by Brignole et al. (28%/year) [16]. The main explanation for this discrepancy is that patients from the study of Brignole et al. presented more than one syncopal episode, suggesting a more advanced disease [16]. Overall, 42% of patients in this study displayed a bifascicular block, with right BBB being associated with right axis deviation, meaning that patients were exposed to a higher risk of AV block [16]. Our results are in agreement with those obtained in a retrospective study by Pierre et al. These authors found that in patients with syncope and BBB, the risk of developing AV block was 13.8% [32]. There are only a few randomized published studies on ILR. The paper by Krahr et al. is the sole prospective randomized study published to date that reports on the utility of ILR as an initial approach, while demonstrating its superiority over conventional testing [11]. In this study, a diagnosis was established in 52% of ILR group patients versus 20% of conventional group patients. The conventional investigation strategy included a monitoring period of 2–4 weeks using an external loop recorder, followed by tilt-table testing and EPS [11]. Compared with our study, the main differences with the study by Krahr et al. were the absence of an EPS investigation in the ILR group and the type of patients included, as only 25% of patients presented had BBB [11]. Recently, Moya et al. reported the value of ILR implantation in patients with syncope and BBB and a negative EPS [20]. In their study, patients exhibited one or more syncope episodes and 80% had arrhythmia events, demonstrating that their population was quite different from our study that included only patients with one syncope episode. Accordingly, our study results support ILR implantation at an earlier stage, even after the first syncope episode, in order to detect significant arrhythmic events. To date, prophylactic pacemaker implantation has been classified as class IIa, level B in the current recommendations for patients with syncope and BBB that is found not to be caused by AV block after other likely causes, specifically ventricular tachycardia, have been excluded [19]. By contrast, ILR implantation in patients with recurrent syncope is categorized as class I, level B, while unexplained isolated syncope is categorized as class II, level B but without differentiation between patients with one or more syncopal episode [19]. Our study findings highlight the clinical impact of early diagnosis even in patients with one syncope episode.

Study implications

Our randomized prospective study is the first to compare an ILR strategy with conventional follow-up in patients presenting a first syncope episode along with BBB and negative EPS results. Our study results stress the superiority of the ILR strategy over conventional follow-up, with the former approach being four times more likely to detect significant arrhythmias, especially AV block, even after the first syncope episode. Early diagnosis in this patient subset allows for early pacemaker implantation—although this strategy remains to be validated [33]—thereby preventing unnecessary hospitalizations or syncope recurrence, which can be particularly harmful for elderly patients. Our study
findings confirm that AV block was the main mechanism for syncope recurrence in patients exhibiting BBB and one syncope episode, being responsible for 75% of events in this specific patient population, with a 10% annual incidence.

Study limitations

While the type of strategy may have an impact on prognosis, it also depends on the patients enrolled. Our patients were selected on the basis of one single syncope episode, negative EPS and BBB. Accordingly, the percentage of events in our population is quite different compared with the high percentage of arrhythmia events reported by Moya et al. in a selected population with more than one syncope episode (80% of events) [20]. It should, however, be noted that ILR is not necessary in patients with a low recurrence risk and benign syncope [34]. In addition, the sample size of our population was small and, ideally, a larger number of patients presenting LBBB, RBBB or bifascicular block would be necessary for each patient group. Furthermore, a longer follow-up duration (e.g. a minimum of 3–5 years/patient) would have allowed us to determine the cumulative incidence of heart block. The cost implications of the different testing strategies were not evaluated in our study. Thus, in order to establish the cost-effectiveness of ILR over conventional strategies, further studies are still warranted. Our study did not prove that early pacemaker implantation is superior to a monitoring strategy; a study was recently initiated to evaluate both strategies (SPRITELY study) [34].

Conclusions

This randomized prospective study demonstrated that in patients with isolated syncope, BBB and negative EPS results, an ILR strategy proved largely superior to conventional clinical follow-up in detecting recurrent events, with a potential impact on therapeutic management. In this patient subset, the prevalence of arrhythmic events that were detected using ILR was 36.6% at 2.5 years (14.6% incidence/year) versus 10.8% (4.3% incidence/year) for conventional follow-up. This observation highlights the usefulness of early monitoring in patients with BBB and negative EPS even after the first syncope episode, although an empiric pacemaker strategy remains to be validated in this selected population.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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