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The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older people

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Abstract **Objectives** To evaluate the usage and diagnostic yield of the implantable loop-recorder (ILR) in detection of the mechanism of syncope and in guiding therapy in patients aged ≥ 65 years and comparing them with those <65 years.

Design This was a two-hospital, observational, prospective study in consecutive patients with unexplained syncope who underwent an ILR implantation. Between November 1997 and December 2002, a total of 2052 patients with syncope were evaluated (local population of 590,000 inhabitants). The diagnosis remained unexplained in 371 (18%). Of these, 103 patients (5% of the total, 28% of those with unexplained syncope) received an ILR.

Results There were 70 (76%) patients aged ≥ 65 years and 25 (24%) <65 years. ILR implantation was 110 and 9 per million inhabitants per year, respectively. During a mean follow-up of 14 ± 10 months, syncope was recorded in 52 patients. Compared with younger patients those older had a 2.7 higher syncope recurrence rate (56% vs 32%, $P = 0.03$); arrhythmias were 3.1 times more likely to be

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responsible for syncope (44% vs 20%, $P = 0.03$). More patients ≥ 65 years finally received ILR-guided therapy (42% vs 20%, $P = 0.04$). Among the 29 patients (25 of those ≥ 65 years) who received specific antiarrhythmic therapy, only one (3%), had recurrence of syncope during the subsequent follow-up of 40 ± 18 months.

Conclusions In patients referred for investigation of unexplained syncope, the older subjects are more likely to have an indication for ILR implantation than those younger, ILR has a higher diagnostic value, an arrhythmia is more likely to be detected and successfully treated.

Data pooled from four studies [1–4], in patients with unexplained syncope at the end of a complete conventional investigation, showed that the implantable loop-recorder (ILR) was able to demonstrate syncope/ECG correlation in 34%; of these 52% had a bradycardia or asystole at the time of the recorded event, 11% had tachycardia and 37% had no rhythm variation [5]. Only limited experience is available in older subjects [6].

Methods

This was a two-centre, prospective, observational study, performed in 103 consecutive patients, who received implantation of an ILR to detect the mechanism of otherwise unexplained syncope. According to current guidelines [5,7,8], we considered eligible for ILR implantation those patients who had both severe (high risk or high frequency) syncope that justified the need for a precise diagnosis and specific therapy and a negative work-up. High risk or high frequency syncope was defined as: (1) very frequent, with reduced quality of life, or (2) were recurrent and unpredictable (absence of premonitory symptoms) thus exposing patients to ''high risk'' of trauma; or (3) occurred during the prosecution of a 'high risk' activity (e.g., driving, machine operator, flying, competitive athletics, etc.). The indication for ILR implantation and the diagnostic criteria were both predefined by the two centres when they began their ILR experience in 1997 and thereafter remained constant. Patients were informed that ILR implantation could result in non-pharmacological therapy, e.g., pacemaker insertion, and these devices were not given to patients who were not willing to accept the eventual therapeutic recommendations. Some patients in this study had also been included in the database of a previous study [4,9,10].

The ILR (Reveal or Reveal Plus, Medtronic, USA) is an implantable ECG event monitor which is placed subcutaneously under local anaesthesia; the manufacturer's manual indicates a battery life of 14 months. The device has a solid-state loop memory, and the current version can store up to 42 min of continuous ECG. The device memory is sufficient to record the ECG for a substantial period before activation which is inevitably after consciousness has been restored. Automatic activation is also available in case of occurrence of predefined arrhythmias in the Reveal Plus model (which was implanted in 81 patients).

After the implantation, the patients were usually discharged within 24 h, with scheduled follow-up visits including ILR interrogation every three months, unless symptoms occurred. In case of battery depletion before documentation of a syncopal relapse, patients were asked to undergo a second ILR implantation.

The primary end-point of the study was the ECG diagnosis made by analysis of the signals obtained during the first syncopal episode that was correctly recorded by the device. Presyncopal episodes were not considered. Moreover, based on clinical features and ECGs we inferred the likely clinical diagnosis.

In particular, based on the results of the ISSUE study [4,9,10], the mechanism of syncope was considered likely to be due to a primary cardiac arrhythmia when sudden onset AV block or bradycardia or atrial/ventricular tachyarrhythmias were detected at the time of the syncopal attack. Conversely, the mechanism of syncope was considered likely to be neurally-mediated when no rhythm variations were detected in the absence of other competing diagnoses or brady- or tachyarrhythmias occurred which were gradual and progressive in their onset and termination.

Those patients who had an arrhythmia recorded at the time of syncope received arrhythmia-guided specific therapy. These patients continued to be followed-up with a similar schedule of hospital visits initially after three months and then every year, unless symptoms occurred.

Statistical analysis

Comparison between the two groups was performed by means of the Fisher's exact test, their odds ratio was calculated by the χ^2 test. The time to the onset of events was analyzed by means of Kaplan—Meier survival curves, which were compared using the log rank test. A P value of 0.05 or less was considered significant.

Results

Incidence

Between December 1997 and December 2002 a total of 2057 patients with syncope was referred to our centres (Fig. 1). In 18% of these patients the diagnosis remained unexplained at the end of the conventional investigation. An ILR was implanted in 103 patients who fulfilled the inclusion criteria; of these, 78 patients (76%) were $\geq$65 years (mean age 74 $\pm$ 6 years; 43 males) and 25 (24%) were <65 years (mean age 52 $\pm$ 8 years; 14 males). The enroling hospitals are the only two referral centres in the areas for investigation of syncope and receive both in- and outpatients. Since the overall population of these areas is 590,000 inhabitants with 25% of the population being $\geq$65 years, we estimate a rate of 110 ILR implants/million inhabitants/year in the older and nine implants/million inhabitants/year in the younger groups.

The clinical characteristics of the patients are listed in the Table 1.

Diagnostic yield

Overall, during a mean follow-up of 14 $\pm$ 10 months, an ECG-documented syncope occurred in
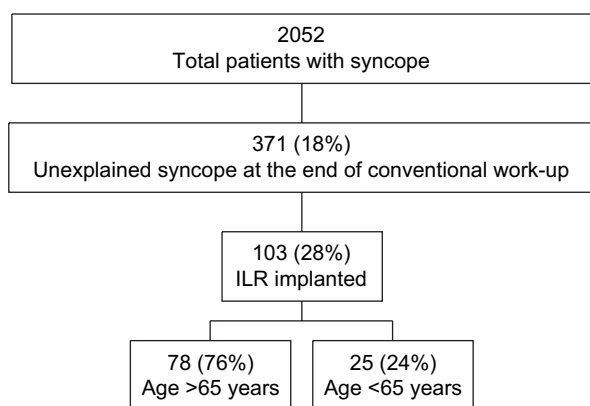
Table 1 Patient characteristics	
Total number with ILR	103
Age, years	69 $\pm$ 11
Sex	57 men, 46 women
Previous syncope, mean number	11 $\pm$ 5
Structural heart disease:	39 (38%)
− previous myocardial infarction	12 (11%)
− dilated cardiomyopathy	6 (6%)
− valvular heart disease	2 (2%)
Bifascicular bundle branch block	26 (25%)

52 patients (50%). An additional four patients had syncope, but they were unable to activate the ILR. In three cases, a second ILR was needed, due to battery exhaustion of the first device before a diagnosis was made.

Among the 78 patients $\geq$65 years, 44 (56%) had an ECG recording during syncope; an arrhythmia was detected in 42 (81%) (Table 2). The most frequent arrhythmia was a sudden onset of paroxysmal (15 patients) or persistent (three patients) AV block reported in 23% of cases; in all but three cases, ventricular asystole > 3 s was present. Fig. 2 shows a typical example. Another frequent arrhythmia was a gradual and progressive sinus bradycardia which usually led to a ventricular pause > 3 s reported in 14% of cases. Fig. 3 shows a typical example

Compared with the younger patients, the older ones had 2.7 times higher probability of a diagnostic ECG recording and 3.1 higher probability of an arrhythmia being recorded. The actuarial probability of an ECG detection during syncope was 37% (CI $\pm$6%) and 25% (CI $\pm$9%) at 1 year and 58% (CI $\pm$6%) and 61% (CI $\pm$12%) at 2 years, respectively, in the old and young groups (difference statistically not significant) (Fig. 4).

As a consequence of ECG-documented syncope, a final diagnosis was 3.8 times more frequently made in older than in younger patients (59% vs 36%) (Table 3); the higher diagnostic value was the higher prevalence of primary cardiac arrhythmias in the older group.

Adverse events

During the ILR phase of the follow-up, four patients, all aged $\geq$65 years, died, one of them of sudden death, whose recording is unavailable; the others died of a non-cardiac cause (lung disease, cancer, pulmonary embolism). Five syncope-related traumatic episodes occurred in three patients, all aged $\geq$65 years. Thus, four patients

Figure 1   Patient flow diagram.

Table 2 Electrocardiographic diagnosis

	Age $\geq$ 65 ($n = 78$)	Age < 65 ($n = 25$)	Odds ratio (95% CI)	P value
Total ECG recordings (pts, %)	44 (56%)	8 (32%)	2.7 (1.0–8.0)	0.03
Any arrhythmia (pts, %):	34 (44%)	5 (20%)	3.1 (1.0–10.6)	0.03
− Persistent/paroxysmal AV block	18 (23%)	3 (12%)	2.2 (0.5–12.0)	ns
− Sinus bradycardia, sinus arrest	11 (14%)	2 (8%)	1.9 (0.4–29.4)	ns
− Atrial tachycardia/fibrillation	3 (4%)	0 (0%)	−	ns
− Ventricular tachycardia/fibrillation	2 (3%)	0 (0%)	−	ns
No arrhythmia (pts, %)	10 (13%)	3 (12%)	1.1 (0.2–2.0)	ns

$\geq$65 years (5%) had adverse events possibly related to ILR (not significant vs younger).

Treatment

More patients $\geq$65 years finally received ILR-guided therapy (42% vs 20%, odds ratio 2.9) (Table 4). In particular 31 patients received specific antiarrhythmic therapy guided by ILR finding of an important arrhythmia at the time of syncope relapse: pacemaker (28), implantable defibrillator (1), catheter ablation (1), and amiodarone (1). Follow-up data were obtained in 29 of these patients (25 of whom $\geq$65 years) and only one

(3%), aged 55, had recurrence of syncope during a period of 40 ± 18 months with an actuarial probability of 5% (CI $\pm$5%) at 3 years; in this patient, syncope was attributed to ventricular lead fracture. One patient died of heart failure shortly after pacemaker implant.

Discussion

In a consecutive population of patients referred for unexplained syncope, the elderly are more likely to receive an ILR implantation than younger patients. Indeed, the patients $\geq$65 years which represent
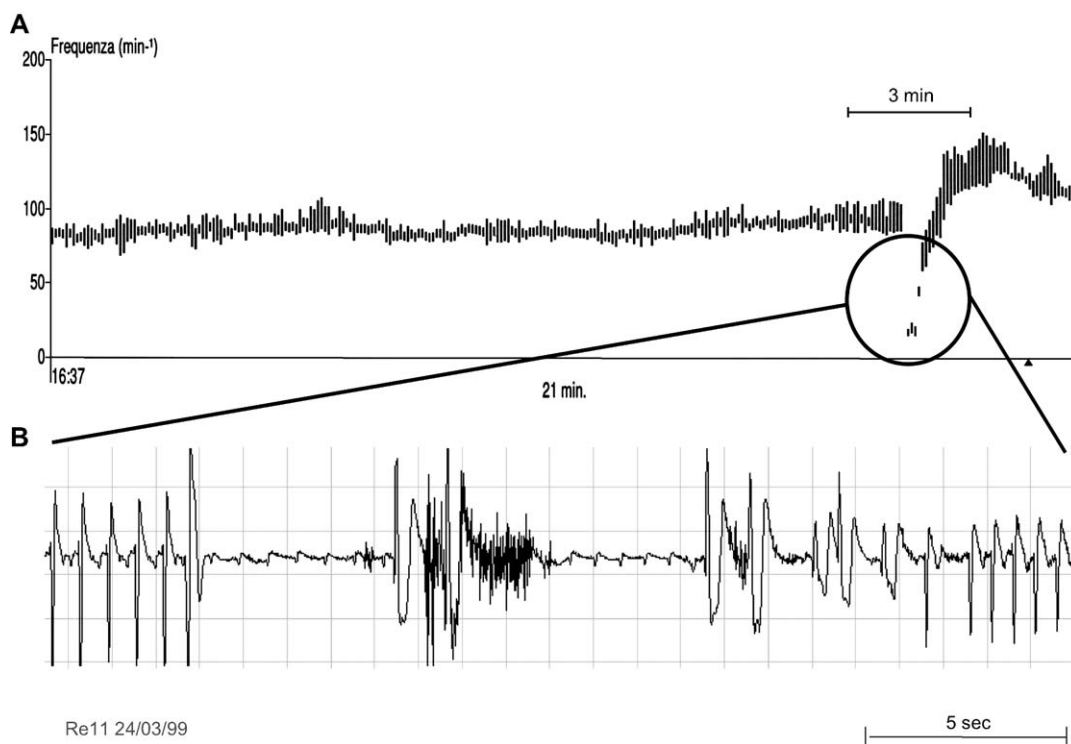

Figure 2 A sudden onset AV block was detected at the time of the syncopal attack. Trace A: heart rate trend before and at the time of syncope. Trace B: expanded ECG at the time of syncope showing a sudden onset AV block with two prolonged ventricular pauses (blocked P waves). According to the literature [4–6], this pattern was considered likely to be a primary cardiac arrhythmia due to intrinsic disease of the His-Purkinje conduction system, i.e., the ECG documentation of a Stokes–Adams attack.
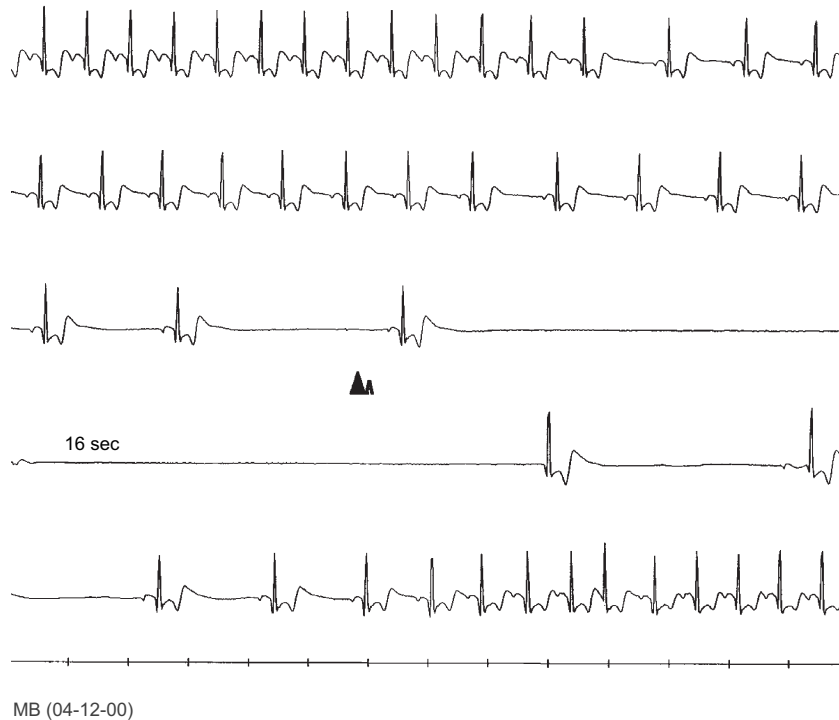
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Figure 3 Sinus bradycardia occurred at the time of syncopal recurrence which was gradual and progressive in its onset and termination. A 16 s pause was detected which was probably responsible for the loss of consciousness. According to the literature [4,5,7], this pattern was considered likely to be a neurally-mediated reflex.

the 25% of the district's population, received 75% of the ILRs. Furthermore, in older patients ILR has a higher diagnostic value, an arrhythmia, mainly a bradyarrhythmia, is more likely to be detected and effective therapy started. In older patients a diagnosis was made every 1.7 patients selected
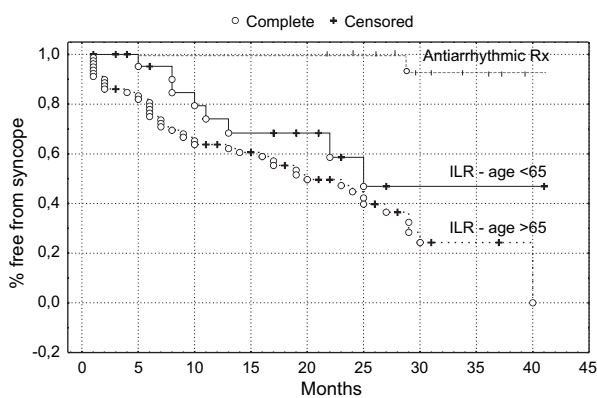

Figure 4 Actuarial curves of ECG-documented recurrence of syncope with ILR in the 78 patients ≥65 years and in the 25 patients <65 years. The comparison between the two groups was not significant (log rank, $P = 0.12$). In comparison, the actuarial curve of recurrence of syncope in 29 patients who had received any antiarrhythmic therapy guided by ILR documentation of arrhythmia at the time of syncope is superimposed.

for ILR implantation. In another study [11], logistic regression analysis of baseline variables found that age was the only independent variable that predicted bradyarrhythmic syncope and the need for pacing; advancing age was associated with earlier recurrence of syncope.

Given that the same inclusion criteria based on high risk or high frequency of syncope was used for selection of younger as well as of older patients, there are several reasons that may explain the higher usage of ILR in the older population. First, the need for a precise diagnosis in patients with structural heart disease or bundle branch block which suggest a cardiac cause (and an ominous outcome). It is well known that, in these settings, even when the conventional evaluation is unremarkable, a cardiac cause cannot be completely excluded [5,9,10]. Actually, in this study, despite a completely negative evaluation, the ILR was able to detect a likely primary arrhythmia in 33% of cases who subsequently received the proper specific therapy, namely pacemaker, implantable defibrillator or catheter ablation. Structural heart disease or bundle branch block were almost exclusively present in patients ≥65 years. Second, history has limited value in the diagnosis of cause of syncope in the elderly population; it is often difficult to differentiate from the history cardiac

Table 3 Final clinical diagnosis

	Age $\geq$ 65 (n = 78)	Age < 65 (n = 25)	Odds ratio (95% CI)	P value
Total diagnosis	46 (59%)[a]	9 (36%)[a]	3.8 (1.2—12.4)	0.04
Primary cardiac arrhythmia likely	26 (33%)	3 (12%)	3.7 (0.9—14.9)	ns (0.06)
Neurally-mediated syncope likely	18 (23%)	5 (20%)	1.2 (0.4—4.2)	ns
Hysteria	1 (1%)[a]	1 (4%)[a]	—	ns
Epilepsy	1 (1%)[a]	0 (0%)	—	ns

[a] The diagnosis was made during follow-up by reappraisal of the history and new clinical evidence.

from neurally-mediated syncope; more frequently in the elderly the onset of syncope is sudden with little or no prodrome and the occurrence of related trauma is therefore higher [5,12,13]. For all these reasons again a precise diagnosis by means of an ILR may be justified. Third, an ILR implantation can be recommended if an arrhythmia is suspected which could benefit from specific therapy e.g. pacemaker or implantable defibrillator. An arrhythmic syncope is more likely in the elderly; in an ISSUE substudy [14] young age was the strongest predictor of non-arrhythmic syncope. Pragmatically, the patients (and their physicians) are more reluctant to accept a pacemaker in the young.

An ILR is indicated when an arrhythmia is the likely cause of syncope and arrhythmic syncope is more frequent in the elderly, then also its diagnostic value should be higher in the elderly. That was exactly what we found in the present study. A presumptive diagnosis was made in 59% of patients and an arrhythmia was found in 81% of those who had an ECG recording at the time of syncope. A therapy could be started in 42% of patients who would have been otherwise untreated. Its high diagnostic value makes an ILR very attractive in the elderly and its use will increasingly be appropriate instead of, or before, many current conventional investigations [15]. In particular, ILR-guided therapy was virtually able to abolish syncopal recurrences in the patients who had an arrhythmia recorded at the time of syncope. To our knowledge this is the first report that shows evidence of the

benefit of ILR-guided therapy. Indeed, all the other studies on this topic limited their follow-up to the time of ECG diagnosis.

Nevertheless, ILR strategy is not free of risks due to syncope recurrence, mainly in the elderly. We observed a 5% rate of adverse events during the follow-up period. Therefore, this approach implies the need for a careful initial risk stratification in order to exclude from such a strategy patients with potentially life threatening conditions.

Limitation of the study

Although the population came from a consecutive series and the indication for ILR was uniform and predefined on clinical grounds, nevertheless the criteria for implantation were necessarily partly subjective and the patients who received ILR implantation were ultimately only 1/3 of those with unexplained syncope and about half of these had an ILR diagnosis. Patients who received the implantation of an ILR were informed of the possibility of an eventual pacemaker implant. This could have limited the relative number of implantations of ILRs especially in the young. On the other hand, we are convinced that the implantation of a diagnostic device is justified only if a resulting invasive therapy will be accepted.

It must be pointed out that an ILR is able to document eventually an arrhythmia which might be responsible for the syncope. From that finding the likely clinical diagnosis can only be inferred. In order to limit this uncertainty, we chose as an

Table 4 ILR-based therapy

	Age $\geq$ 65 (n = 78)	Age < 65 (n = 25)	Odds ratio (95% CI)	P value
Any therapy:	33 (42%)	5 (20%)	2.9 (0.9—10.0)	0.04
— Pacemaker	24 (31%)	4 (16%)	2.3 (0.7—9.0)	ns
— Implantable defibrillator	1 (1%)	0 (0%)	—	ns
— Catheter ablation	1 (1%)	0 (0%)	—	ns
— Others (drugs, by-pass graft)	7 (9%)	1 (4%)	2.4 (0.3—202)	ns
No therapy	45 (58%)	20 (80%)	0.3 (0.0—1.1)	0.04

end-point the documentation of a correlation between syncope and ECG findings. Asymptomatic arrhythmias and presyncopal episodes were not considered as previous studies have shown a less than optimal correlation between ECG findings and asymptomatic or presyncopal episodes vs those with syncopal episodes [4,16]. Other authors have used less strict inferential diagnostic criteria and consequently have obtained a higher diagnostic yield [16,17].

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