Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia

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Aims
Implantable cardioverter defibrillator (ICD) therapy is recommended in patients with Brugada syndrome (BS) who experienced aborted sudden cardiac death (SCD) or syncope while the risk stratification of ventricular arrhythmias is a difficult step in patients with atypical symptoms. Implantable loop recorder (ILR) use has been proposed to study patients with unexplained recurrent syncopal events, but its usefulness remains to be defined in patients with BS. In this retrospective study we aimed to investigate the effectiveness of ILR as a diagnostic tool in BS patients suspected of low or moderate risk of SCD.

Methods and results
We gathered data from 11 ILR recipients with supposed risk of ventricular arrhythmia, issue of Amiens registry of 204 patients with BS. We reported clinical events before and after implant, electrocardiogram (ECG) characteristics, ILR findings, and its limitations as well as tried to specify ILR utility in diagnosis approach and its consequent contribution to guide the optimal therapy. Within the 11 patients (8 men, 3 women), 9 were symptomatic, and 5 had a spontaneous Type 1 ECG pattern. During mean follow-up period of 33 months, 8 patients had a recurrence of symptoms with a mean delay of 9 months after implant. Bradycardia (two atrioventricular blocks and two sinus bradycardia) was detected in four out of eight patients (50%), and there was no ventricular arrhythmia in any patient during symptomatic events which included six vasovagal syncopes and two epileptic seizures. Two initially asymptomatic patients did not experience any symptoms after ILR implant and their ILR recordings did not reveal any arrhythmias.

Conclusion
The ILR contributed to the exclusion of a ventricular arrhythmia as a mechanism of an atypical syncope in patients with electrocardiographic BS and the suspension of the ICD implant. Episodes of transient symptomatic bradycardia were the most common findings suggesting the vagal mechanism of symptoms. The use of ILR should be considered in selected patients with atypical syncope and spontaneous or transient Type 1 ECG pattern.

Keywords
Brugada syndrome • Implantable loop recorder • Syncope • Ventricular arrhythmia

Introduction
The implantable cardioverter defibrillator (ICD) is considered as the only efficient therapy in reducing sudden cardiac death (SCD) in patients with Brugada syndrome (BS).1,2 Implantable cardioverter defibrillator use is unanimously justified in cardiac arrest survivors, patients with a history of sustained ventricular tachycardia or syncope. The European Society of Cardiology (ESC) guidelines for diagnosis and treatment of syncope3 recommend its use in BS patients with spontaneous Type 1 electrocardiogram (ECG) and unexplained syncope (Class IIa, B recommendations). The use of implantable loop recorders (ILRs) in patients from the general population, with unexplained syncopes has been evaluated by several studies.4–7 Implantable loop recorders might be considered in patients with BS and Type 1 pharmaco-induced pattern, but its use has not been proved until now and no level of evidence has been specified.3 Patients with Type 1 ECG pattern and unexplained syncope,8 as well as asymptomatic...
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patients with spontaneous Type 1 pattern,2 are considered to be at a moderate risk of ventricular arrhythmias and it is not certain that the benefit in reducing SCD by ICD would not be counterbalanced by complications of device therapy.9,10

Identifying the best strategy in such patients is a major goal and the use of ILR would provide some supplementary information, precise aetiology of an unexplained syncope, and thus some guidance to the therapy. We aimed to investigate the effectiveness of ILR as a diagnostic tool in BS patients suspected of a low or moderate risk of SCD.

Methods

We retrospectively looked at clinical data and device interrogation in 11 patients (5.4%) with ILR issue of BS registry of 204 patients in Amiens University Hospital over the period of 9 years between 2001 and 2010. We used the same ILR for all patients (Reveal® DX ICM, Medtronic), fitted with continuous monitoring and symptom-driven activation functions. For each patient, we precised ILR indication (according to ESC recommendations), follow-up duration, symptomatic events delay, and described automatic and triggered ILR recordings during symptoms. We also reported arrhythmic events independent of initial symptoms, as well as ECG artefacts. Finally, we described the clinical outcome of these patients considered at moderate risk of SCD.

Results

Patients characteristics

Out of 204 patients with BS diagnosed in our centre, 22 (10%) had a history of syncope. Fifteen of them with a spontaneous Type 1 ECG pattern were treated with either ICD or hydroquinidine in case of negative electrophysiological study (EPS) on treatment. Implantable loop recorder was implanted in seven other patients as well as in two patients with atypical symptoms: one with presyncope and one with dizziness.

Eight men and three women, mean age 44 years, were included in the study (Table 1). Two patients were asymptomatic: the first one with family history of several SCDs, the second one with positive EPS in spite of hydroquinidine treatment. Spontaneous Type 1 ECG pattern was present in four out of five symptomatic and one asymptomatic patient. In patients with two or three ECG patterns, the BS was diagnosed with ajmaline challenge (Patients 2–5, 7, and 11). Class Ia, B of ESC guidelines on use of ILR concerned three patients with Type 1 ST segment elevation and unexplained syncope. There was no clear recommendation or precise evidence level for ILR implantation in eight other patients.

Follow-up and device interrogation findings

Average follow-up time after ILR implant was 33 months. Three patients needed ILR replacement for battery depletion. During the follow-up period, 8 of 11 patients experienced at least one syncope, including one patient with initial syncope not reported until now. Among nine symptomatic patients, eight (88%) had recurrence of symptoms with a mean delay of 9 ± 13 months and one patient had no symptoms during the follow-up. Seven patients (78%) experienced the recurrence during the first 12 months and one patient at 41st month and following device replacement.

Six patients (75%) presented vasovagal syncope and two others (25%), typical epileptic fits.

Implantable loop recorder data were available for 11 patients and all these symptomatic events were recorded. There were no ventricular arrhythmias. Two patients (25%) presented atrioventricular block (Figure 1), two other (25%) sinus bradyarrhythmia, and four patients (50%) had normal sinus rhythm during symptoms.

Two initially asymptomatic patients did not experience any symptoms after ILR implant during, respectively, 2 and 3 years’ follow-up and their ILR recordings did not reveal any arrhythmias. Three patients (27%) reported palpitations documented by ILRs as supra-ventricular tachycardias.

Implantable loop recorder limitations

In five patients (45%) automatically triggered recordings showed artefacts and in two other cases the QRS complexes were transiently misdetected. Four patients did not trigger the ILR recordings during four synapses and two episodes of dizziness. Two patients triggered the device while suffering from chest pain.

Discussion

The purpose of this study was to assess the utility of ILR in patients with BS and presumed moderate risk of ventricular arrhythmias. From the cohort of 204 patients with BS, we retrospectively analysed the recordings in 11 patients with one or two spontaneous ECG pattern, who either experienced atypical syncope or were asymptomatic. Bradycardia including two atrioventricular blocks and two sinus bradyarrhythmias was the major finding in four of eight patients who experienced recurrence of their symptoms. Normal recordings were found in four other patients including two vasovagal synapses and two typical epileptic seizures. Implantable loop recorder recordings revealed no arrhythmias in three asymptomatic patients.

The recurrence rate of vasovagal synapses was higher (66%) and they occurred with a shorter delay as compared with studies which included patients with unexplained syncope and without diagnosed BS (Table 2).4,7,11–13 Furthermore, four (36%) of our patients experienced repeated synapses suggesting the predisposition of patients with BS to vasovagal mechanism of synapses. The percentages of patients with recurrence of syncope reported by Edwards-son in multicentre retrospective PICTURE study7 were 19, 26, and 36% after 3, 6, and 12 months vs. 37, 75 and 78%, respectively, in our study. The recurrence rate of syncope reported by Brignole et al.13 was only 33% at 1 year. Of nine symptomatic patients within our study, ILR-guided diagnosis was obtained in eight cases or 89 vs. 53% reported by Lombardi et al.11 or 52% in the RUST study4 which compared ILR and conventional Holter monitoring for diagnosis of unexplained syncope in general population. Nevertheless, in those studies, the mean follow-up time after ILR implant was shorter and the number of included subjects higher than in our study. The difference would probably be related to higher predisposition to vasovagal symptoms in BS patients.
## Table 1  General characteristics of patients, recurrent symptoms, and implantable loop recorder findings

| Clinical presentation, Spontaneous ECG pattern | Symptoms (before ILR implant) | Follow-up duration (months) | Symptoms’ recurrence delay (months) | Symptoms and ILR findings | Other ILR findings | ILR limitations |
|---------------------------------------------|-------------------------------|-----------------------------|-----------------------------------|---------------------------|--------------------|------------------|
| Patient no. 1: ECG Type 3, 2, 1 EPS—       | Palpitations and syncope      | 59                          | 6                                 | 7 pre-syncopes: 3 with 2’ Mobitz AVB, 4 with sinus rhythm | Several episodes of SVT | None             |
| Patient no. 2: ECG Type 2, EPS + hydroquinidine | Syncope with prodromal symptoms | 61                          | 41                                | 1 vasovagal syncope with 2’ Mobitz AVB | None | 5 episodes of artefacts |
| Patient no. 3: ECG Type 2, EPS — family history of SCD | Dizziness palpitations, syncope | 52                          | 10                                | 3 pre-syncopes with sinus bradycardia, 1 syncope without ILR triggering | None | Misdetection of QRS complexes, artefacts |
| Patient no. 4: ECG Type 2 family history of epilepsy | Dizziness, palpitations, pre-syncope | 24                          | 4                                 | Several pre-syncopes and 1 syncope; sinus rhythm | None | Artefacts |
| Patient no. 5: ECG Type 2, EPS—        | Pre-syncope and syncope with prodromal symptoms | 28                          | 6                                 | 2 syncopes with prodromal symptoms; sinus rhythm | 4 episodes of SVT | None |
| Patient no. 6: ECG Type 1, EPS + hydroquinidine | Dizziness, pre-syncope          | 24                          | 0                                 | Asymptomatic | None | None |
| Patient no. 7: ECG Type 2, family history of SCD | Asymptomatic                   | 29                          | 0                                 | Asymptomatic | None | None |
| Patient no. 8: ECG Type 1, EPS + hydroquinidine | Asymptomatic                   | 34                          | 0                                 | Asymptomatic | None | None |
| Patient no. 9: ECG Type 1, EPS + family history of SCD | Epileptic fit                   | 16                          | 3                                 | 4 epileptic fits; sinus rhythm | 3 episodes of paroxysmal AF | Artefacts |
| Patient no. 10: ECG Type 1, EPS—   | Unexplained syncope            | 26                          | 1                                 | 2 syncopes; sinus rhythm | None | None |
| Patient no. 11: ECG Type 2, EPS—  | Unexplained syncope            | 18                          | 1                                 | 2 pre-syncopes with sinus bradycardia | None | Artefacts |

ILR, implantable loop recorder; EPS, electrophysiological study; AVB, atrioventricular block; SVT, supra-ventricular tachycardia; SCD, sudden cardiac death.
The use of ILR in diagnosis of unexplained syncopes in BS patients has not been assessed until now. A Canadian study of 35 patients with BS reported three cases of ILR implanted for unexplained symptoms (syncope or palpitations) and negative electrophysiological study. Giustetto et al. reported no tachyarrhythmic events documented by seven ILRs implanted on the basis of high clinical profile of BS judged by physician including one EPS-induced patient, five not induced, and one not tested patient. During the follow-up one patient experienced vasovagal syncope with sinus rhythm on ILR recording. In our 11 cases ILR recordings contributed to distinguish vasovagal mechanism of symptoms from the dreaded ventricular arrhythmias and allowed to assure the patients and comfort the physician in his diagnosis approach.

Implantable cardioverter defibrillator therapy in patients with BS and atypical syncopes is undoubtedly more controversial than in cardiac arrest survivals. The rate of appropriate ICD shocks in patients with BS reported by Sacher et al. after 39 months mean follow-up was lower in patients with history of syncope as compared with cardiac arrest survivals (0 vs. 45%). Data reported by Probst et al. in FINGER BS Registry including 1029 individuals showed that the cardiac event rate per year 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. On the other hand, it has been recently reported that the incidence of ICD-related complications in this population is up to 28% including deaths related to device malfunction. Identifying patients at a high risk of SD is a major challenge. The data on prognostic value of EPS are conflicting. Significance of a family history of SCD in risk evaluation may be taken into account only if associated with spontaneous ST segment elevation. More recent study by Sarkozy reported that the family history of SD is not predictive for future arrhythmic events even if considering only SD in first-degree relatives or SD in first-degree relatives at a young age.

In spite of the small size of our ILR recipients group, the absence of ventricular arrhythmias recorded in 33 months follow-up supports hypothesis of a low risk of cardiac events in BS patients with a history of syncope. One can suggest that the risk evaluation based on clinical data and ECG is reliable and the patients with Type 1 ECG pattern and without a history of ventricular arrhythmia might have a good prognosis. Our reassuring results, even if the follow-up duration was limited, allowed for suspending or delaying ICD implant. Nevertheless, their interpretation should be cautious, since we do not have sufficient data on real cardiac risk progression and long-term prognosis of BS. Usual precautions and drugs contraindications are obviously still considered and our patients continue to be systematically re-evaluated. We believe that ILR implant should be consistently taken into account to identify the optimum therapeutic strategy in patients with BS and atypical symptoms associated to spontaneous or pharmaco-induced Type 1 ECG pattern.

Limitations of implantable loop recorder

Artefacts and QRS complexes transient misdetection, occurring in six patients (54%), lead to inappropriate recordings generating energy over consumption and saturating device memory and possible deletion of previously recorded episodes. Another limitation consists of an inappropriate device triggering either for an unjustified reason, leading to a futile memory saturation or, on the contrary, the lack of triggering during typical symptoms which concerned six symptomatic events in four of our patients. The rate of such failed recordings in PICTURE Study was 11%.

Table 2 Published data on recurrence of syncope in studies evaluating implantable loop recorder

| Year of publication | Number of patients | 3 months | 6 months | 12 months | >12 months |
|---------------------|--------------------|----------|----------|-----------|------------|
| Khran et al.        | 2001               | 60       |          | 52        |            |
| Lombardi et al.     | 2005               | 34       |          | 53        |            |
| Farwell et al.      | 2005               | 201      |          | 43        |            |
| Brignole et al.     | 2006               | 392      |          | 33        |            |
| Edvardsson et al.   | 2010               | 570      | 19       | 26        | 36         |
Conclusions
The ILR contributed to the exclusion of a ventricular arrhythmia as a mechanism of atypical syncope in patients with electrocardiographic BS. Episodes of transient symptomatic bradycardia were the most common findings suggesting the vagal mechanism of symptoms that seem more frequent than in the general population. It allows for a continual monitoring in patients with a supposed risk of ventricular arrhythmias for many years and may delay the insertion of ICD. The ILR should be systematically taken into account in patients with atypical syncope and spontaneous or transient Type 1 ECG pattern.

Conflict of interest: none declared.

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