ORIGINAL ARTICLE

Korean J Intern Med 2025;40:616-625
https://doi.org/10.3904/kjim.2024.364

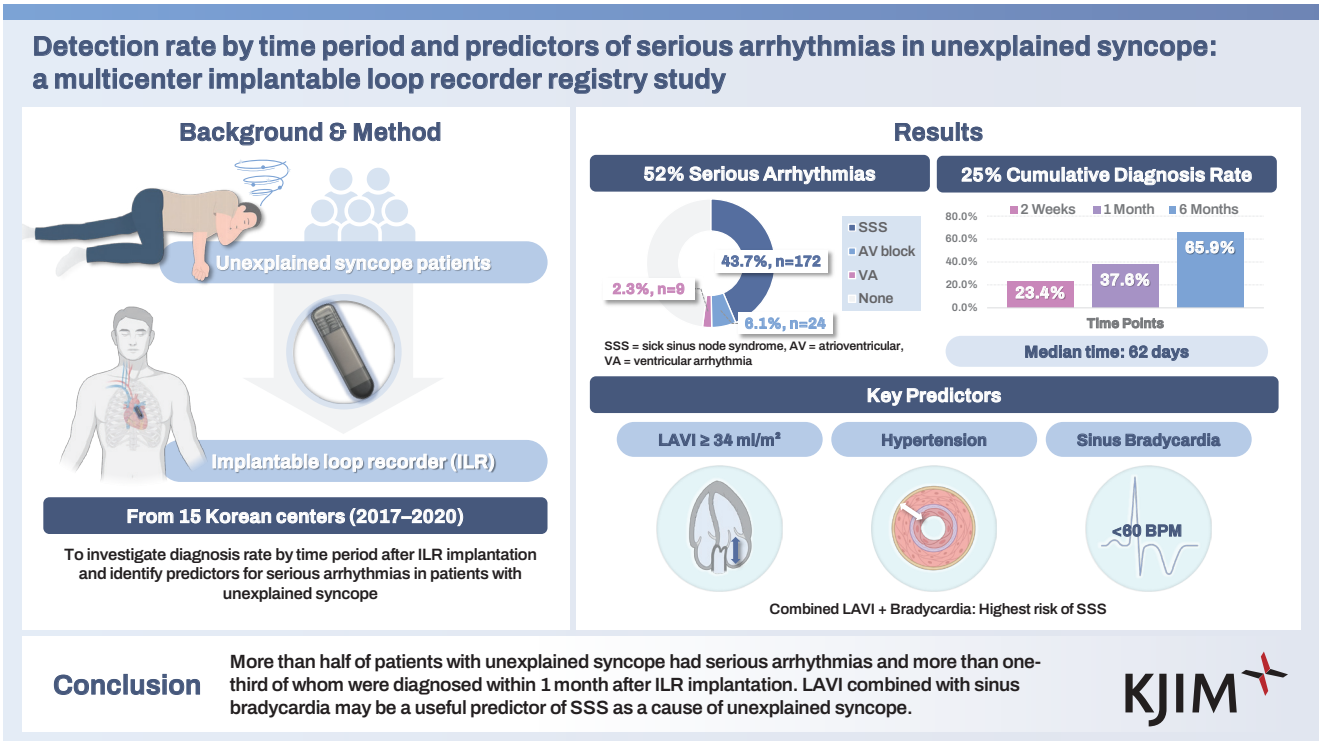
Detection rate by time period and predictors of serious arrhythmias in unexplained syncope: a multicenter implantable loop recorder registry study

Juwon Kim[1,*], Il-Young Oh[2,*], Myung-Jin Cha[3], Jinhee Ahn[4], So-Ryoung Lee[5], Sung Ho Lee[6], Jae-Sun Uhm[7], Pil-Sung Yang[8], Jaemin Shim[9], Hyoung-Seob Park[10], Junbeom Park[11], Jun Hyung Kim[12], Ki-Hun Kim[13], Jumsuk Ko[14], Hong Euy Lim[15,†], and Ju Youn Kim[1]

[1]Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [2]Cardiovascular Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam; [3]Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [4]Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Pusan University College of Medicine, Busan; [5]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; [6]Division of Cardiology, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [7]Department of Cardiology, Severance Hospital, Yonsei University College of Medicine, Seoul; [8]Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam; [9]Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine and Korea University Anam Hospital, Seoul; [10]Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Keimyung University Dongsan Hospital, Keimyung University College of Medicine, Daegu; [11]Division of Cardiology, Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul; [12]Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon; [13]Division of Cardiology, Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan; [14]Division of Cardiology, Department of Internal Medicine, Wonkwang University School of Medicine, Iksan; [15]Division of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

*These authors contributed equally to this manuscript.

[†]Present affiliation: Division of Cardiology, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, Korea (E-mail: hongeuy1046@gmail.com)



pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

Background/Aims: Although an implantable loop recorder (ILR) is a valuable tool for investigation of unexplained syncope, there are limited data regarding time course to diagnosis and predictors of serious arrhythmias as a cause of unexplained syncope. We sought to investigate diagnosis rate by time period after ILR implantation and identify predictors of serious arrhythmias in patients with unexplained syncope.

Methods: We identified 394 patients who received ILR implantation for unexplained syncope enrolled in the Korean ILR registry.

Results: Serious arrhythmias were documented in 205 patients (52.0%). One hundred seventy-two patients (43.7%) had sick sinus-node syndrome (SSS), 24 (6.1%) had atrioventricular block, and nine (2.3%) had ventricular arrhythmia. Of these, 48 (23.4%) and 77 (37.6%) were diagnosed within two weeks and one month after ILR implantation, respectively. Median time to diagnosis was 62 days. In multivariable analysis, left atrial volume index (LAVI) ≥ 34 mL/m^2 (hazard ratio [HR] 1.582), hypertension (HR 1.788), sinus bradycardia with a heartrate less than 60 beats per minute (HR 1.762), and LAVI ≥ 34 mL/m^2 combined with sinus bradycardia (HR 1.911) were independent predictors of SSS. Cumulative detection rate of SSS was significantly higher in patients with LAVI ≥ 34 mL/m^2 than those with LAVI < 34 mL/m^2 ($p < 0.001$).

Conclusions: More than half of patients with unexplained syncope had serious arrhythmias, and more than one-third of these arrhythmias were diagnosed within one month after ILR implantation. LAVI combined with sinus bradycardia may be a useful predictor of SSS as a cause of unexplained syncope.

Keywords: Echocardiography; Implantable loop recorder; Sick sinus syndrome; Syncope

INTRODUCTION

Syncope is a transient loss of consciousness resulting from cerebral hypoperfusion, typically marked by sudden onset, brief duration, and full spontaneous recovery [1]. Syncope can be broadly categorized into reflex syncope, syncope due to orthostatic hypotension, and cardiac syncope [2]. Comprehensive investigation is needed to accurately diagnose the underlying cause [1,2] because cardiogenic syncope due to serious arrhythmias can result in fatal outcomes [3]. However, timely diagnosis is very challenging due to the unpredictable and temporary nature of cardiac arrhythmias [4,5].

Long-term electrocardiography (ECG) monitoring devices such as an implantable loop recorders (ILRs) are widely used to diagnose, screen, and monitor various cardiac arrhythmias [6,7]. According to current guidelines, long-term ambulatory ECG monitoring with ILR is recommended in patients with unexplained syncope, particularly when a thorough evaluation fails to reveal an underlying cause [1,2].

Previously, several studies have investigated the diagnostic usefulness of ILR and the clinical predictors of pacemaker implantation in patients who underwent ILR due to unexplained syncope [5,8-12]. However, the number of patients included in those studies was limited, and they focused primarily on predicting pacemaker implantation without considering predictors of clinically serious arrhythmias [13]. Furthermore, the significance of echocardiography was not evaluated. Therefore, we sought to investigate the diagnosis rate by time period after ILR implantation and identify predictors of serious arrhythmias in patients with unexplained syncope from a relatively large cohort population.

METHODS

Study population and ILR implantation

This multicenter cohort study included 795 patients who underwent ILR implantation at 15 institutes in Korea between January 2017 and December 2020. Among these patients, 394 who had unexplained syncope were finally enrolled in the study (Fig. 1). This study complied with the Declaration of Helsinki, and the Institutional Review Board approved the study protocol (approval number: SMC-2021-10-011). Written informed consent was waived as this was a retrospective study of de-identified administrative data.

Comprehensive evaluations including 12-lead ECG, Holter monitoring, a treadmill test, echocardiography, and head-up tilt test were performed to find the underlying cause of syncope. Patients exhibiting the following clinical features of reflex syncope were excluded: (i) typical progressive prodrome

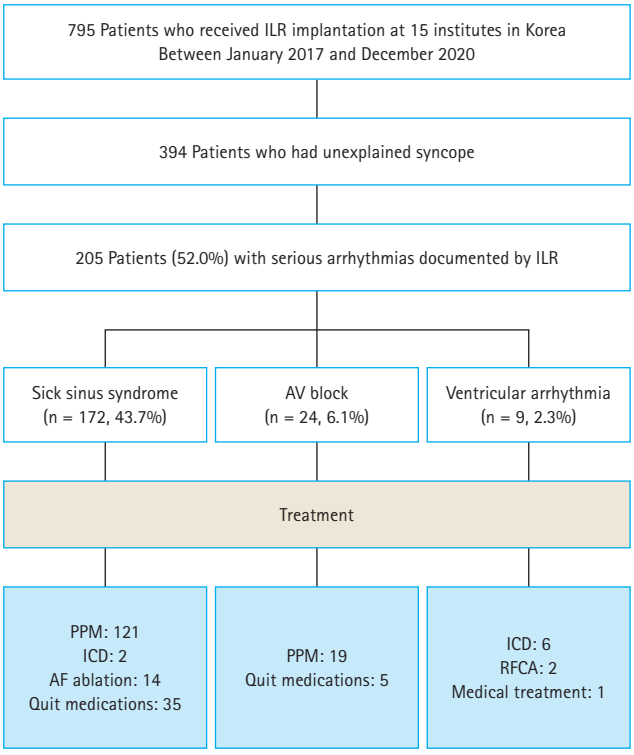


Figure 1. Study flow. ILR, implantable loop recorder; AV, atrioventricular; PPM, permanent pacemaker; ICD, implantable cardiac defibrillator; AF, atrial fibrillation; RFCA, radiofrequency catheter ablation.

(light-headedness, pallor, feeling of warmth, sweating, nausea, or vomiting); (ii) definite precipitating factors (standing, pain, fear, or overheating); or (iii) specific triggers (micturition, defecation, swallow, or cough). ILR implantation was conducted at each operator's discretion if the underlying cause was not clear. According to the reimbursement policy of the Korean national health insurance, ILR implantation is permitted if a patient has experienced at least two episodes of unexplained recurrent syncope or one or more episodes of syncope in the presence of structural heart disease.

An ILR (Reveal LINQ ICM, Reveal Plus, or Reveal DX-XT; Medtronic Inc., Minneapolis, MN, USA or Confirm^{TM}; Abbott, Chicago, IL, USA) was implanted beneath the skin in the left side of the chest near the nipple line under local anesthesia. During follow-up, interrogation of the ILR was regularly performed every three or six months. If dizziness, syncope, palpitations, or any other symptoms occurred, ILR interrogation was conducted as soon as possible, and the results were confirmed by electrophysiologists at each institute. Follow-ups were performed only in person, and remote monitoring was not allowed.

Data collection, definitions, and outcomes

Baseline characteristics, 12-lead ECG, echocardiography, ILR interrogation, and clinical outcome data were collected according to a standardized report form and protocol. Baseline 12-lead ECG findings were derived from the baseline ECG recorded before ILR implantation. Sinus bradycardia (< 60 beats per minute) was also determined based on the baseline 12-lead ECG obtained prior to ILR implantation. Structural heart disease included coronary artery disease, ischemic or non-ischemic cardiomyopathy, hypertrophic cardiomyopathy, congestive heart failure, and moderate to severe valvular heart diseases. Intraventricular conduction delay included right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, and bi-fascicular block. Echocardiographic findings within three months prior to ILR implantation were assessed. Left atrial (LA) volume was measured using the biplane area-length method, and the LA volume index (LAVI) was then derived by dividing LA volume by body surface area. Left ventricular ejection fraction was measured using the biplane Simpson's method.

A final diagnosis of cardiac arrhythmia as the cause of syncope was based on a relationship between symptoms and ECG findings of ILR. In the present study, the arrhythmic causes of syncope were classified into three categories: sick sinus-node syndrome (SSS), atrioventricular (AV) block, and ventricular arrhythmia (VA). SSS was defined as a pause of three seconds or more or bradycardia less than 40 beats per minute in an awake state and also included tachycardia-bradycardia patterns. AV block was defined as third-degree AV block, second-degree AV block Mobitz type 2, or high-grade AV block based on evidence of asystole lasting five seconds or more during atrial fibrillation while awake. VA was defined as a heart rate exceeding 160 beats per minute originating from the ventricles and lasting for at least 30 seconds.

Statistical analysis

Continuous variables were analyzed using the unpaired t-test or Mann–Whitney rank-sum test and are presented as means and standard deviations or medians with interquartile ranges according to their distributions, which were assessed using the Kolmogorov–Smirnov test and visual inspection of Q-Q plots. All discrete and categorical variables are presented as numbers and relative frequencies (percentages) and were compared using the chi-square test or Fisher's exact

https://doi.org/10.3904/kjim.2024.364

test. A multivariable Cox proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) to find independent predictors of serious arrhythmia among patients who underwent ILR implantation for unexplained syncope. Multivariable Cox proportional hazard models were constructed using clinically relevant variables. Cumulative incidences of arrhythmia detection according to LAVI, hypertension, and sinus bradycardia less than 60 beats per minute are presented as Kaplan–Meier estimates and were compared using log-rank tests. Statistical analyses were performed using SPSS 25.0 for Windows (IBM Corp., Armonk, NY, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Detection and treatment of arrhythmia causes

Among a total of 394 patients, 205 (52.0%) had serious arrhythmias documented by ILR. One hundred seventy-two patients (43.7%) had SSS, 24 (6.1%) had AV block, and nine (2.3%) had VA (Fig. 1). Among the 196 patients with serious bradycardias including SSS and AV block, 142 (72.4%) received a permanent pacemaker or an implantable cardiac defibrillator (ICD). Fourteen patients (7.1%) underwent atrial fibrillation ablation due to tachycardia-bradycardia syndrome, and 40 patients (20.4%) were recommended to discontinue medications that cause bradycardia. Of nine patients with VA, six (66.7%) underwent ICD implantation, two (22.2%) underwent radiofrequency catheter ablation, and one (11.1%) was prescribed anti-arrhythmic medications. Median time to diagnosis was 62 days (interquartile range: 17–301 days). Figure 2 shows the number of patients diagnosed with serious arrhythmias during the follow-up period after ILR implantation. Forty-eight patients (23.4%), 77 patients (37.6%), and 135 patients (65.9%) were diagnosed within two weeks, one month, and six months after ILR implantation, respectively. After six months, the

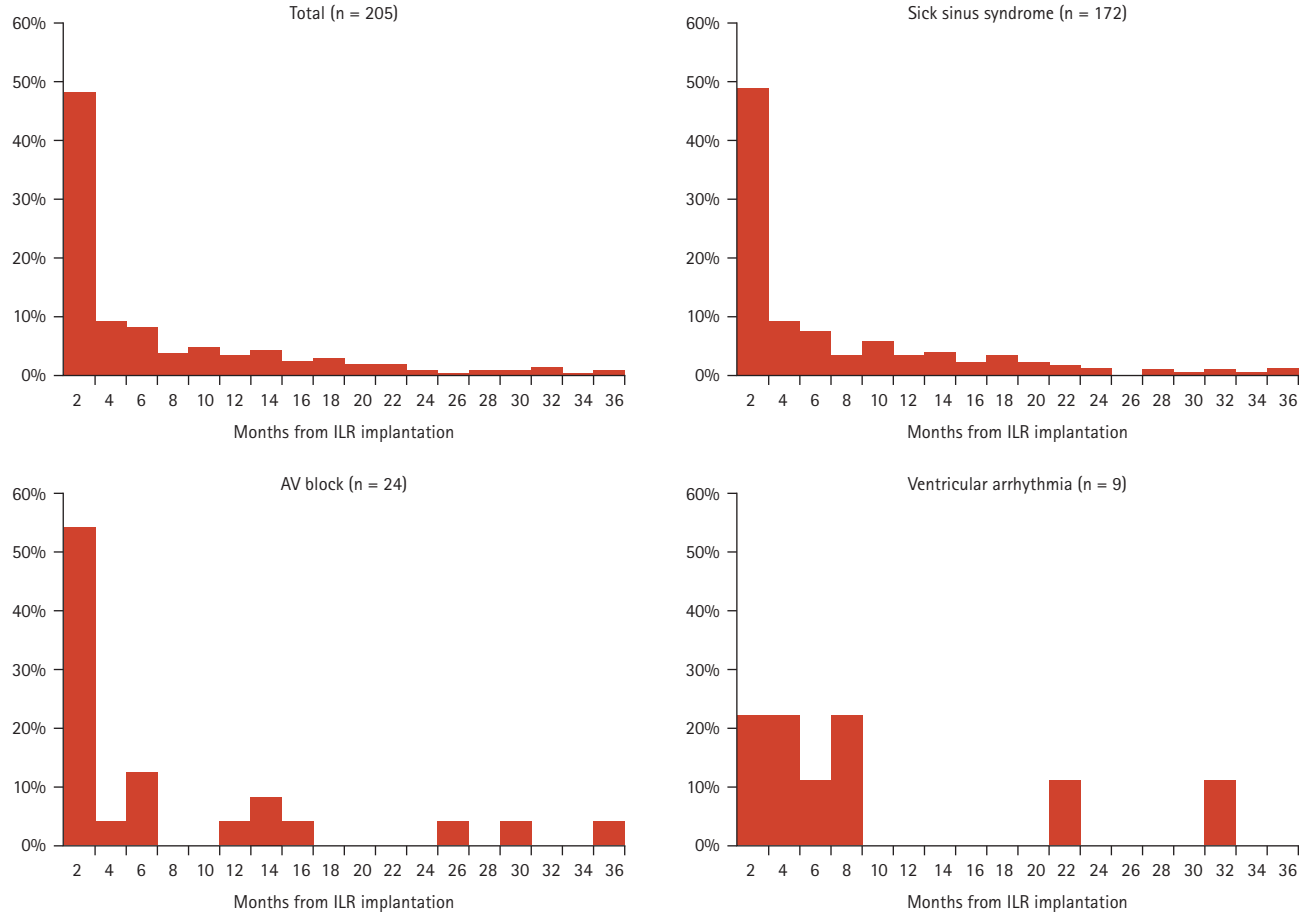


Figure 2. Number of patients diagnosed with serious arrhythmia after ILR implantation. ILR, implantable loop recorder; AV, atrioventricular.

detection rate of serious arrhythmias decreased gradually (Fig. 2). Representative cases of each serious arrhythmia are presented in Supplementary Figure 1. As the number of ILR implantations for unexplained syncope gradually increased, the diagnostic yield of ILR slightly decreased. However, the detection rate of serious arrhythmias did not change significantly (Supplementary Fig. 2).

Baseline characteristics

Baseline characteristics of the patients are presented in Table 1. Compared to patients without documented serious arrhythmias, patients with SSS were older and had a higher

Table 1. Baseline characteristics

Characteristic	Total (N = 394)	Sick sinus syndrome (N = 172, 43.7%)	AV block (N = 24, 6.1%)	Ventricular arrhythmia (N = 9, 2.3%)	Arrhythmia detection (–) (N = 189, 48.0%)	*p* value
Age (yr)	64.8 ± 15.0	67.4 ± 13.1	64.2 ± 11.2	59.8 ± 16.8	62.7 ± 16.6	0.019
Sex, male	227 (57.6)	92 (53.5)	14 (58.3)	6 (66.7)	115 (60.8)	0.510
Comorbidities						
Diabetes mellitus	87 (22.1)	41 (23.8)	7 (29.2)	1 (11.1)	38 (20.1)	0.559
Hypertension	191 (48.5)	97 (56.4)	13 (54.2)	1 (11.1)	80 (42.3)	0.006
Peripheral artery disease	19 (4.8)	8 (4.7)	0 (0.0)	0 (0.0)	11 (5.8)	0.553
Previous stroke	45 (11.4)	22 (12.8)	3 (12.5)	1 (11.1)	19 (10.1)	0.874
Structural heart disease	102 (25.9)	48 (27.9)	6 (25.0)	3 (33.3)	45 (23.8)	0.787
Coronary artery disease	50 (12.7)	22 (12.8)	1 (4.2)	1 (11.1)	26 (13.8)	0.617
ICMP	9 (2.3)	4 (2.3)	0 (0.0)	0 (0.0)	5 (2.6)	0.829
DCMP	4 (1.0)	2 (1.2)	0 (0.0)	0 (0.0)	2 (1.1)	0.945
HCMP	15 (3.8)	6 (3.5)	1 (4.2)	1 (11.1)	7 (3.7)	0.712
Other congestive heart failure	9 (2.3)	5 (2.9)	0 (0.0)	1 (11.1)	3 (1.6)	0.220
Moderate to severe VHD	15 (3.8)	9 (5.2)	4 (16.7)	0 (0.0)	2 (1.1)	0.001
Baseline 12-lead ECG						
PR interval (ms)	175.4 ± 33.2	178.3 ± 30.9	195.0 ± 58.8	162.6 ± 19.5	171.1 ± 29.9	0.004
QRS duration (ms)	96.4 ± 20.2	95.6 ± 19.7	103.8 ± 30.7	92.4 ± 15.1	96.4 ± 19.1	0.286
Sinus bradycardia (< 60 BPM)	102 (25.9)	61 (35.5)	6 (25.0)	2 (22.2)	33 (17.5)	0.008
IVCD	37 (9.4)	16 (9.3)	4 (16.7)	1 (11.1)	16 (8.5)	0.633
RBBB	17 (4.3)	6 (3.5)	1 (4.2)	1 (11.1)	9 (4.8)	
LBBB	7 (1.8)	4 (2.3)	1 (4.2)	0 (0.0)	2 (1.1)	
LAFB	5 (1.3)	2 (1.2)	0 (0.0)	0 (0.0)	3 (1.6)	
LPFB	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	
Bi-fascicular block	7 (1.8)	4 (2.3)	2 (8.3)	0 (0.0)	1 (0.5)	
Echocardiography						
LVEF (%)	61.8 ± 7.2	61.8 ± 6.8	61.3 ± 6.5	61.9 ± 5.5	61.9 ± 7.7	0.987
LA diameter (mm)	39.2 ± 7.1	41.8 ± 8.0	39.9 ± 8.0	38.3 ± 6.6	36.7 ± 6.7	< 0.001
LAVI (mL/m^2)	38.0 ± 20.0	44.4 ± 24.6	41.3 ± 24.6	40.4 ± 16.3	31.5 ± 11.1	< 0.001

Values are presented as mean ± standard deviation or number (%).
AV, atrioventricular; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; VHD, valvular heart disease; ECG, electrocardiography; BPM, beats per minute; IVCD, intraventricular conduction delay; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; LVEF, left ventricular ejection fraction; LA, left atrial; LAVI, LA volume index.

https://doi.org/10.3904/kjim.2024.364

prevalence of hypertension and valvular heart disease. Sinus bradycardia (< 60 beats per minute) was more prevalent in patients with SSS than those without documented serious arrhythmias. In addition, LA diameter and LAVI were significantly larger in patients with SSS than in those without documented serious arrhythmias.

Patients with AV block had a higher prevalence of valvular heart disease and any intraventricular conduction delay, as well as a significantly longer PR interval than those without documented serious arrhythmias. However, there were no significant differences in baseline characteristics between patients with VA and those without documented serious arrhythmias.

Independent predictors of arrhythmias in unexplained syncope

Based on multivariable analysis, the presence of hypertension, sinus bradycardia less than 60 beats per minute, and LAVI ≥ 34 mL/m^2 were independent predictors of SSS in patients who underwent ILR implantation for unexplained syncope (Table 2). LAVI as a continuous variable was also independently associated with SSS (Supplementary Table 1). Figure 3 shows the cumulative detection rate of SSS according to hypertension, sinus bradycardia, LAVI, and LAVI combined with sinus bradycardia. Patients with hypertension (Fig. 3A), sinus bradycardia (Fig. 3B), or LAVI ≥ 34 mL/m^2 (Fig. 3C) had a significantly higher risk of SSS than those without hypertension and sinus bradycardia or with a LAVI < 34 mL/m^2. The risk of SSS was significantly higher in sinus bradycardia patients with an enlarged LA (≥ 34 mL/m^2) than in those without sinus bradycardia or an enlarged LA (HR 1.911, 95% CI 1.188–3.072, p = 0.008, Fig. 3D).

However, there were no significant risk factors for AV block or VA in patients who underwent ILR implantation for unexplained syncope (Supplementary Tables 2, 3).

DISCUSSION

The present study evaluated the diagnosis rate by time period after ILR implantation and identified predictors of serious arrhythmias in patients with unexplained syncope based on data from the Korean ILR registry cohort. Our major findings are as follows. (1) More than half (52.0%) of patients had serious arrhythmias documented by ILR. Among them, 83.9% had SSS, 11.7% had AV block, and 4.4% had VA.

Table 2. Independent predictors for sick sinus syndrome in patients who received ILR implantation for unexplained syncope

Variable	Univariate analysis		Multivariate analysis[a)]	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.020 (1.009–1.031)	< 0.001	1.009 (0.991–1.028)	0.317
Sex, male	1.136 (0.841–1.533)	0.406	0.975 (0.632–1.503)	0.907
Diabetes mellitus	1.398 (0.984–1.987)	0.062	0.996 (0.613–1.617)	0.987
Hypertension	1.655 (1.223–2.238)	0.001	1.788 (1.138–2.809)	0.012
Structural heart disease[b)]	1.206 (0.864–1.684)	0.270	1.151 (0.742–1.785)	0.531
Sinus bradycardia (< 60 BPM)	1.796 (1.314–2.455)	< 0.001	1.762 (1.137–2.729)	0.011
PR interval, per 1 ms increase	1.005 (1.001–1.010)	0.013	1.002 (0.994–1.009)	0.681
QRS duration, per 1 ms increase	1.001 (0.992–1.009)	0.894	0.995 (0.980–1.010)	0.493
Any intraventricular conduction delay[c)]	1.124 (0.671–1.881)	0.658	1.856 (0.787–4.380)	0.158
LVEF, per 1% increase	0.995 (0.974–1.016)	0.620	0.985 (0.961–1.010)	0.230
LAVI ≥ 34 mL/m^2	2.082 (1.437–3.016)	< 0.001	1.582 (1.012–2.474)	0.034

ILR, implantable loop recorder; HR, hazard ratio; CI, confidence interval; BPM, beats per minute; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

[a)]The discriminant ability of multivariable model was 0.675 (95% CI 0.619–0.730). All variables in Table 2 were used for adjustment.

[b)]Structural heart disease included coronary artery disease, ICMP, DCMP, HCMP, other congestive heart failure, and moderate to severe valvular heart disease.

[c)]Any intraventricular conduction delay included RBBB, LBBB, LAFB, LPFB, and bifascicular block.

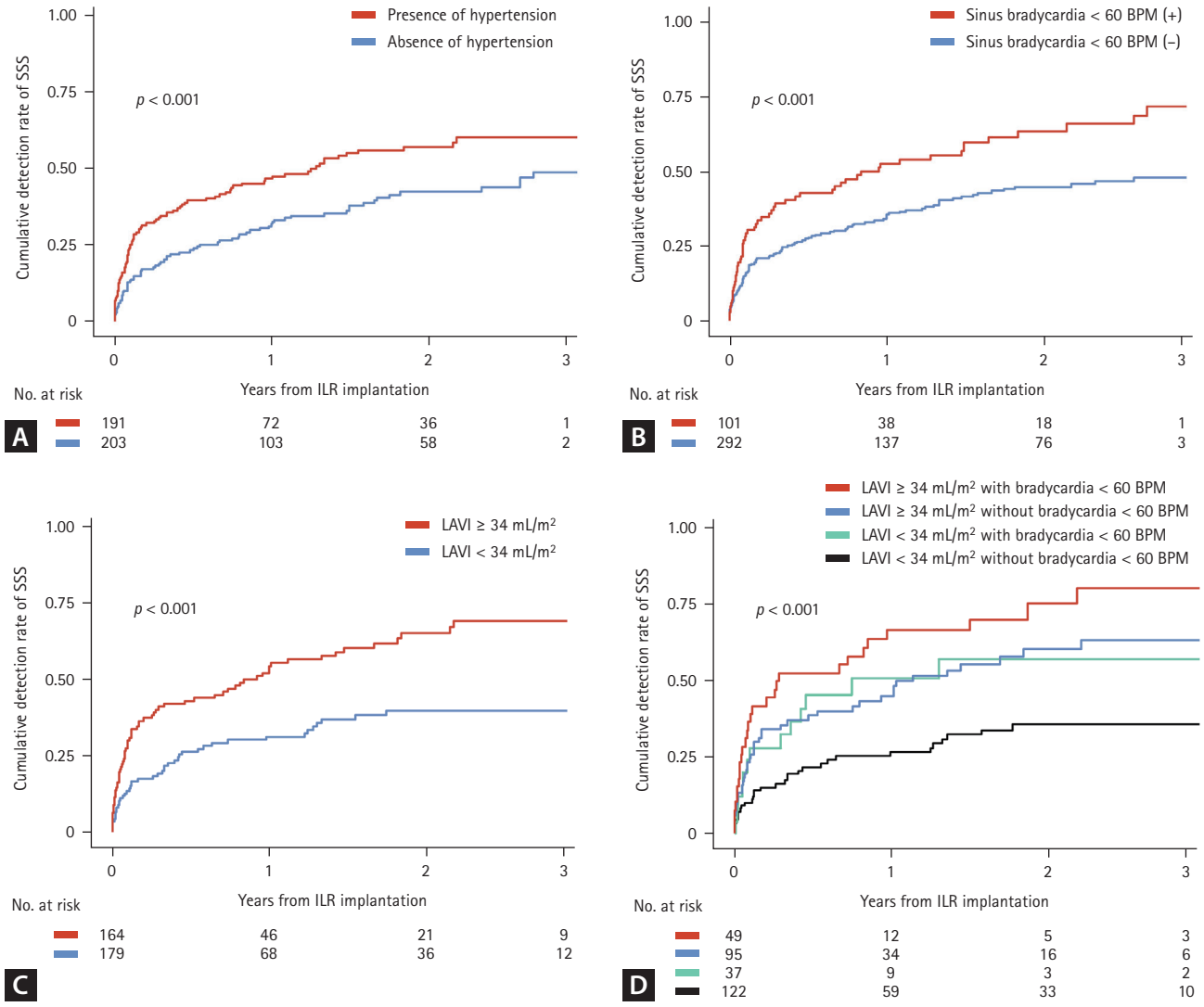


Figure 3. Cumulative detection rate of sick sinus syndrome in patients who underwent ILR implantation for unexplained syncope. (A) Kaplan–Meier curves for the incidence of SSS after ILR implantation according to the presence of hypertension, (B) Kaplan–Meier curves for the incidence of SSS after ILR implantation according to the presence of bradycardia (< 60 BPM), (C) Kaplan–Meier curves for the incidence of SSS after ILR implantation according to LAVI (34 mL/m^2), (D) Kaplan–Meier curves for the incidence of SSS after ILR implantation according to LAVI (34 mL/m^2) and sinus bradycardia (< 60 BPM). ILR, implantable loop recorder; SSS, sick sinus syndrome; BPM, beats per minute; LAVI, left atrial volume index.

(2) Serious arrhythmias were diagnosed in 23.4%, 37.6%, and 65.9% of patients within two weeks, one month, and six months after ILR implantation, respectively. (3) The presence of hypertension, sinus bradycardia less than 60 beats per minute, and LAVI were independent predictors of SSS as the underlying cause of syncope and (4) the cumulative detection rate of SSS was significantly higher in patients with both enlarged LA (≥ 34 mL/m^2) and sinus bradycardia (< 60 beats per minute) compared to those with fewer than two of these conditions.

Identification of predictors of serious arrhythmic syncope is of great importance to prevent sudden cardiac death and adverse events due to syncope [3]. Several physical examination and ECG findings are considered high-risk indicators of cardiogenic syncope [1,2], but there have not been sufficient validation studies to determine whether these high-risk factors are predictors of serious arrhythmias in patients with unexplained syncope. In previous studies, old age, first-degree AV block, atrial fibrillation, and distal conduction system disease were identified as major predic-

https://doi.org/10.3904/kjim.2024.364

tors of cardiogenic syncope [5,8-13]. Based on these findings, some studies have proposed a scoring system called the DROP score (D: distal conduction disease; R: no related historical precipitants; O: old age exceeding 65 years; P: PR prolongation) to predict future permanent pacemaker requirement in syncope patients who have received an ILR [12]. However, these studies were limited by the small number of enrolled patients, and most of them focused solely on predicting permanent pacemaker implantation. Moreover, there are limited data regarding the significance of echocardiography findings in predicting serious arrhythmias as the underlying cause of syncope.

Our study was conducted on a relatively large cohort population, and we demonstrated that enlarged LA volume (LAVI ≥ 34 mL/m^2) and sinus bradycardia (< 60 beats per minute) could predict underlying sinus node dysfunction in patients with unexplained syncope. There are some plausible explanations for our findings. Enlarged LA volume is considered a strong indicator of atrial remodeling [14]. Importantly, atrial cardiomyopathy by progressive atrial remodeling is widely recognized as a common mechanism contributing to the development of both sinus node dysfunction and atrial tachyarrhythmias such as atrial fibrillation [15-18]. Furthermore, atrial cardiomyopathy, characterized by atrial structural fibrosis, electrical remodeling, and molecular changes, may manifest initially as sinus node dysfunction without concurrent atrial arrhythmias [19]. In the early stage of atrial cardiomyopathy, only sinus bradycardia may be observed, and atrial fibrillation may be undetected during the initial investigation of syncope because it often presents in paroxysmal form. Therefore, it is possible that sinus node dysfunction or tachycardia-bradycardia syndrome caused by paroxysmal atrial fibrillation could be latent in patients with enlarged LA volume experiencing unexplained syncope. The observed difference in the relationship between LA enlargement and SSS compared to AV block may be attributed to the distinct pathophysiological mechanisms underlying these conduction disorders. SSS is closely associated with atrial remodeling and fibrosis, processes that are intrinsically linked to LA enlargement. In contrast, AV block primarily involves degenerative changes in the AV node or the His-Purkinje system [20], which are less directly influenced by atrial remodeling. Although both SSS and AV block are degenerative conduction disorders associated with aging, the localized nature of AV node degeneration might explain why LA size does not differ significantly in patients with AV block.

In the present study, the diagnostic yield of ILR for detecting underlying arrhythmic causes of syncope was 52.0%, which is higher than that reported in previous studies (16–48%) [8-11]. This may be due to the strict and limited reimbursement policy of Korean health insurance. Interestingly, among the serious arrhythmias, the underlying cause of syncope was diagnosed in approximately one-quarter (23.4%) and more than one-third (37.6%) of patients within two weeks and one month after ILR implantation, respectively. Non-invasive single-lead ECG patches may play a complementary role in early diagnosis. However, ILR implantation remains indispensable for long-term monitoring and diagnosis, more than half of which were achieved after the first month.

Limitations

Some limitations of the present study should be addressed. First, this study was an observational retrospective study. Potential selection bias could have influenced the study findings. However, the multi-center nature of the study and use of the same implantation criteria (insurance criteria) largely addresses this limitation. Second, physicians' assessments concerning ILR interrogation and clinical history of syncope may have differed. We attempted to exclude patients exhibiting the typical clinical features of reflex syncope, but patients with bradycardia due to reflex syncope may have been included. Third, diastolic function or functional measurements of the LA other than LA volume were not assessed. Fourth, patients with substantial structural heart diseases, such as heart failure with reduced ejection fraction, hypertrophic cardiomyopathy, and moderate to severe valvular heart disease, were not excluded from the analyses. These conditions can independently serve as causative factors for syncope, potentially confounding the observed associations.

Conclusions

More than half of patients with unexplained syncope had serious arrhythmias, and more than one-third of these patients were diagnosed within one month after ILR implantation. LAVI measured by echocardiography as well as sinus bradycardia was an independent predictor of SSS as the underlying cause of unexplained syncope.

KEY MESSAGE

1. In this relatively large cohort study (n = 394), we evaluated diagnosis rate by time period after ILR implantation and identified predictors of serious arrhythmias in patients with unexplained syncope.
2. Serious arrhythmias were diagnosed in approximately one-quarter and more than one-third of patients within two weeks and one month after ILR implantation, respectively. A non-invasive single-lead ECG patch could serve as a supplementary tool for early diagnosis. However, ILR implantation is essential for long-term monitoring and diagnosis, given that the majority of diagnoses occurred after the first month.
3. LAVI measured by echocardiography and sinus bradycardia were independent predictors of SSS as the underlying cause of unexplained syncope.

REFERENCES

1. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2017;70:e39-e110.
2. Brignole M, Moya A, de Lange FJ, et al.; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J 2018;39:1883-1948.
3. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med 2002;347:878-885.
4. Brignole M, Ungar A, Bartoletti A, et al.; Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) GROUP. Standardized-care pathway vs. usual management of syncope patients presenting as emergencies at general hospitals. Europace 2006;8:644-650.
5. Lee SH, Kim TH, Oh YS, et al. Usefulness of an implantable loop recorder in diagnosing unexplained syncope and predictors for pacemaker implantation. J Korean Med Sci 2020;35:e11.
6. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. Eur Heart J 2006;27:351-356.
7. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. Circulation 2001;104:46-51.
8. Onuki T, Shoji M, Sugiyama H, et al. Clinical predictors for bradycardia and supraventricular tachycardia necessitating therapy in patients with unexplained syncope monitored by insertable cardiac monitor. Clin Cardiol 2021;44:683-691.
9. Palmisano P, Accogli M, Zaccaria M, et al. Predictive factors for pacemaker implantation in patients receiving an implantable loop recorder for syncope remained unexplained after an extensive cardiac and neurological workup. Int J Cardiol 2013;168:3450-3457.
10. Tonegawa-Kuji R, Inoue YY, Nakai M, et al. Clinical predictors of pacing device implantation in implantable cardiac monitor recipients for unexplained syncope. CJC Open 2022;5:259-267.
11. William J, Nanayakkara S, Chieng D, et al. Predictors of pacemaker requirement in patients receiving implantable loop recorders for unexplained syncope: a systematic review and meta-analysis. Heart Rhythm 2024;21:1703-1710.
12. Xiao X, William J, Kistler PM, et al. Prediction of pacemaker requirement in patients with unexplained syncope: the DROP score. Heart Lung Circ 2022;31:999-1005.
13. Zangiabadian M, Soltani K, Gholinejad Y, et al. Predictors of pacemaker requirement in patients with implantable loop recorder and unexplained syncope: a systematic review and meta-analysis. Clin Cardiol 2024;47:e24221.
14. Lee JM, Kalman JM. Sinus node dysfunction and atrial fibrillation: two sides of the same coin? Europace 2013;15:161-162.
15. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-809.
16. Chang HY, Lin YJ, Lo LW, et al. Sinus node dysfunction in atrial fibrillation patients: the evidence of regional atrial substrate remodelling. Europace 2013;15:205-211.
17. Sparks PB, Jayaprakash S, Vohra JK, Kalman JM. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. Circulation 2000;102:1807-1813.
18. Yeh YH, Burstein B, Qi XY, et al. Funny current downregulation and sinus node dysfunction associated with atrial tachyarrhythmia: a molecular basis for tachycardia-bradycardia syndrome. Circulation 2009;119:1576-1585.
19. Manoj P, Kim JA, Kim S, et al. Sinus node dysfunction: current understanding and future directions. Am J Physiol Heart Circ Physiol 2023;324:H259-H278.
20. Zoob M, Smith KS. The aetiology of complete heart-block. Br Med J 1963;2:1149-1153.

https://doi.org/10.3904/kjim.2024.364

Received : October 26, 2024
Revised : November 29, 2024
Accepted : December 19, 2024

Correspondence to
Ju Youn Kim, M.D., Ph.D.
Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-3496, Fax: +82-2-3410-3849
E-mail: kzzoo921@gmail.com
https://orcid.org/0009-0003-2452-4423

CRedit authorship contributions
Juwon Kim: conceptualization, methodology, resources, investigation, data curation, formal analysis, validation, writing - original draft, writing - review & editing, visualization, supervision; Il-Young Oh: conceptualization, investigation, data curation, formal analysis, writing - review & editing, visualization, supervision, project administration; Myung-Jin Cha: conceptualization, methodology, resources, data curation, validation, writing - review & editing; Jinhee Ahn: conceptualization, methodology, resources, data curation, validation, writing - review & editing; So-Ryoung Lee: conceptualization, methodology, resources, data curation, validation, writing - review & editing; Sung Ho Lee: conceptualization, methodology, resources, data curation, validation, writing - review & editing; Jae-Sun Uhm: methodology, resources, data curation, validation, writing - review & editing; Pil-Sung Yang: methodology, resources, data curation, validation, writing - review & editing; Jaemin Shim: methodology, resources, data curation, validation, writing - review & editing; Hyoung-Seob Park: methodology, resources, data curation, validation, writing - review & editing; Junbeom Park: methodology, resources, data curation, validation, writing - review & editing; Jun Hyung Kim: methodology, resources, data curation, validation, writing - review & editing; Ki-Hun Kim: methodology, resources, data curation, validation, writing - review & editing; Jumsuk Ko: methodology, resources, data curation, validation, writing - review & editing; Hong Euy Lim: conceptualization, methodology, resources, investigation, data curation, formal analysis, validation, writing - review & editing, visualization, supervision, project administration; Ju Youn Kim: conceptualization, methodology, resources, investigation, data curation, formal analysis, validation, writing - original draft, writing - review & editing, visualization, supervision, project administration, funding acquisition

Conflicts of interest
The authors disclose no conflicts.

Funding
This study was supported by a grant from the Korean Heart Rhythm Society (KHRS 2021-2).

Supplementary Table 1. Independent predictors for sick sinus syndrome among the patients who received ILR implantation for unexplained syncope (LAVI as a continuous variable)

Variable	Univariate analysis		Multivariate analysis[a)]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.020 (1.009–1.031)	< 0.001	1.007 (0.989–1.025)	0.459
Sex, male	1.136 (0.841–1.533)	0.406	0.941 (0.610–1.452)	0.784
Diabetes mellitus	1.398 (0.984–1.987)	0.062	0.989 (0.609–1.605)	0.963
Hypertension	1.655 (1.223–2.238)	0.001	1.894 (1.196–3.001)	0.007
Structural heart disease[b)]	1.206 (0.864–1.684)	0.270	1.113 (0.720–1.722)	0.630
Bradycardia less than 60 BPM	1.796 (1.314–2.455)	< 0.001	1.604 (1.020–2.524)	0.041
PR interval, per 1ms increase	1.005 (1.001–1.010)	0.013	1.002 (0.995–1.009)	0.597
QRS duration, per 1ms increase	1.001 (0.992–1.009)	0.894	0.993 (0.978–1.008)	0.333
Any intraventricular conduction delay[c)]	1.124 (0.671–1.881)	0.658	2.048 (0.870–4.822)	0.101
LVEF, per 1% increase	0.995 (0.974–1.016)	0.620	0.988 (0.964–1.013)	0.351
LAVI, per 1 mL/m^2 increase	1.011 (1.006–1.016)	< 0.001	1.023 (1.008–1.039)	0.003

ILR, implantable loop recorder; LAVI, left atrial volume index; HR, hazard ratio; CI, confidence interval; BPM, beats per minute; LVEF, left ventricular ejection fraction; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

[a)]The discriminant ability of multivariable model was 0.680 (95% CI 0.625–0.734). All variables in Supplementary Table 1 were used for adjustment.

[b)]Structural heart disease included coronary artery disease, ICMP, DCMP, HCMP, other congestive heart failure, and moderate to severe valvular heart disease.

[c)]Any intraventricular conduction delay included RBBB, LBBB, LAFB, LPFB, and bifascicular block.

Supplementary Table 2. Independent predictors for atrioventricular block in patients who received ILR implantation for unexplained syncope

Variable	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.005 (0.979–1.031)	0.721	0.987 (0.940–1.035)	0.585
Sex, male	0.938 (0.416–2.112)	0.877	0.787 (0.186–3.321)	0.743
Diabetes mellitus	1.853 (0.766–4.483)	0.171	2.842 (0.757–10.677)	0.122
Hypertension	1.505 (0.673–3.366)	0.320	1.692 (0.407–7.038)	0.470
Structural heart disease[b]	1.038 (0.412–2.615)	0.938	0.994 (0.282–3.495)	0.992
Bradycardia less than 60 BPM	1.091 (0.433–2.751)	0.853	0.441 (0.081–2.409)	0.345
PR interval, per 1 ms increase	1.013 (1.006–1.021)	< 0.001	1.011 (0.994–1.029)	0.196
QRS duration, per 1 ms increase	1.019 (1.003–1.035)	0.020	1.031 (0.995–1.069)	0.096
Any intraventricular conduction delay[c]	2.195 (0.748–6.445)	0.153	0.701 (0.095–5.189)	0.728
LVEF, per 1% increase	0.986 (0.933–1.043)	0.630	1.023 (0.942–1.111)	0.591
LAVI ≥ 34 mL/m^2	1.128 (0.379–3.363)	0.829	1.289 (0.344–4.823)	0.707

ILR, implantable loop recorder; HR, hazard ratio; CI, confidence interval; BPM, beats per minute; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

[a]The discriminant ability of multivariable model was 0.754 (95% CI 0.598–0.910). All variables in Supplementary Table 2 were used for adjustment.

[b]Structural heart disease included coronary artery disease, ICMP, DCMP, HCMP, other congestive heart failure, and moderate to severe valvular heart disease.

[c]Any intraventricular conduction delay included RBBB, LBBB, LAFB, LPFB, and bifascicular block.

https://doi.org/10.3904/kjim.2024.364

Supplementary Table 3. Independent predictors for ventricular arrhythmia in patients who received ILR implantation for unexplained syncope

Variable	Univariate analysis		Multivariate analysis[a)]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.990 (0.953–1.027)	0.585	0.968 (0.914–1.025)	0.265
Sex, male	0.664 (0.166–2.657)	0.563	1.401 (0.288–6.820)	0.676
Diabetes mellitus	0.592 (0.074–4.745)	0.622	1.084 (0.111–10.599)	0.945
Hypertension	0.161 (0.020–1.288)	0.085	0.218 (0.025–1.920)	0.170
Structural heart disease[b)]	1.552 (0.388–6.207)	0.534	1.473 (0.256–8.477)	0.665
Any intraventricular conduction delay[c)]	1.458 (0.181–11.720)	0.723	1.348 (0.133–13.684)	0.801
LAVI ≥ 34 mL/m^2	3.548 (0.687–18.320)	0.131	5.186 (0.708–37.998)	0.105

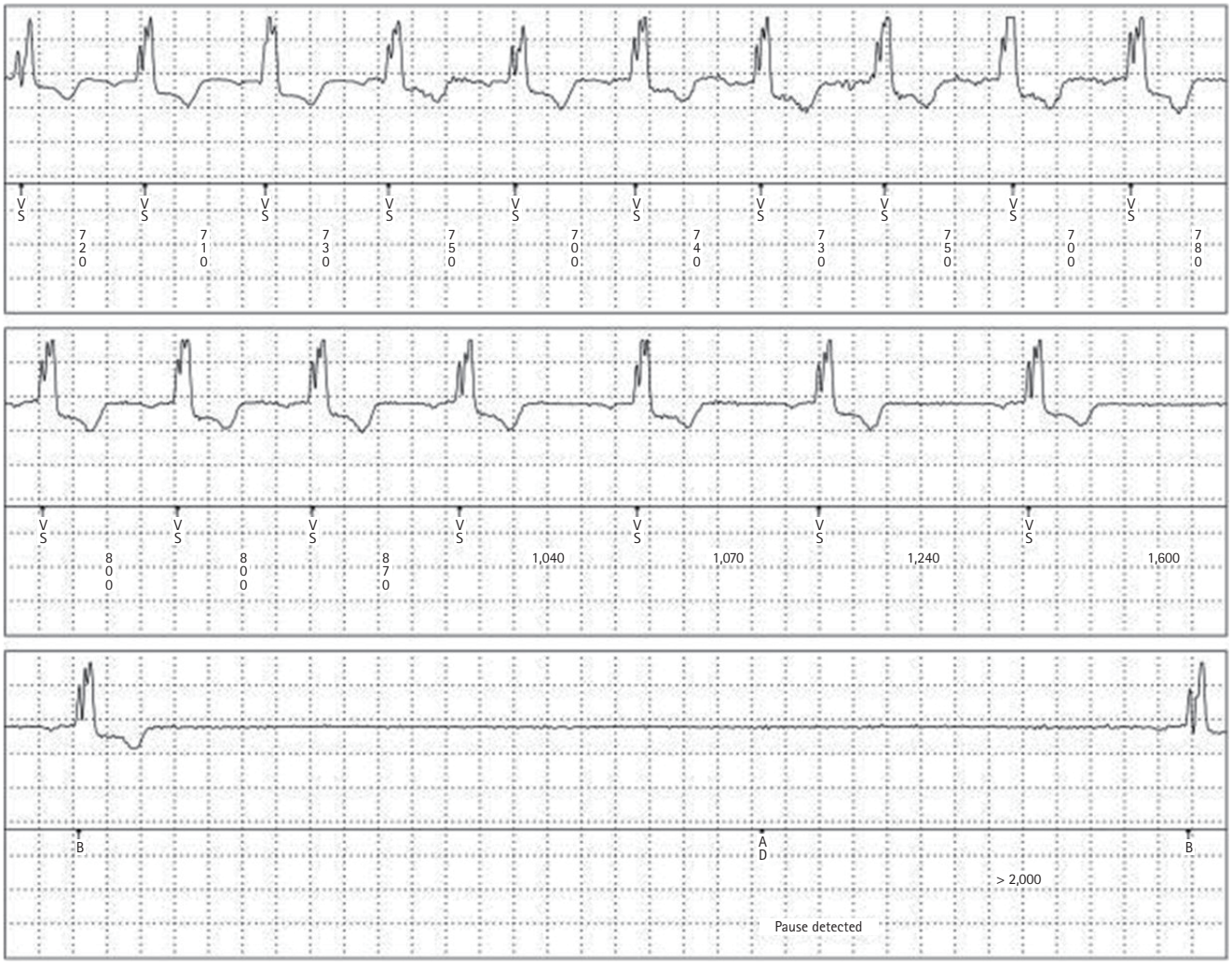
ILR, implantable loop recorder; HR, hazard ratio; CI, confidence interval; LAVI, left atrial volume index; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

[a)]The discriminant ability of multivariable model was 0.788 (95% CI 0.604–0.973). All variables in Supplementary Table 3 were used for adjustment.

[b)]Structural heart disease included coronary artery disease, ICMP, DCMP, HCMP, other congestive heart failure, and moderate to severe valvular heart disease.

[c)]Any intraventricular conduction delay included RBBB, LBBB, LAFB, LPFB, and bifascicular block.

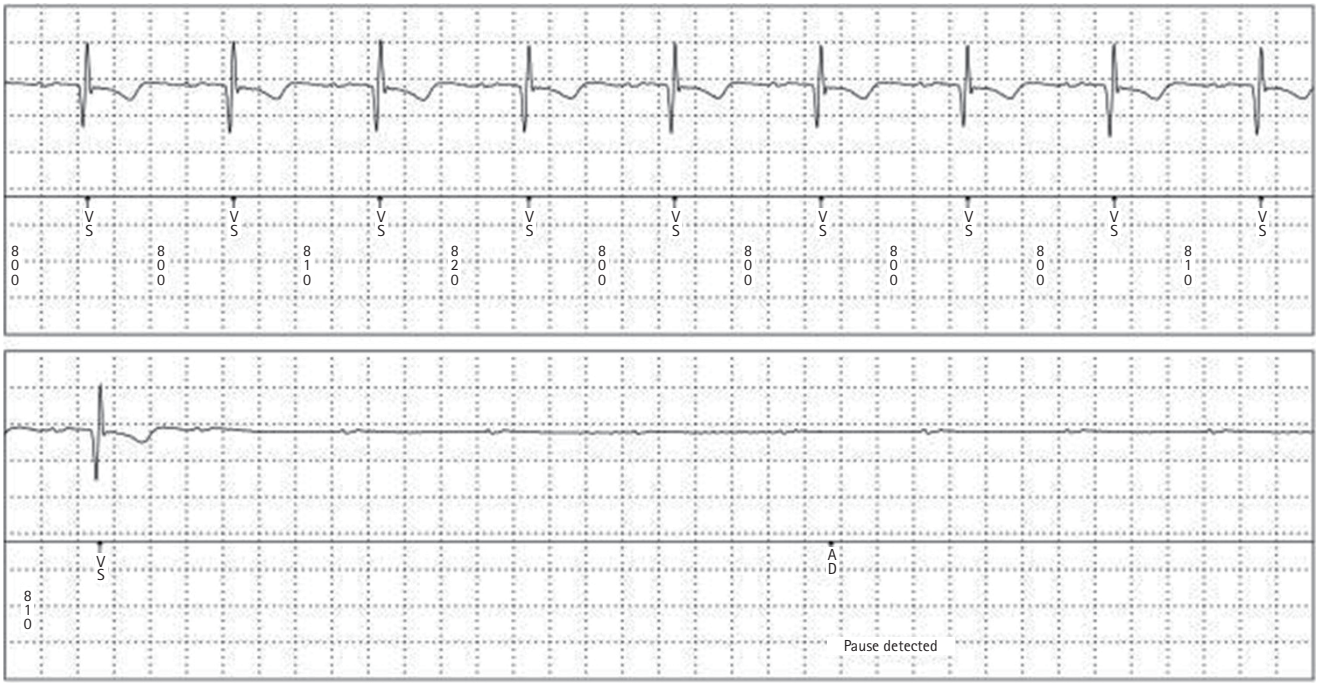
A Sick sinus syndrome
- 73 years old female
- Syncope with 7 seconds sinus pause
- PPM implantation



Supplementary Figure 1. Representative cases in patients with unexplained syncope. (A) Sick sinus syndrome. (B) AV block. (C) Ventricular tachycardia. AV, atrioventricular; PPM, permanent pacemaker; ICD, implantable cardiac defibrillator.

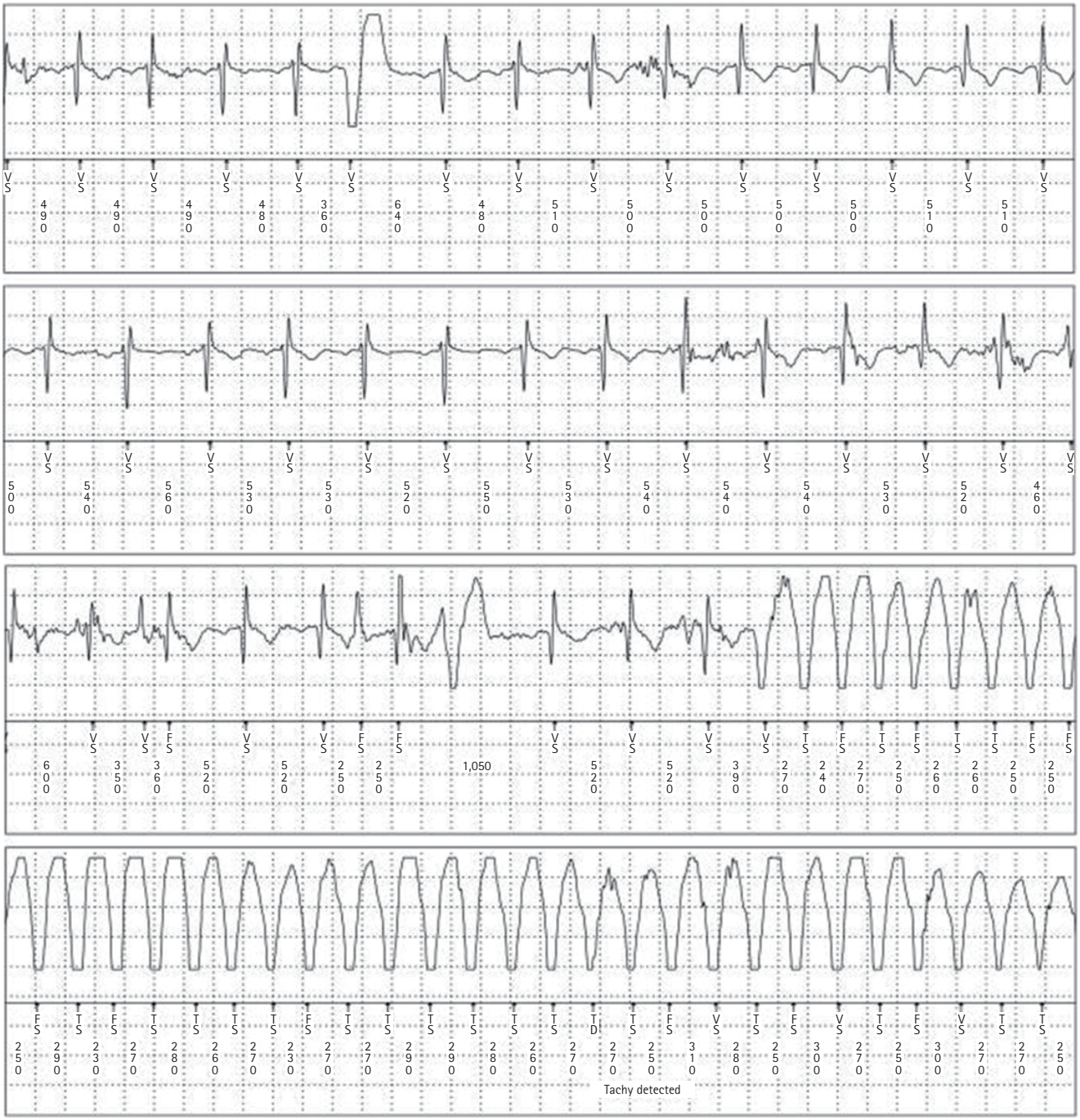
https://doi.org/10.3904/kjim.2024.364

B AV block
- 68 years old male
- Syncope with high degree AV block (8 seconds pause)
- PPM implantation



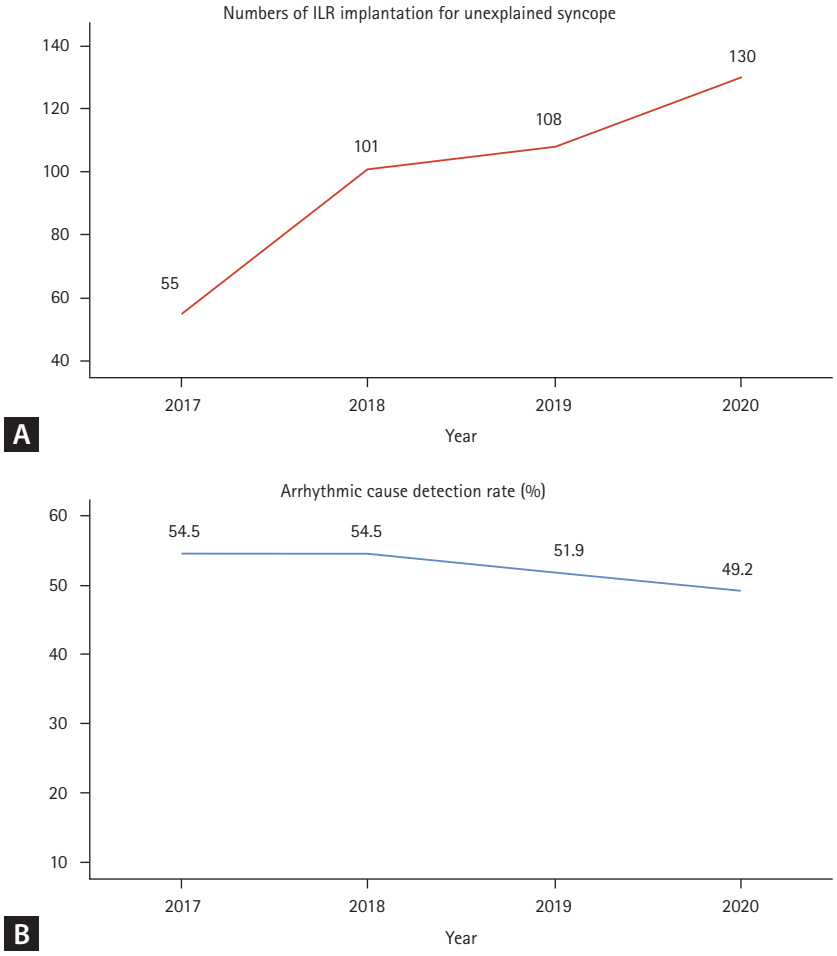
Supplementary Figure 1. Continued.

C Ventricular tachycardia
- 59 years old male
- Syncope with sustained ventricular tachycardia
- ICD implantation



Supplementary Figure 1. Continued.

https://doi.org/10.3904/kjim.2024.364



Supplementary Figure 2. Annual trend of ILR implantation (A) and arrhythmia detection rate (B) in patients with unexplained syncope. ILR, implantable loop recorders.