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Implantable loop recorders in patients with unexplained syncope: Clinical predictors of pacemaker implantation

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Abstract

Background: *Implantable loop recorders (ILR) are a valuable tool for the investigation of unexplained syncopal episodes. The aim of this retrospective single center study was to identify predictive factors for pacemaker implantation in patients with unexplained syncope who underwent ILR insertion.*

Methods: *One hundred six patients were retrospectively analyzed (mean age 59.1 years; 47.2% male) with unexplained syncope and negative conventional testing who underwent ILR implantation. The primary study endpoint was detection of symptomatic or asymptomatic bradycardia requiring pacemaker implantation.*

Results: *The average follow-up period after ILR implantation was 20 ± 15 months. Pacemaker implantation according to current guidelines was necessary in 22 (20.8%) patients, mean duration until index bradycardia was 81 ± 88 (2–350) days. Ten (45.5%) patients received a pacemaker due to sinus arrest, 7 (31.8%) patients due to third-degree atrioventricular block, 2 (9.1%) patients due to second-degree atrioventricular block and 1 (4.5%) patient due to atrial fibrillation with a slow ventricular rate. Three factors remained significant in multivariate analysis: obesity, which defined by a body mass index above 30 kg/m² (OR: 7.39, p = 0.014), a right bundle branch block (OR: 9.40, p = 0.023) and chronic renal failure as defined by a glomerular filtration rate of less than 60 mL/min (OR: 6.42, p = 0.035).*

Conclusions: *Bradycardia is a frequent finding in patients undergoing ILR implantation due to unexplained syncope. Obesity, right bundle branch block and chronic renal failure are independent clinical predictors of pacemaker implantation.* (Cardiol J 2019; 26, 1: 36–46)

Key words: implantable loop recorder, unexplained syncope, pacemaker

Introduction

Syncope is common in the general population and is an important clinical problem with adverse outcomes from associated physical trauma, negative impact on life quality and increased cardiovascular risk [1, 2]. In addition, the investigation of syncope imposes a significant economic burden on society [3]. With a cumulative lifetime incidence of about 40% [4], syncope accounts for 1–3% of emergency department visits [1].

To investigate the underlying cause of syncope is often a difficult task, because underlying abnormalities are usually not present at the time of clinical evaluation. The European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope highlight the use of implantable loop recorders (ILRs) by including ILRs in

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class I recommendations for an evaluation of recurrent unexplained syncope, either in the early phase in non-high risk patients or after a comprehensive workup in high risk patients [5]. The ability of ILRs to continuously monitor cardiac rhythm over long periods makes them powerful diagnostic tools for patients with unexplained syncope [6]. Using ILRs, in the majority of patients a diagnosis can be established by performing long-term symptom — rhythm correlation [7–9]. Cardiac arrhythmias as primary cause of syncopes are common and most of them are caused by bradyarrhythmic events [10]. In cases of recurrent syncopal events due to bradyarrhythmia, pacemaker (PM) implantation significantly improves patient symptoms and prognosis [11]. Study data on possible predictive factors for bradycardia requiring PM implantation in patients with unexplained syncope receiving an ILR is limited [12, 13].

The aim of the present study was to identify clinical predictors of significant bradycardia requiring PM implantation in patients who underwent ILR implantation due to unexplained syncope.

Methods

Study design

The present study is a retrospective single center study, including patients who received an ILR due to unexplained syncope after conventional diagnostic work-up. A comprehensive review of patient charts was performed to identify possible clinical predictive factors for PM implantation due to bradyarrhythmias in the study population. The study protocol was approved by the human ethics committee of the Charité — Universitätsmedizin Berlin (ethic application number: EA1/234/14). All patients gave their written informed consent for scientific data analyses on a retrospective basis at hospital admission.

Study population

The study population included all consecutive patients referred to this institution (Department of Cardiology, University Hospital Charité) between February 2009 and August 2014, who underwent ILR implantation for further investigation of unexplained syncope. The diagnostic algorithm prior to ILR implantation included clinical evaluation, a 12-lead surface electrocardiogram (ECG) and echocardiography and, if considered appropriate, coronary angiography or cardiac stress testing, Holter monitoring, invasive electrophysiology and cardiac magnetic resonance imaging (cMRI). Details on the extent of conventional and special diagnostic tests are outlined in Table 1A. Clinical data for anamneses, features of the syncopal episodes, demographics, comorbidities, laboratory results, ECG parameters, echocardiographic findings and concomitant medical treatment were collected from the medical records stored on the hospital database (Tables 1A and 1B). Patients with coronary artery disease, valvular heart disease stage ≥ II, cardiomyopathy (HCM, DCM, ARVC), septum hypertrophy ≥ 14 mm or left ventricular ejection fraction (LVEF) < 55% were included under the term 'structural heart disease'. Moderate to severe structural heart disease was defined as valvular heart disease stage ≥ II or LVEF < 45%.

After hospital discharge all patients had routinely ILR interrogations at 4-month intervals at the documented outpatient clinic. In addition, patients had follow-up after each event suggestive for bradyarrhythmic or tachyarrythmic episodes to analyze stored ILR data.

ILR implantation

The ILR implantation in the present study population was performed by a cardiologist at this institution. At the time of implantation automatic activation was programmed to detect bradyarrhythmias (< 40 bpm) and tachyarrhythmias (> 170 bpm). Automatic algorithms for detection of atrial fibrillation (AF) were activated if available. The following types of ILR were used: 47 (44.3%) patients received a Reveal® DX 9528 (Medtronic, Minneapolis, MN, USA), 44 (41.5%) patients a Reveal® XT 9529 (Medtronic, Minneapolis, MN, USA), 5 (4.7%) patients a Confirm™ (St. Jude Medical, St. Paul, MN, USA) and 10 (9.4%) patients a BioMonitor (Biotronik, Berlin, Germany). Patients were instructed to activate the ILR manually in case of symptoms.

Study end points

Primary end point of this study was implantation of a PM due to documented bradyarryhthmic events. Within the ILR baseline detection setting bradyarrhythmic events were defined either by pauses of more than 3 s or by a heart rate of less than 40 bpm. Tachyarrhythmic episodes were defined as ventricular heart rate of more than 170 bpm. Secondary endpoint included syncope recurrence, AF and flutter and ventricular tachycardia after the index event.

PM implantation

Pacemaker implantation due to documented bradycardia was performed according to the ESC

Table 1A and B. Baseline demographic and clinical characteristics of the study population before insertion of an implantable loop recorder.

Table 1A.

Parameter	All patients (n = 106)	Patients with PM (n = 22)	Patients without PM (n = 84)	P
Study population				
Age [years]	59.12 ± 17.49 (21–89)	62.18 ± 12.68 (32–76)	58.32 ± 18.52 (21–89)	0.588
Age ≥ 75 years	19 (8.4%)	3 (13.6%)	16 (19.0%)	0.758
Male gender	50 (47.17%)	10 (45.5%)	40 (47.6%)	1
Female gender	56 (52.83%)	12 (54.5%)	44 (52.4%)	1
Hight [cm]	170.13 ± 8.63 (152–200)	170.64 ± 8.56 (158–190)	170.00 ± 8.697 (152–200)	0.734
Hight male [cm]	175.06 ± 8.58 (156–200)	175.60 ± 9.13 (158–190)	174.93 ± 8.56 (156–200)	0.658
Hight female [cm]	165.73 ± 5.90 (152–184)	166.50 ± 5.54 (158–176)	165.52 ± 6.04 (152–184)	0.581
BMI > 30 kg/m²	22 (20.8%)	11 (50.0%)	11 (13.1%)	**< 0.001**
BMI [kg/m²]	26.39 ± 5196 (17.3–42.1)	30.03 ± 5.21 (22.4–40.5)	25.43 ± 4.78 (17.3–42.1)	**< 0.001**
BMI male [kg/m²]	28.03 ± 5.23 (19.5–42.1)	30.66 ± 4.87 (22.4–37.7)	27.37 ± 5.17 (19.5–42.1)	0.056
BMI female [kg/m²]	24.92 ± 4.747 (17.3–40.5)	29.51 ± 5.63 (23.1–40.5)	23.67 ± 3.64 (17.3–34.1)	0.001
Cardiologic work-up				
Clinical examination	106 (100%)	22 (100%)	84 (100%)	1
Holter ECG	83 (78.3%)	17 (81.0%)	66 (80.5%)	1
Echocardiography	106 (100%)	22 (100%)	84 (100%)	1
Stress echocardiography	10 (9.6%)	3 (14.3%)	7 (8.4%)	0.418
Ergometry	34 (32.1%)	7 (33.3%)	27 (32.5%)	1
Coronary angiography	91 (85.8%)	21 (95.5%)	70 (83.3%)	0.067
Electrophysiology testing	38 (35.8%)	9 (42.9%)	29 (34.9%)	0.613
Laboratory findings before ILR implantation				
Creatinin [mg/dL]	1.003 ± 0.72 (0.54–7.54)	1.07 ± 0.49 (0.64–2.41)	0.99 ± 0.77 (0.54–7.54)	0.357
GFR [mL/min]	77.58 ± 22.18 (6.84–133.68)	71.456 ± 26.81 (23.95–133.68)	79.18 ± 20.69 (6.84–133.01)	0.134
GFR < 60 mL/min	21 (19.8%)	10 (45.5%)	11 (13.1%)	**0.002**
Hb [g/dL]	13.70 ± 1.31 (9.2–17.5)	13.60 ± 1.28 (11.3–15.7)	13.73 ± 1.322 (9.2–17.5)	0.562
TSH [mU/L]	1.49 ± 1.03 (0.01–6.52)	1.82 ± 1.41 (0.57–6.52)	1.41 ± 0.92 (0.01–4.64)	0.24
Potassium [mmol/L]	4.045 ± 0.37 (3.1–5.9)	4.047 ± 0.307 (3.4–4.6)	4.045 ± 0.38 (3.1–5.9)	0.669
ECG characteristics				
Right bundle branch block	8 (7.7%)	5 (23.8%)	3 (3.6%)	**0.008**
Left bundle branch block	4 (3.8%)	0	4 (4.8%)	1
Left anterior hemiblock	6 (5.8%)	1 (4.8%)	5 (6.0%)	0.580
Left posterior hemiblock	0	0	0	–
Intraventricular conduction delay	0	0	2 (2.4%)	1
Any bundle branch block	20 (18.9%)	6 (27.3%)	14 (16.7%)	0.229
First degree AVB	11 (10.6%)	2 (9.5%)	9 (10.8%)	1
Heart rate [bpm]	70.70 ± 15.24 (38–118)	70.52 ± 14.71 (52–118)	70.747 ± 15.46 (38–118)	0.843
PR interval [ms]	164.47 ± 30.28 (120–268)	169.33 ± 29.53 (124–252)	163.32 ± 30.53 (120–268)	0.322
QRS duration [ms]	95.92 ± 20.697 (60–186)	100.68 ± 18.46 (76–146)	94.80 ± 21.14 (60–186)	0.082
QT duration [ms]	402.11 ± 37.73 (304–510)	411.78 ± 34.14 (336–466)	399.76 ± 38.395 (304–510)	0.158
QTc duration [ms]	423.54 ± 43.81 (98–570)	432.32 ± 25.16 (380–487)	421.48 ± 47.02 (98–570)	0.144

Table 1B.

Parameter	All patients (n = 106)	Patients with PM (n = 22)	Patients without PM (n = 84)	P
Associated cardiovascular and neurological disorders				
TIA or stroke	15 (14.2%)	3 (13.6%)	12 (14.3%)	1
Diabetes type II	19 (17.9%)	5 (22.7%)	14 (16.7%)	0.538
Arterial hypertension	67 (63.8%)	19 (86.4%)	48 (57.8%)	0.013
Metabolic syndrome	27 (25.5%)	10 (45,5%)	17 (20,2%)	**0.026**
Systolic BP [mmHg]	122.88 ± 17.07 (80–170)	126.19 ± 17.99 (80–162)	122.048 ± 16.84 (90–170)	0.137
Diastolic BP [mmHg]	73.47 ± 10.64 (50–100)	77.24 ± 13.74 (55–100)	72.52 ± 9.57 (50–95)	0.121
Congestive heart failure	18 (17.1%)	3 (13.6%)	15 (18.1%)	0.759
Atrial fibrillation	29 (27.6%)	10 (45.5%)	19 (22.9%)	0.058
Coronary heart disease	26 (28.3%)	7 (31.8%)	19 (27.1%)	0.787
Cardiomyopathy (HCM, DCM, ARVC)	7 (6.6%)	1 (4.5%)	6 (7.1%)	1
Structural heart disease	47 (44.3%)	11 (50.0%)	36 (42.9%)	0.632
Moderate to severe structural heart disease	17 (16.0%)	3 (13.6%)	14 (16.7%)	1.0
LVEF [%]	57.60 ± 6.45 (35–72)	56.59 ± 6.05 (40–65)	57.87 ± 6.55 (35–72)	0.544
LVEF normal	88 (73.6%)	19 (86.3%)	69 (80.1%)	0.567
LVEF slightly reduced	14 (13.2%)	4 (18.2%)	10 (11.9%)	0.482
LVEF moderat reduced	4 (3.8%)	1 (4.5%)	3 (3.6%)	1
LVEF highly reduced	0	0	0	–
Second or higher degree valve defect	14 (14.4%)	3 (14.3%)	11 (14.5%)	1
Left ventricular hypertrophy	47 (44.3%)	13 (59.1%)	34 (46.6)	0.339
Septal diameter [mm]	12.17 ± 4.10 (6–32)	12.10 ± 1.83 (9–15)	12.20 ± 4.53 (6–32)	0.321
Concomittant medication				
Beta-blocker	58 (54.7%)	16 (72.7%)	42 (50.0%)	0.091
ACEI	36 (34%)	7 (31.8%)	29 (34.5%)	1
AT1-blockers	31 (29.2%)	11 (50.0%)	20 (23.8%)	**0.033**
Aldosterone antagonist	2 (1.9%)	0	2 (2.4%)	1
Digitalis	1 (0.9%)	0	1 (1.2%)	1
Class III anti-arrhythmic drugs	1 (0.9%)	0	1 (1.2%)	1
Class I anti-arrhythmic drugs	0	0	0	-
Calcium channel blockers	23 (21.7%)	8 (36,4%)	15 (17.9%)	0.081
Diuretics	33 (31.1%)	10 (45.5%)	23 (27.4%)	0.124
Syncope anamnesis				
Additional presyncopes	43 (40.6%)	9 (40.9%)	34 (40.5%)	0.971
1 syncope	17 (16.0%)	2 (9.1%)	15 (17.9%)	0.809
2–3 syncopes	34 (32.1%)	7 (31.81%)	27 (32.1%)	0.809
4–5 syncopes	15 (14.2%)	3 (13.6%)	12 (14.3%)	0.809
> 5 syncopes	40 (37.7%)	9 (40.9%)	31 (36.9%)	0.809
Trauma during syncope	46 (56.8%)	8 (50,0%)	38 (58.5%)	0.583
Family history of syncopes	13 (15.7%)	2 (11,1%)	11 (16.9%)	0.724
Family history of unexplained sudden death	12 (13.6%)	1 (5,6%)	11 (15.7%)	0.446
Prodromal symptoms	64 (64.0%)	13 (61.9%)	51 (64.6%)	0.804
Diziness	39 (39.0%)	9 (42.9%)	30 (38.0%)	0.802
Nausea	14 (14.0%)	3 (14.3%)	11 (13.9%)	1
Emesis	1 (1.0%)	0 (0.0%)	1 (1.3%)	1
Impaired vision	11 (11.0%)	3 (14.3%)	8 (10.1%)	0.695
Perspiration	13 (13.0%)	1 (4.8%)	12 (15.2%)	0.290
Sensation of cold	0	0	0	–
Palpipation	19 (17.9%)	3 (14.3%)	16 (20.3%)	0.536

Data are presented as number (percentage) or mean ± standard deviation (range). ACEI — angiotensin-converting enzyme inhibitor; ARVC — arrhy-thmogenic right ventricular cardiomyopathy; AT1-blockers — angiotensin II receptor antagonists; AVB — atrioventricular block; BMI — body mass index; BP — blood pressure; DCM — dilated cardiomyopathy; ECG — electrocardiogram; GFR — glomerular filtration rate; Hb — hemoglobin; HCM — hypertrophic cardiomyopathy; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack; TSH — thyroid-stimulating hormone; PM — pacemaker

guidelines for cardiac pacing and cardiac resynchronization therapy [11, 14] in the following cases: 1) Patients with symptoms which can clearly be attributed to ILR documented bradycardia. Symptoms included syncope, presyncope, dizziness, angina pectoris and dyspnoe. 2) Patients with a documented bradycardia during a possible reflex syncope and pauses due to sinus arrest or atrioventricular block (AV block) longer than 6 s. 3) Patients with a relevant but asymptomatic bradycardia documented by ILR. Following bradyarrhythmias were considered significant even in the absence of symptoms: Sinus arrest due to sinus dysfunction with pauses ≥ 3 s with an exception of young trained persons, during sleep and when bradycardia is induced by concomitant drugs; Mobitz II second-degree AV block or third-degree AV block, AF with slow ventricular conduction leading to intermittent pauses of at least 3 s during day time without reversible cause.

Statistical analysis

Mean values ± standard deviation (SD) and range were reported to describe continuous variables. Percentages were presented to report categorical variables. For univariate testing differences between PM and non-PM implantation patients were analyzed by Mann-Whitney U-test for non-normally distributed variables. Categorical variables were compared using the Fisher exact test. Thereafter a multivariate stepwise logistic regression analysis was performed to identify clinical predictors of PM implantation. Univariate and multivariate analyses were adjusted by age and gender. Kaplan–Meier survival curves were used to present time course to syncopal recurrence and to occurrence of bradyarrhythmia. All p-values are two-sided, and a p-value of < 0.05 was considered to be statistically significant. All analyses were performed using SPSS® for Windows Version 22.0 (SPSS Inc.).

Results

Patient population

Between February 2009 and August 2014 a total of 106 patients (age 59.1 ± 17.5; 50 [47.2%] male) met the inclusion criteria of this study. Demographic characteristics and comorbidities of the study population group are shown in Tables 1A and 1B. Amongst the study population, Holter monitoring (24 h to 5 days) was done in 83 (78.3%) patients. Coronary angiography was performed in 91 (85.8%) patients to exclude coronary artery disease. Stress echocardiography was performed in 10 (9.6%) and ergometry in 34 (32.1%) patients. There were 38 (35.8%) patients who had electrophysiology testing performed prior to ILR insertion. The majority of patients (88; 73.6%) had normal LVEF, 14 (13.2%) patients had slightly reduced LVEF and only 4 (3.8%) patients had moderately reduced LVEF. Forty-six (56.8%) patients had a trauma secondary to syncope. Eighty-nine (83.7%) patients experienced two or more syncopal episodes prior to ILR insertion. Twelve (13.6%) patients had a family history of sudden cardiac death. Atrial fibrillation was known before ILR implantation in 29 (27.6%) patients. The mean PR interval was 164.6 ± 30.3 ms with no significant difference ($p = 0.322$) between the group receiving a PM (169.3 ± 29.5 ms) and the group not receiving a PM (169.3 ± 30.5 ms). Mean heart rate (HR) at ILR implantation was 70.7 ± 15.2 bpm. All patient characteristics used for univariate analyses are depicted in Tables 1A and 1B.

Follow-up. Data and study endpoints

Details on patient follow-up are depicted in Figure 1. Mean follow-up in this study population was 19.8 ± 15.4 (0.1–58.8) months. No death was recorded in the study population during the follow-up period. Overall, diagnosis is based on the ILR was made in 46 (43.4%) patients. The most common diagnosis was non-arrhythmic syncope (19 patients). In 22 (20.8%) patients a PM was implanted due to documented bradyarrhythmic episodes, of whom 10 (45.5%) patients were male (age 62.2 ± 12.7 years). The median time from ILR insertion to documented bradycardia and consecutive PM implantation was 81 ± 88 (range 2 to 350) days. Ten (45.5%) patients had a PM implanted for sinus arrest, 2 (9.1%) patients had a second-degree AV block, 7 (31.8%) patients showed third-degree AV block and 1 (4.5%) patient had AF with a slow ventricular rate. In 10 (45.5%) patients a PM was implanted due to syncope recurrence with documented significant bradyarrhythmic episodes, whereas in 12 (54.5%) patients significant bradycardia was considered an indication for PM implantation even in the absence of symptoms. Two (9.1%) patients suffered from a recurrent syncope after PM implantation.

In 5 (4.7%) patients, new tachyarrhythmic episodes were found during ILR monitoring. In 3 (2.8%) of these patients paroxysmal supraventricular tachycardia (AV-nodal reentry tachycardia, atrial flutter) was recorded, which was successfully treated by catheter ablation. In 1 patient a paroxysmal

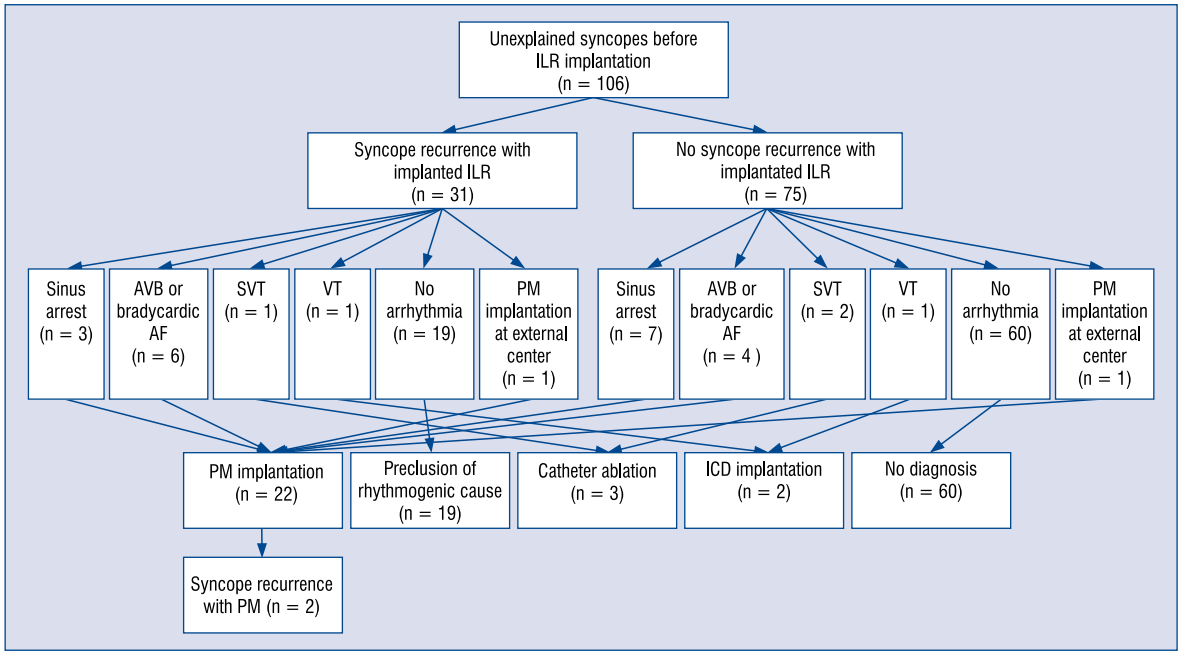

Figure 1. Follow-up data of the overall study population after implantable loop recorder (ILR) implantation; AF — atrial fibrillation; AVB — atrioventricular block; ICD — implantable cardioverter-defibrillator; PM — pacemaker; SVT — supraventricular tachycardia; VT — ventricular tachycardia.

supraventricular tachycardia was associated with syncope recurrence. Two (1.9%) patients underwent implantable cardioverter-defibrillator (ICD) implantation because of documented ventricular tachycardia. In 4 (3.8%) patients an oral anticoagulation therapy was initiated due to first time detection of AF or atrial flutter. Figure 2 depicts the time course of diagnosis, either exclusion of an arrhythmogenic cause due to syncopal recurrence without documented rhythm disorders (Fig. 2A) or documentation of relevant bradyarrhythmic events necessitationg PM implantation (Fig. 2B).

Clinical predictors of PM implantation

In the univariate analyses, (Table 2) the following factors were associated with PM implantation after additional adjustment for gender and age: obesity, defined by a body mass index (BMI) above 30 kg/m^2 (odds ratio [OR]: 8.096; 95% confidence interval [CI] 2.619–25.023; $p < 0.001$), renal failure with a glomerular filtration rate (GFR) of less than 60 mL/min calculated using the Cockcroft-Gault formula (OR: 6.147; 95% CI 1.857–20.352; $p = 0.003$), a right bundle branch block (RBBB) (OR: 8.058; 95% CI 1.740–37.327; $p = 0.008$), arterial hypertension (OR: 6.255; 95% CI 1.332––29.378; $p = 0.020$), medical treatment with AT1-receptor blockers (OR: 3.254; 95% CI 1.085–9.753; $p = 0.035$) and the metabolic syndrome (OR: 3.262; 95% CI 1.147–9.275; $p = 0.027$).

Variables which were significant predictors of PM implantation in univariate analysis were further analyzed by a multivariate regression analysis. From six factors which were determined by multivariate regression analysis, the following factors were identified as independent predictive factors of PM implantation (Table 2): Obesity, defined by a BMI above 30 kg/m^2 (OR: 7.388; 95% CI 1.495–36.506; $p = 0.014$), a RBBB (OR: 9.401; 95% CI 1.357–65.117; $p = 0.023$) and renal failure with a GFR of less than 60 mL/min [2] (OR: 6.420; 95% CI 1.156–35.655; $p = 0.035$).

The rate of PM implantation according to the presence of risk factor in the present study population is displayed in Figure 3. A combination of two or more predictors significantly increased the rate of PM implantation.

Discussion

The current study aimed to identify clinical predictors of bradycardia necessitating PM implantation in patients with unexplained syncope during ILR monitoring. In the present study, bradycardia

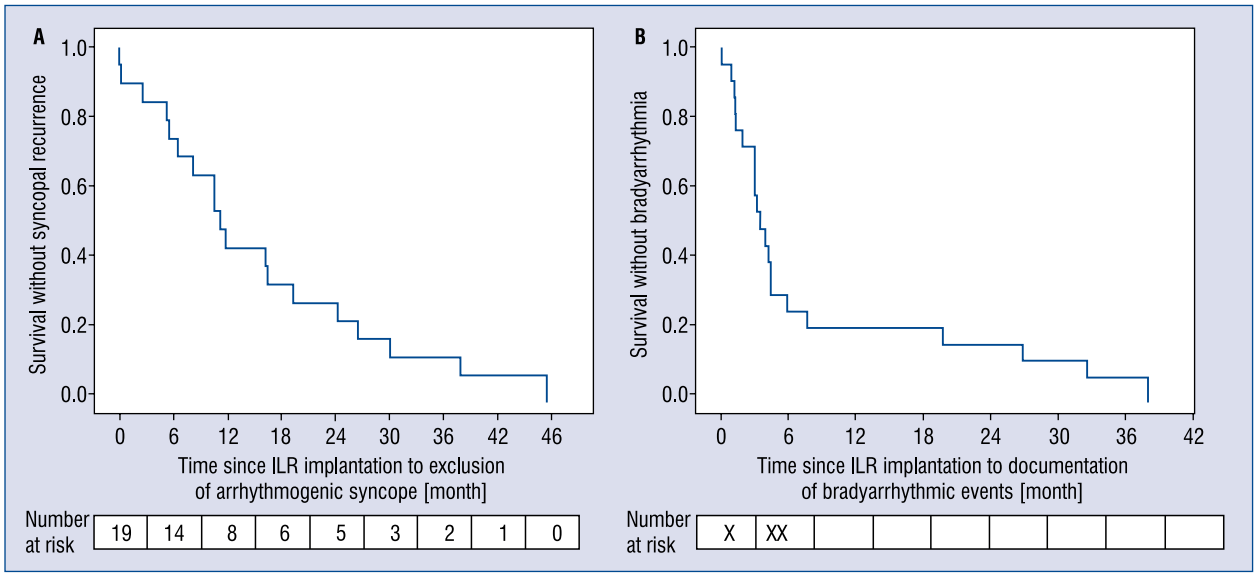

Figure 2. Time course after implantable loop recorder (ILR) insertion of exclusion of an arrrhythmogenic cause due to syncopal recurrence without documented rhythm disorders (**A**) and time course of documented relevant bradyarrhythmia necessitating pacemaker implantation (**B**).

Table 2. Predictors of pacemaker implantation in the overall study population according to odds ratio (OR) calculated by univariate and multivariate analysis.

Variable	Univariate analysis*			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
BMI > 30 kg/m^2	8.096	2.619–25.023	< 0.001	7.388	1.495–36.506	0.014
GFR < 60 mL/min	6.147	1.857–20.352	0.003	6.42	1.156–35.655	0.035
Right bundle branch block	8.058	1.740–37.327	0.008	9.401	1.357–65.117	0.023
Arterial hypertension	6.255	1.332–29.378	0.02	4.064	0.611–27.041	0.147
AT1-blockers	3.254	1.085–9.753	0.035	1.05	0.205–5.380	0.954
Metabolic syndrome	3.262	1.147–9.275	0.027	0.43	0.078–2.358	0.331

*Adjusted for age and sex; BMI — body mass index; CI — confidence interval; GFR — glomerular filtration rate

requiring PM implantation was found in 22 out of 106 patients (20.8%). This proportion is comparable to previous published data (14–21%) [9, 15]. The overall diagnosis rate was higher than reported by others (43.4%), whereas data from large registries reveal a final diagnosis in approximately 30% of the patients [9, 12, 13, 15].

Obesity, chronic renal failure with a GFR < 60 mL/min and RBBB were identified as significant independent clinical predictors of PM implantation. In addition, the existence of two or more predictors significantly increased the rate of PM implantations. All three identified risk factors are possible markers for an underlying medical condition that may be associated with an impairment of the electrical impulse generating and conduction system of the heart.

Chronic renal failure

A negative impact of chronic kidney disease (CKD) on cardiac function and alterations of cardiac rhythm stability has been known for a long time. The cardiorenal syndrome refers to the interconnection of heart and kidney dysfunctions and is related to poor clinical outcomes [16]. Chronic kidney disease has been shown to be a risk factor of sudden cardiac death caused by cardiomyopathy, myocardial inflammation, myocardial fibrosis, arrhythmias and conduction abnormalities [17, 18]. Sudden cardiac death in patients with chronic renal failure is associated with increased levels of inflammatory markers such as high-sensitivity C-reactive protein and interleukin 6 which are both linked to fibrotic changes of the myocardium and the electrical conduction system itself [19]. Previ-

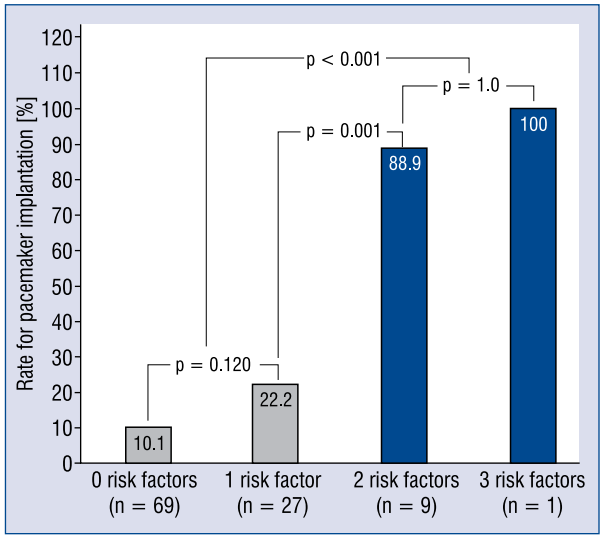

Figure 3. Risk of pacemaker implantation in the overall study population according to the number of independent predictive risk factors. A combination of two or more predictors significantly increased the risk of pacemaker implantation.

ous studies reported that CKD is independently associated with alterations in left atrial function (left atrial volume and atrial strain rate) as well as ventricular strain rates, both markers for myocardial fibrosis [20, 21]. Accordingly, cMRI studies revealed myocardial fibrotic alterations in patients with CKD [22]. Based on these alterations in myocardial interstitial structure chronic changes in sinus node function and cardiac conduction system are reasonable [23, 24]. However, renal failure has not been identified as an independent risk factor for bradyarrhythmic events as yet. In the present study a highly significant association between PM implantation and bradyarrhythmic event in patients with a GFR of less than 60 mL/min was found, this measurement is defined as cutoff for a CKD stage 3.

Obesity and metabolic syndrome

Several studies have demonstrated an association between obesity and cardiac arrhythmias with increased risk of sudden cardiac death and AF [25, 26]. Obesity is associated with pathological myocardial changes such as myocyte hypertrophy, fibrosis, focal myocardial disarray, fatty infiltration, and increased epicardial fat [27]. The effect of myocardial fibrosis on sinus node function and the electrical conduction system has been described previously [28]. Thus, previous animal studies have shown that metabolic syndrome and obesity induce alterations of sinus node function due to fat accumulation around nodal cardiomyocytes and changes in sympathetic innervation [29, 30]. Moreover, obesity associated increased leptin and reduced adiponectin levels might also contribute to increased atrial fibrosis [31]. Amongst the present study population 10 (9.4%) patients had PM implanted due to sinus arrest.

Long-term effects of myocardial fibrosis on the electrical conduction systems have been described in the context of various cardiac diseases. Thus, functional alterations in the AV-node associated with increased fibrosis were reported in animal models of heart failure [32]. In a large-scale Australian cohort study the risk of hospitalization with a primary diagnosis of AV block has been shown to significantly increase with an increment of BMI [33]. In addition to structural changes as an underlying cause of sinus node and electrical conduction system dysfunction in obese patients, functional alterations associated with sleep apnea have also been documented in these patients [34, 35] severe sleep apnea is a known risk factor of sudden cardiac death. However, the role of bradyarrhythmias in patients with severe sleep apnea and a potential beneficial effect of PM therapy in patients with prolonged episodes of asystole is still controversial [35]. Amongst the present study population, sleep apnea induced bradycardia is rather unlikely as bradyarrhythmic episodes necessitating PM implantation occurred solely during daytime. Among this study population 9 (8.5%) patients had PM implanted for AV block.

Right bundle branch block

The 2013 ESC guidelines on cardiac pacing state that PM implantation may be considered in selected patients with unexplained syncope and bundle branch block (BBB) (recommendation class IIb) [11]. The Bradyarrhythmia detection in the BBB (B4) Study analyzed the clinical outcomes of patients with syncope and BBB followed a systematic diagnostic approach, including electrophysiological study and ILR implantation [36]. Although the most common cause of syncope in these patients was bradyarrhythmia, mostly due to paroxysmal AV block, other etiologies of syncope were identified in 17.6% of the study population. The PRESS Study, a prospective multicenter study randomized 101 patients with bifascicular block and unexplained syncope implanted with a dual chamber PM to either DDD pacing mode with a 60 ppm lower rate or DDI mode with 30 ppm lower rate [37]. The use of a dual chamber PM programmed to DDD 60 ppm led to

a significant reduction of the combination of syncope/presyncope compared with DDI 30 ppm programming [37]. The composite primary end point occurred in 23 patients, whereas only 14 patients developed a class I indication for permanent pacing during the course of the study. In addition, several studies focusing on the outcome of patients with bifascicular block and previous syncope reported consistent rates of AV block development over time [38]. However, none of these studies was designed to identify clinical predictors of bradyarrhythmic events necessitating PM implantation. In the present group of syncopal patients, the incidence of left bundle branch block (LBBB) was relatively low, which might explain why statistical significance was not achieved in this subgroup. Moreover, in elderly patients with LBBB and unexplained syncope, PM implantation was often the therapy of choice in the present institution instead of ILR implantation.

Comparison of previous studies evaluating predictors of PM implantation

Several studies analyzed the effectiveness of ILRs or prolonged monitoring in predicting the cause of syncope, reporting a diagnostic yield up to 78% [9, 39–41]. However, only few studies were specifically designed to identify clinical predictors of bradycardia requiring PM implantation in patients with unexplained syncope undergoing ILR monitoring. Previous work by Palmisano et al. [12] identified age > 75 years, a history of trauma secondary to syncope and asymptomatic bradycardia as independent predictive factors for bradyarrhythmias necessitating PM implantation in patients receiving an ILR due to unexplained syncope. In addition, Ahmed et al. [13] recently found that age > 75 years, female sex, a history of injury secondary to syncope and a prolongation of the PR interval over 200 ms are independent predictors of PM implantation in these patients.

Differences between the present results and previous studies are probably related to the relatively small cohort of patients and high heterogeneity. Thus, the present study and work by Palmisano et al. [12] and Ahmed et al. [13] differs in terms of patient characteristics, clinical work-up preceding ILR implantation, cohort size, type and programming of implanted ILRs. Palmisano et al. [12] enrolled 56 patients with a mean age of 68.1 years (61% male), whereas our study population included 106 patients with a mean age of 59.1 years (50% male). Thus, the rates of PM implants were also analyzed in this study cohort in patients < 75 years vs. patients ≥ 75 years and no statistically significant difference was found. A possible explanation for this finding might be that older patients were treated with syncope and particularly those with subsequent traumatic injury and a lower threshold for implanting a PM instead of considering ILR monitoring.

In the study population of Palmisano et al. [12] only 11 patients had bradyarrhythmic events necessitating PM implantation, which may have led to an overinterpretation of the validity in identified predictive factors. The study population of Ahmed et al. [13] consisted of 200 patients with a mean age of 61.7 years (45% male). However, compared to Ahmed et al. [13] the frequency of hypertension, diabetes and coronary artery disease in the present study population was higher and the incidence of RBBB and LBBB was lower.

Clinical impact

As previous studies have shown that recurrent syncope increases both mortality and morbidity [42], early diagnosis and timely therapeutic intervention is essential in patients presenting with unexplained syncope. ILRs have been shown to be a useful and cost-effective tool in the diagnosis for patients with unexplained syncope [41, 43, 44], however this method has the drawback of a prolonged period of observation with possible syncopal recurrences before diagnosis and therapeutic intervention.

As a cardiac cause of syncope was established in 22.4% of syncopal patients with ILR (128 out of 570) in the PICTURE (Place of Reveal in the Care pathway and Treatment of patients with unexplained Recurrent Syncope) registry [9], in identification of predictors of arrhythmic syncope, it is important to identify patients at higher risk of developing future bradyarrhythmic events. A risk stratification for patients with unexplained syncope based on predictive factors which can easily be assessed during the initial work-up might help to identify patients necessitating PM implantation and thereby expedite timely device therapy.

Limitations of the study

The study presented here has two main limitations. First, it is retrospective single center analysis of a relatively small cohort of patients. Second, overall RBBB was documented in only 8 (7.7%) patients. Thus, despite the statistical significance the relatively small number of patients with RBBB may have introduced bias in to the interpretation of the results.

Conclusions

The present study identified patients in a population receiving ILR due to unexplained syncope obesity, RBBB and chronic renal failure with a GFR < 60 mL/min as independent predictors of future bradyarrhythmic events requiring PM implantation. Moreover, a combination of two or more of these predictive factors significantly increased the risk of PM implantation. Thus, PM implantation might be directly considered in patients if all identified predictive factors are present to reduce mortality and morbidity associated with recurrent syncope. However, a large prospective, multicenter study is necessary to corroborate these findings.

Conflict of interest: None declared

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