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Predictive factors for pacemaker implantation in patients receiving an implantable loop recorder for syncope remained unexplained after an extensive cardiac and neurological workup

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ABSTRACT

Background: Several previous implantable loop recorder (ILR) studies have shown bradyarrhythmic events requiring a pacemaker implantation in a significant proportion of patients with unexplained syncope (US). The aim of this observational, two-centre, study was to identify the predictive factors for pacemaker implantation in a population of patients receiving an ILR for US with suspected arrhythmic aetiology.
Methods: Fifty-six patients (mean age 68 years, 61% male) with a history of US and negative cardiac and neurological workup, who underwent ILR implantation, were enrolled. After the implantation, a follow-up visit was undertaken after symptomatic events or every 3 months in asymptomatic subjects. The end-point of the study was the detection of a bradyarrhythmia (with or without a syncopal recurrence) requiring pacemaker implantation.
Results: After a median ILR observation of 22 months, a clinically significant bradyarrhythmia was detected in 11 patients (20%), of which 9 cases related to syncopal relapses. In the multivariable analysis, three independent predictive factors for pacemaker implantation were identified: an age >75 years (odd ratio [OR]: 29.9; $p = 0.035$); a history of trauma secondary to syncope (OR: 26.8; $p = 0.039$); and the detection of periods of asymptomatic bradycardia, not sufficient to explain the mechanism of syncope, during conventional ECG monitoring (through 24 h Holter or in hospital telemetry), performed before ILR implantation (OR: 24.7; $p = 0.045$).
Conclusions: An advanced age, a history of trauma secondary to syncope, and the detection of periods of asymptomatic bradycardia during conventional ECG monitoring were independent predictive factors for bradyarrhythmias requiring pacemaker implantation in patients receiving an ILR for US.

1. Introduction

Syncope is common in the general population [1] and is perceived as an important clinical problem with adverse outcomes from associated physical trauma, negative impact on quality of life, and potentially fatal events [2]. In about 30% of patients with syncope, despite evaluation including a complete and extensive neurological and cardiac work-up, it is impossible to identify the responsible mechanisms [3,4]. Several studies involving long-term ECG monitoring through the Implantable Loop Recorder (ILR) have shown an underlying arrhythmic aetiology, predominantly bradyarrhythmic events, in 18–65% of patients with unexplained syncope (US) [3,5–13]. Because the patients with documented symptomatic bradyarrhythmias often benefit from pacemaker implantation, as evidenced by an effective prevention of syncopal relapse and significantly improved prognosis [14], their early identification is a relevant objective of initial evaluation of patients with US.

Accordingly, the main objective of this study was to identify the predictive factors for pacemaker implantation in a population of patients receiving an ILR for US with suspected arrhythmic aetiology. Secondary objective was to identify, in the same population, the predictors of syncopal recurrence after ILR implantation.

2. Methods

2.1. Study population

The study population was derived from the evaluation of a large consecutive series of patients referred for syncope to two participating centres. It consisted of 56 patients with a history of US (of suspected arrhythmic nature) and negative cardiac and

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neurological workup, who underwent ILR implantation between March 2002 and January 2012.

All patients included in the analysis underwent an extensive cardiac and neurological workup in order to exclude any possible cardiac or neurological cause of transient, self-limiting loss of consciousness. The initial screening included a careful medical history (with description of the last syncopal episode including the characteristics of syncopal onset and recovery and duration of the event), evaluation of medication, physical examination, resting ECG, two-dimensional echocardiogram and 24 h Holter or >24 h telemetry. The strategy was to push diagnostic work-up until the syncope mechanism was clearly documented. The type and number of diagnostic procedures performed in each patient are detailed in Table 1. In 47 (84%) patients a nitrate-potentiated head-up tilt test (HUTT) had been performed according to the Italian Protocol [15] to exclude a vasovagal aetiology of syncopal episodes. Forty-nine (88%) patients underwent electrophysiological study (EPS) to confirm normal infra-Hisian conduction (HV interval <70 ms), a Wenckebach point during incremental atrial pacing >150 b.p.m., normal corrected sinus node recovery time (>550 ms), absence of inducible sustained ventricular and supraventricular arrhythmia. Exercise tests were performed in 26 (46%) patients when clinically indicated. Cardiac catheterization with coronary angiogram was performed in 12 (21%) patients to exclude coronary disease and ischemia-driven arrhythmias.

2.2. ILR implantation

In all patients included in the study, ILR implantation was indicated for high risk syncope without a demonstrated cause of syncope by a comprehensive evaluation [4]. High risk syncope was defined as the presence of clinical or ECG features suggesting an arrhythmic aetiology [4] and/or the presence of recurrent and unpredictable (absence of premonitory symptoms) syncopal episodes thus exposing patients to "high risk" of trauma or occurred during the prosecution of a "high risk" activity (e.g., driving, machine operator, flying, competitive athletics, etc.) [16,17].

Twelve (21%) patients included in the study before July 2007 received an ILR Reveal Plus 9526 model (Medtronic, Inc., Minneapolis, MN, USA). After July 2007, the patients received an ILR equipped with a longlife battery: 14 (25%) a Reveal DX 9528 model, and 30 (54%) a Reveal XT 9529 model (both by Medtronic, Inc.).

2.3. Follow-up

At the time of implantation and follow-up, no patients received medication for syncope. In all patients, other drug treatments in progress were continued without significant dosage modification. After the implantation, a follow-up visit was undertaken after symptomatic events or every 3 months in asymptomatic subjects to retrieve from the memory of the ILR the time and date of episodes of bradycardia or tachycardia and the corresponding electrocardiographic tracing. The end-point of the study was the detection of one or more bradyarrhythmic events (with or without a syncopal recurrence) requiring a pacemaker implantation (see below). For the aims of this study, in the patients still carrying an active ILR, follow-up was concluded in June 2012.

2.4. Indications for pacemaker implantation

All patients who during follow-up had a syncope recurrence and those in which a clinically significant but asymptomatic arrhythmia were documented by ILR, underwent a careful clinical evaluation in order to assess the possible indication for pacemaker implantation.

In both participating centres the implant decision was strictly based on the current guidelines for pacemaker implantation [18,19]. Specifically pacemaker implantation was indicated in the following cases: 1) syncopal episodes related to bradycardia and/or sinus arrest due to sinus dysfunction spontaneous or drug induced where alternative drug therapy is lacking; 2) syncopal episodes related to prolonged asystole (>3 s) where the circumstances of the episodes and clinical features suggest a neurally-mediated mechanism (irrespective of the result of HUTT, if performed), in patients over 40 years of age, after failure of other therapeutic options; 3) syncopal episodes related to II- or III-degree AV block; 4) syncopal episodes related to atrial fibrillation with slow ventricular response (<30 b.p.m.) and/or ventricular pauses >3 s spontaneous or drug induced where alternative drug therapy is lacking; 5) severe bradycardia (with heart rate <30 b.p.m.) and/or sinus arrest (>3 s) due to sinus dysfunction spontaneous or induced by a drug for which there is no alternative, without documented symptom rhythm correlation; 6) II- or III-degree AV block with asystole >3 s and/or escape rhythm with a heart rate <30 b.p.m., whilst awake, without documented symptom rhythm correlation; and 7) atrial fibrillation with slow ventricular response (<30 b.p.m.) and/or ventricular pauses >3 s spontaneous, without documented symptom rhythm correlation.

In cases of detection of one or more bradyarrhythmic events requiring the implantation of a pacemaker according to the criteria listed above, ILR observation was stopped and the device was removed. In other cases of diagnosis established, ILR observation was continued or stopped according to physician's judgement. Finally, in all cases of diagnosis not established, ILR observation was continued until end of device life or end of follow-up.

3. Statistical methods

Descriptive statistics were reported as means ± standard deviation for normally distributed continuous variables and compared by means of Student's t-test. Continuous variables with skewed distribution were reported as medians with 25th to 75th percentiles. Categorical variables were compared between groups using the χ^2 or Fisher's exact test as appropriate. The cumulative incidence and event-free curves were based on Kaplan–Meier analyses, stratified by study groups and compared using the log-rank test. Odd ratios (ORs) were reported with their 95% confidence intervals (CIs). In order to identify the independent predictors of the need for pacemaker implantation (primary objective), and of the syncopal recurrence during ILR observation (secondary objective), univariable analyses were first carried out and predictors with a significance level of <5% were included in multivariable models. The multivariable analyses were performed using a logistic regression model. p Values of <0.05 were considered statistically significant. The data were analysed using the statistical software package Statistica version 6.1 (StatSoft Inc., Tulsa, Oklahoma).

4. Results

4.1. Patient characteristics and results of work-up preceding ILR implantation

Clinical characteristics and details related to pre-implantation syncopal events were available for all patients and are listed in Table 2.

Table 1
Number and percentage of patients who performed tests to complete cardiac and neurological work-up in overall population and comparison between patients who during the study received a pacemaker and those who did not.

	All patients (n = 56)	Patients receiving pacemaker (n = 11)	Patients not receiving pacemaker (n = 45)	p Value
Cardiac work-up				
Medical examination, n (%)	56 (100.0)	11 (100.0)	45 (100.0)	–
Resting ECG, n (%)	56 (100.0)	11 (100.0)	45 (100.0)	–
Carotid sinus massage, n (%)	51 (91.1)	10 (90.9)	41 (91.1)	0.983
Two-dimensional echo, n (%)	56 (100.0)	11 (100.0)	45 (100.0)	–
24 h Holter or >24 h telemetry, n (%)	56 (100.0)	11 (100.0)	45 (100.0)	–
Exercise stress test, n (%)	26 (46.4)	4 (36.4)	22 (48.9)	0.455
Tilt test, n (%)	47 (83.9)	10 (90.9)	42 (93.3)	0.780
EPS, n (%)	49 (87.5)	10 (90.9)	39 (86.7)	0.703
Coronary angiogram, n (%)	12 (21.4)	2 (18.2)	10 (22.2)	0.770
Neurological work-up				
Medical examination, n (%)	56 (100.0)	11 (100.0)	45 (100.0)	–
Basal EEG, n (%)	12 (21.4)	1 (9.1)	11 (24.4)	0.266
Sleep deprived EEG, n (%)	4 (7.1)	0	4 (8.9)	0.305
Brain NMR or CT scan, n (%)	25 (44.6)	6 (54.6)	19 (42.2)	0.461
Carotid doppler, n (%)	44 (78.6)	9 (81.8)	35 (77.8)	0.770

CT: computed tomography; EEG: electroencephalogram; EPS: electrophysiological study; NMR: nuclear magnetic resonance.