Syncope and loss of consciousness after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: Prevalence and characteristics in long-term follow-up

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BACKGROUND Syncope is a significant prognostic factor in patients with Brugada syndrome (BrS). However, the risk of ventricular arrhythmia in patients with nonarrhythmic loss of consciousness (LOC) is similar to that in asymptomatic patients. LOC events after implantable cardioverter-defibrillator (ICD) implantation may provide insights into underlying causes of the initial LOC episode.

OBJECTIVE The purpose of this study was to examine LOC characteristics following ICD implantation.

METHODS We retrospectively analyzed 112 patients with BrS (mean age 47 years; 111 men) who were treated with an ICD. The patients were classified into 3 groups based on symptoms at implantation: asymptomatic (35 patients); LOC (46 patients); and ventricular tachyarrhythmia (VTA) (31 patients). We evaluated the incidence and cause of LOC during long-term follow-up after ICD implantation.

RESULTS During mean follow-up of 12.2 years, 41 patients (37%) experienced LOC after ICD implantation. Arrhythmic LOC occurred in 5 asymptomatic patients, 14 LOC patients, and 16 patients with VTA. Nonarrhythmic LOC, similar to the initial episode, occurred after ICD implantation in 6 patients with prior LOC (2 with neurally mediated syncope and 4 with epilepsy). Most epileptic patients experienced LOC during rest or sleeping, and did not show an abnormal encephalogram during initial evaluation of the LOC episodes.

CONCLUSION After ICD implantation, 13% of patients had nonarrhythmic LOC similar to the initial episode. Accurate classification of LOC based on a detailed medical history is important for risk stratification, although distinguishing arrhythmic LOC from epilepsy-related LOC episodes can be challenging depending on the circumstances and characteristics of the LOC event.

KEYWORDS Brugada syndrome; Implantable cardioverter-defibrillator; Syncope; Neurally mediated syncope; Epilepsy; Ventricular tachyarrhythmia

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Introduction

Spontaneous type 1 electrocardiographic (ECG) findings and symptoms are predictors of sudden cardiac death (SCD) in patients with Brugada syndrome (BrS). Syncopal episodes in BrS usually are associated with ventricular tachyarrhythmias (VTAs).[1–3] However, patients with BrS often have autonomic dysfunction,[2] and some episodes of loss of consciousness (LOC), such as neurally mediated syncope (NMS), are low-risk events.[2,3] The risk of ventricular arrhythmia in patients with NMS is similar to that in asymptomatic patients.[3] Determining the etiology of LOC episodes is important for identifying patients with BrS who are at risk for SCD. After implantable cardioverter-defibrillator (ICD) implantation, LOC episodes may occur; however, some patients may have LOC due to nonarrhythmic causes. The details of LOC events after ICD implantation may reveal the cause of the first episode; however, this has not yet been investigated. In this study, we performed long-term follow-up of patients with BrS after ICD implantation and retrospectively analyzed the details of LOC episodes.

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KEY FINDINGS

- Syncope is a significant prognostic factor in patients with Brugada syndrome (BrS).
- Loss of consciousness (LOC) may be due to nonarrhythmic syncope. Thus, by investigating post–implantable cardioverter-defibrillator (ICD) LOC events in detail, the underlying cause of the LOC may be determined.
- Approximately 40% of all patients experience LOC after ICD implantation. Ventricular tachyarrhythmia (VTA) is the most common cause of LOC. Thirteen percent of patients had nonarrhythmic LOC similar to the initial episode, and their causes were epilepsy and neurally mediated syncope.
- Distinguishing epilepsy from VTAs can be challenging because epilepsy and VTAs in BrS share similar symptoms and situations.
- After repeated electroencephalographies and other neurological examinations, the patients were finally diagnosed with epilepsy-related LOC. When LOC recurs without ICD therapy, epilepsy can be considered a differential diagnosis, and further investigations should be conducted.

Methods

Patients

This study included 112 patients with BrS who were treated with an ICD. None of the participants belonged to the same family. Patients were classified into 3 groups based on symptoms at ICD implantation: asymptomatic group (35 patients), LOC group (46 patients), and VTA group (31 patients). Patients in the VTA group had documented ventricular fibrillation (VF) or sustained ventricular tachycardia (VT). The LOC and VTA groups were defined as symptomatic patients. Physical examination, baseline ECG, echocardiography, and coronary angiography were performed, and underlying structural cardiac abnormalities were excluded. BrS was diagnosed according to the Expert Consensus Statements.[1] This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University. Analysis of the *SCN5A* gene was performed in 78 patients in compliance with the guidelines for human genome studies of the Ethics Committee of Okayama University.

Assessment of patients with LOC

Before receiving an ICD, all patients with LOC underwent careful diagnostic workup for the arrhythmic origins of the events. We interviewed for initial event details to obtain information on the situations and characteristics of LOC. The 2017 ACC/AHA/HRS guideline definitions were used for evaluating the several types of syncopal events.[4] Electroencephalography (EEG) was performed in 24 patients with LOC. Experienced neurologists analyzed all EEGs to differentiate LOC from epilepsy. LOC episodes were discussed and categorized by experienced cardiologists and neurologists.

ECG and electrophysiological study assessment

We recorded a standard 12-lead ECG and additional V_1–V_3 leads in the third intercostal space for the detection of spontaneous type 1 ECG. Electrophysiological study (EPS) was performed in most patients to assess risk stratification. The risks were explained to each patient, and written informed consent was obtained before the study. Induction of ventricular arrhythmia was attempted using programmed ventricular stimulation, as previously reported,[5] without antiarrhythmic drug administration. When VF was induced during EPS, cardioversion was initiated after 15 seconds of observation to confirm the absence of spontaneous termination.

ICD implantation

Indication for an ICD was determined based on the J-wave syndromes expert consensus conference report.[1] Single- and dual-chamber ICDs or subcutaneous implantable cardioverter-defibrillators (S-ICDs) were implanted depending on the presence of previous episodes of supraventricular arrhythmias, sinus nodal dysfunction, VT, or the investigator's preference. ICDs were programmed at the time of implantation. Transvenous implantable cardioverter-defibrillators (TV-ICDs) were programmed into 2 zones: VF detection rate was programmed to >222 bpm, and VT zone (188–222 bpm) with antitachycardia pacing and shocks was programmed in all cases. Supraventricular tachycardia discriminators were activated if available. S-ICDs were programmed into 2 zones, which provided morphological discrimination of events with rates in the conditional shock zone (≥200 bpm). The detection cutoff rate for VF was 220 bpm. A high-pass filter (SMART Pass; Boston Scientific Corporation, Natick, MA) was programmed when available. These settings were adjusted during follow-up based on individual clinical history to prevent the recurrence of inappropriate interventions.

Follow-up

We analyzed the long-term incidence and causes of LOC after ICD implantation. Follow-up variables included the episode and situation of LOC after ICD implantation, ECG evaluation, and device interrogation data (complications during follow-up and occurrence of ICD therapy). ICD therapy was classified as appropriate or inappropriate. The time to the first appropriate ICD therapy since ICD implantation and whether the shock was successful in restoring the sinus or paced rhythm were documented. Arrhythmic LOC after ICD implantation was defined as syncope, faintness, or dizziness associated with the appropriate ICD therapy. Nonarrhythmic LOC after ICD implantation was defined as an episode of LOC without ICD therapy, bradycardia, or VTA. When the syncopal episode after ICD implantation

was similar to that before implantation, it was considered to have the same underlying cause.

Statistical analysis

Continuous data are given as mean ± SD. The Fisher exact test or the χ^2 test was used for categorical variables. Continuous variables in the 3 groups were compared using the Bonferroni test analysis of variance. Survival curves were plotted using the Kaplan-Meier method and analyzed using the log-rank test. $P < .05$ was considered significant. All statistical analyses were performed using Stata Version 4.2 (StataCorp, College Station, TX). All authors had full access to, and took full responsibility, for the data integrity.

Results

Baseline characteristics

Baseline clinical and procedural characteristics of the study population are given in Table 1. Thirty-five patients were asymptomatic, 46 patients had at least 1 episode of LOC, and 31 patients presented with an aborted SCD before ICD implantation. Fifteen patients (13%) had documented episodes of sustained atrial tachyarrhythmia (atrial fibrillation [AF] or atrial flutter). Four patients (3.6%) presented with sinus nodal dysfunction. EPS was performed in 106 patients (95%). Sustained VF was induced during EPS in 72 patients (68%). A total of 78 genetic tests (70%) were performed, of which 7 (9.0%) were positive for mutations in the *SCN5A* gene. One hundred patients received TV-ICD implantations (44 single-chamber ICDs, 56 dual-chamber ICDs). Twelve patients received S-ICD implantations.

Features of initial episodes in symptomatic patients

We interviewed 45 of 46 patients in the LOC group and 29 of 31 patients in the VTA group for initial event details to obtain information on the situations and characteristics of LOC. Three patients did not remember the circumstances at the time of LOC or VTA and were treated at another hospital at the time of the initial episodes; therefore, medical histories of the first events were not available. Table 2 lists clinical characteristics of initial symptoms in symptomatic patients. There were no differences in any prodromes between the LOC and VTA groups. Abnormal respiration was more frequently observed during LOC in the VTA group than in the LOC group. Injury was only observed in the LOC group. There were no differences in convulsion, incontinence, and falling down after onset of LOC between the LOC and VTA groups. Patients in the VTA group often experienced symptoms in the supine position during sleep or at rest; however, definitive features were not found. The characteristics of the initial symptoms by specific cause within the LOC group are given in the Supplemental Table.

Table 1 Baseline clinical characteristics of patients according to ICD indication

			Symptomatic		
	Overall	Asymptomatic	LOC	VTA	*P* value*
No.	112	35	46	31	
Clinical characteristics					
Male	111 (99)	35 (100)	45 (98)	31 (100)	.485
Age (y)	46.9 ± 13.5	46.3 ± 13.2	49.3 ± 13.5	44.1 ± 13.7	.981
Family history of sudden death <45 y	28 (25)	15 (43)	9 (20)	4 (13)	.013
SCN5A mutation	7/78 (9.0)	0/24 (0)	5/31 (16)	2/23 (8.7)	.116
ECG markers					
Spontaneous type 1 ECG	88 (79)	31 (89)	33 (72)	24 (77)	.185
Sinus nodal dysfunction	4 (3.6)	0	3 (6.5)	1 (3.2)	.291
Atrial tachyarrhythmia	15 (13)	3 (8.6)	7 (15)	5 (16)	.596
Programmed electrical stimulation					
EPS	106 (95)	35 (100)	44 (95)	27 (87)	
VF induction					
With 1 or 2 extrastimuli	50 (47)	23 (66)	19 (43)	8 (30)	.015
With 3 extrastimuli	72 (68)	30 (86)	30 (68)	12 (44)	.003
Neurological evaluation					
Brain MRI abnormalities	0	0	0/24 (0)	0/1	NS
Electroencephalogram abnormalities	2/25 (8)	0	1/24 (4.2)	1/1 (100)	NS
Initial ICD device					
TV-ICD					
Single	44 (39)	19 (54)	13 (28)	12 (39)	.197
Dual	56 (50)	14 (46)	27 (59)	15 (48)	
S-ICD	12 (11)	2 (5.7)	6 (13)	4 (13)	
Follow-up period (y)	12.2 ± 6.3	12.7 ± 6.4	12.3 ± 5.4	11.2 ± 7.5	.124

Values are given as n (%) or mean ± SD unless otherwise indicated.

ECG = electrocardiography; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; LOC = loss of consciousness; MRI = magnetic resonance imaging; NS = not specified; S-ICD = subcutaneous implantable cardioverter defibrillator; TV-ICD = transvenous implantable cardioverter defibrillator; VF = ventricular fibrillation; VTA = ventricular tachyarrhythmia.

*Asymptomatic patients vs patients with loss of consciousness vs patients with ventricular tachyarrhythmias.

Table 2 Characteristics of initial symptom in the patients with LOC or VTA

	LOC	VTA	*P* value*
No.	45	29	
Prodromes			
Total	16 (36)	5 (17)	.088
Blurred vision	2 (4.4)	0	.250
Related to urination	3 (6.7)	0	.156
Diaphoresis	3 (6.7)	0	.156
Palpitation/chest discomfort	7 (16)	5 (17)	.848
Patient's condition after onset of LOC			
Convulsion	15 (33)	6 (21)	.239
Incontinence	9 (20)	2 (6.9)	.122
Falling down	11 (24)	3 (10)	.131
Any injury	7 (16)	0	.026
Abnormal respiration	9 (20)	14 (48)	.010
Position at the onset of LOC			
Supine	15	13	.295
Sitting	16	9	
Standing	15	4	
Situation at the onset of LOC			
On exertion	8 (18)	3 (10)	.380
Standing up	4 (8.9)	1 (3.5)	.363
Bathing/fever	5 (11)	6 (21)	.258
Rest	12 (27)	10 (35)	.473
Sleeping	13 (29)	12 (41)	.267
Drinking	4 (8.9)	3 (10)	.835
Driving	2 (4.4)	0	.250

Values are given as n (%) unless otherwise indicated.
Abbreviations as in Table 1.
*Patients with loss of consciousness vs patients with ventricular tachyarrhythmias.

Arrhythmic LOC with appropriate ICD therapy

During mean follow-up of 12.2 ± 6.3 years, 41 patients (37%) experienced LOC after ICD implantation. Thirty-five patients (31%) experienced arrhythmic LOC: 5 in the asymptomatic group, 14 in the LOC group, and 16 in the VTA group (Table 3 and Figure 1). Patients with arrhythmic LOC were completely matched with those who received appropriate ICD treatment for ventricular arrhythmia. Figure 2 shows the survival curves for patients with arrhythmic LOC (appropriate ICD therapy). Appropriate therapy was administered more frequently in the VTA group, followed by the LOC and asymptomatic groups. Thirty-five patients received 173 appropriate ICD therapies. Sustained ventricular arrhythmias were terminated by ICD shocks in 34 patients and by antitachycardia pacing in 3 patients. Two patients were terminated due to ICD shocks and tachycardia pacing (Table 3).

Nonarrhythmic LOC events after ICD implantation

Nonarrhythmic LOC was observed in 7 patients in the LOC group but in no patients in the asymptomatic and VTA groups. We finally diagnosed that 3 patients had NMS, and 4 patients had epilepsy. In 6 of the patients, nonarrhythmic LOC after ICD implantation had similar characteristics to the initial LOC episode and was considered to be caused by the same underlying condition (Figure 1). In 1 patient, both arrhythmic LOC resembling the initial episode and nonarrhythmic LOC due to NMS occurred after ICD implantation. In 2 patients, the initial episodes occurred while standing or during urination, with prodromal symptoms such as blurred vision, suggestive of NMS. However, these patients received ICDs because of spontaneous type 1 ECG or easily inducible VF. The characteristics of LOC diagnosed with epilepsy are given in Table 4. All patients were male (mean age 46.5 years). Epileptic LOC occurred after 4.0 ± 6.5 years of follow-up and diagnosed after 4.1 ± 6.6 years. The initial episode occurred during sleep or at rest in 3 patients (75%), with convulsive seizures observed in 3 patients (75%). The details of each case are as follows.

Case 1

A 46-year-old man experienced convulsions with LOC that lasted for several tens of seconds. Over a period of 6 months, he had 3 LOC episodes, all occurring during sleep after drinking. No abnormalities were detected on brain magnetic resonance imaging (MRI) and EEG tests. Epilepsy was suspected because of recurrent seizures, spontaneous recovery without resuscitation, and seizure suppression after carbamazepine administration. However, he had typical type 1 ECG induced by sodium channel blocker administration and VF induced by EPS. He received ICD implantation. After discontinuation of carbamazepine, recurrent LOC without VTA recordings by ICD was observed. The patient was diagnosed with epileptic LOC.

Table 3 Outcomes of patients according to initial symptom

	Overall	Asymptomatic	Symptomatic		*P* value*
			LOC	VTA	
No.	112	35	46	31	
Events of LOC after ICD implantation					
Arrhythmic LOC	35 (31)	5 (14)	14 (30)	16 (52)	.005
Noncardiac LOC	7 (6.3)	0	7 (15)	0	.001
Neurally mediated syncope	3 (2.7)	0	3 (2.7)	0	
Epilepsy	4 (3.6)	0	4 (8.7)	0	
ICD therapy					
Appropriate ICD therapy	35 (31)	5 (14)	14 (30)	16 (52)	.005
Shocks	34 (30)	5 (14)	13 (28)	16 (52)	
Antitachycardia pacing	3 (2.7)	0	3 (2.7)	0	
Inappropriate ICD therapy	27 (24)	13 (37)	8 (17)	6 (19)	.092
Atrial arrhythmia	13 (12)	7 (20)	3 (6.5)	3 (9.7)	
T-wave oversensing	6 (5.4)	4 (11)	1 (2.2)	1 (3.2)	
Sinus tachycardia	4 (3.6)	1 (2.9)	1 (2.2)	2 (6.5)	
Lead fracture	2 (1.8)	1 (2.9)	1 (2.2)	0	
Other	2 (1.8)	0	2 (4.4)	0	

Values are given as n (%) unless otherwise indicated.

Abbreviations as in Table 1.

*Asymptomatic patients vs patients with loss of consciousness vs patients with ventricular tachyarrhythmias.

Case 2

A 59-year-old man collapsed and injured his jaw while waiting for a lift, after consuming alcohol. He experienced 3–5 minutes of LOC without chest symptoms or convulsions. Family history included SCD of his father at age 68 years and 2 brothers at ages 70 and 56 years. Brain MRI and EEG revealed no abnormalities. His ECG revealed first-degree atrioventricular block. Type 1 ECG was not obtained spontaneously but was induced by sodium channel blocker administration. No *SCN5A* mutation was detected. VF was easily induced by EPS, leading to ICD implantation. Recurrent LOC without VTAs occurred 13.9 years later, and neurological examination led to the diagnosis of epilepsy-related LOC.

Case 3

A 28-year-old man groaned, flailed his limb, and experienced generalized convulsions during sleep. There was no response to stimulation; his eyes rolled upward, and he had foaming at the mouth. The patient exhibited snoring-like breathing. Vital signs were stable upon arrival in the ambulance; however, he was unable to provide his name. By the time he was transported to the hospital, he had regained full consciousness. Brain MRI and EEG revealed no abnormalities. Spontaneous type 1 ECG was observed immediately after the LOC episode. VF was not induced during EPS. Because of LOC during sleep and spontaneous type 1 ECG, the patient underwent S-ICD implantation. The patient experienced repeated episodes of LOC without ICD therapy. After readmission

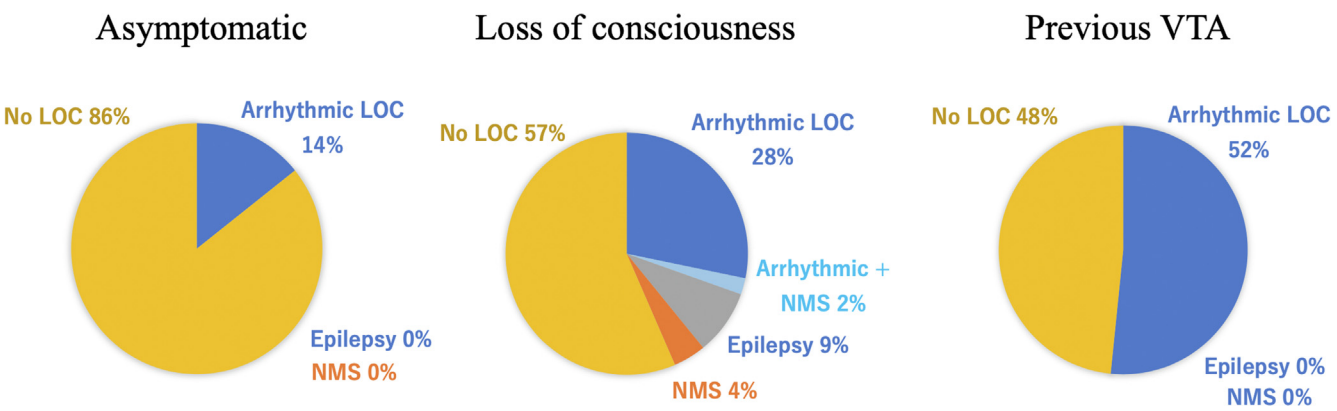

Figure 1 Subsequent episodes of loss of consciousness (LOC) after implantable cardioverter-defibrillator implantation according to the initial symptom. NMS = neurally mediated syncope; VTA = ventricular tachyarrhythmia.

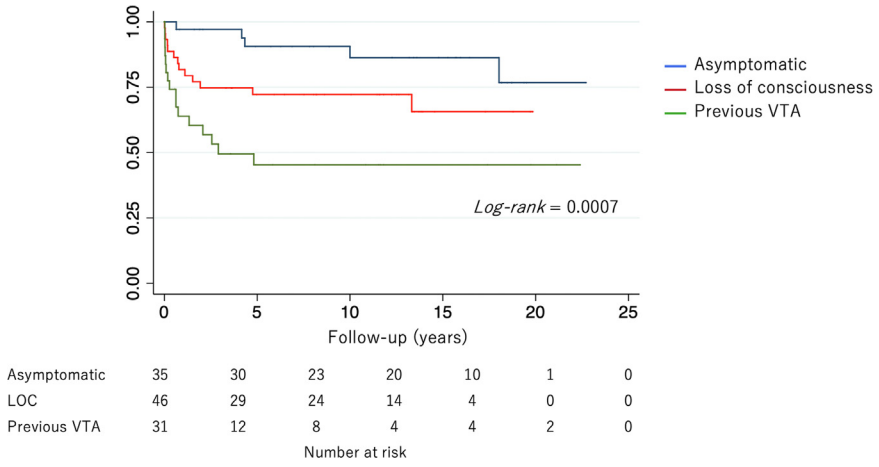

Figure 2 Event-free survival curve for arrhythmic loss of consciousness (appropriate implantable cardiac defibrillator therapy) according to initial symptoms. Appropriate therapy occurred more frequently in patients with previous ventricular tachyarrhythmia, followed by patients with loss of consciousness, and asymptomatic patients. Abbreviations as in Figure 1.

and further evaluation, the patient was diagnosed with epileptic LOC.

Case 4

A 53-year-old man with a history of epilepsy experienced bilateral upper limb stiffness and seizures while eating. He was unresponsive for 5 minutes and exhibited chewing movements. Abnormal EEG findings supported the suspicion of epilepsy. However, typical type 1 ECG was induced by a sodium channel blocker, and VF was easily induced by a single extrastimulus. It was difficult to determine whether all LOC episodes were caused by epilepsy. Therefore, this patient was considered to be at high risk for developing VF. The patient experienced recurrent LOC due to epilepsy 1.9 years after S-ICD implantation.

These cases were difficult to distinguish from VTA cases based on medical history or EEG at initial presentation and were also considered to be at high risk for VF.

Inappropriate ICD therapy and late complications

Twenty-seven patients (24%) experienced 47 inappropriate shocks (event rate 2.5% per year). There were no differences in inappropriate therapy based on symptoms. The causes of inappropriate shocks included atrial arrhythmia in 13 patients (12%), T-wave oversensing in 6 (5.4%), sinus tachycardia in 4 (3.6%), lead fracture in 2 (1.8%), and other in 2 (1.8%) (Table 3).

Table 4 Characteristics at initial presentation in patients finally diagnosed with epileptic unconsciousness

Case no.	Sex	Age (y)	Family history of sudden death <45 y	*SCN5A* mutation	Spontaneous type 1 ECG	Drug-induced type 1 ECG	VF induction	
							With <2 extrastimuli	With 3 extrastimuli
1	M	46	No	No	No	Yes	1	1
2	M	59	No*	No	No	Yes	1	1
3	M	28	No	No	Yes	Yes	0	0
4	M	53	No	No assessments	No	Yes	0	1

Case no.	Neurological evaluation		Condition after onset of LOC			Position at the onset of LOC	Situation at the onset of LOC
	Brain MRI	Electroencephalography	Convulsion	Incontinence	Any injury		
1	No abnormality	No abnormality	Yes	No	No	Supine	Sleeping
2	No abnormality	No abnormality	No	No	Yes	Standing	Standing
3	No abnormality	No abnormality	Yes	No	No	Supine	Sleeping
4	No abnormality	Epilepsy waves	Yes	No	No	Sitting	Rest

Abbreviations as in Table 1.

*Three first-degree relatives experienced sudden death after the age of 45 y.

Late complications of TV-ICDs were registered in 31 patients after 10.6 ± 6.8 years of follow-up (31% of patients with TV-ICDs; event rate 2.9% per year) with lead dysfunction in 27 patients and infection in 4 patients. Two patients with S-ICDs required premature S-ICD replacement due to accelerated battery depletion after 3.2 ± 2.3 years (14% of patients with S-ICDs; event rate 4.2% per year).

Discussion

The present study showed that approximately 40% of the patients experienced LOC after ICD implantation. VTA is the most common cause of LOC, especially in patients with VTAs or LOC episodes. However, 6 patients with previous LOC had nonarrhythmic LOC after ICD implantation. Nonarrhythmic LOC is caused by NMS and epilepsy. NMS can be differentiated by obtaining a careful history of LOC attacks. However, distinguishing epilepsy from VTAs can be challenging because symptoms and situation of VTA attacks in BrS and epilepsy are similar; both attacks often occur at rest or during sleeping and can cause convulsions during LOC; both attacks frequently lack the prodromes; and EEG is frequently normal during epilepsy-free intervals. Although evaluating the cause of LOC before ICD implantation is crucial, some LOC episodes, particularly epilepsy, can be difficult to differentiate from LOC by VTAs. When LOC recurs without ICD therapy, epilepsy can be considered a differential diagnosis, and further investigations should be conducted.

Regarding nonarrhythmic LOC after ICD implantation, Sarkozy et al[6] reported that 15% of 26 patients with syncope had recurrent, most likely vasovagal, syncope during follow-up. Conte et al[7] reported that 8% of patients with a history of syncope who underwent ICD implantation experienced further episodes of syncope during follow-up, without detecting any ventricular arrhythmias by the ICD device. Previous studies have reported that approximately 10% of patients with a history of LOC experience recurrent nonarrhythmic LOC, which is consistent with our results. However, previous studies have not provided detailed information on nonarrhythmic LOC. The novel finding of our study is that approximately 10% of the patients diagnosed with arrhythmic LOC and implanted ICDs had recurrent LOC due to epilepsy. Approximately half of the symptomatic patients remained asymptomatic after ICD implantation. Additionally, as shown in Figure 3, the survival curve for nonarrhythmic LOC demonstrated a more gradual slope compared to arrhythmic LOC. Therefore, long-term follow-up is necessary to confirm the cause of LOC in these patients.

Identifying patients with BrS at risk for SCD is important. Sieira et al[8] had reported the scoring systems for risk assessment. However, in this study, stratifying risk for patients with LOC was challenging (Supplemental Figure). Indeed, a patient with LOC that strongly suggested arrhythmic syncope and had a risk score of 3 points, just LOC, and early familial SCD received appropriate ICD therapy for VF after ICD implantation. Determining the etiology of LOC episodes is important for identifying patients with BrS at risk for SCD. Distinguishing NMS from arrhythmic LOC requires thorough investigation of the circumstances and prodrome of the symptoms.[9,10] Take et al[9] reported that syncope with prodromal symptoms, particularly "blurred vision," are benign symptoms. Additionally, Sacher et al[10] reported that the clinical features of arrhythmic LOC in BrS include the absence (or brief <10 seconds) of prodromes, absence of specific circumstances, brief LOC (<1 minute), and quick return to consciousness.

Distinguishing epilepsy from paroxysmal attacks caused by cardiovascular or psychological disorders has long been challenging.[11,12] Sheldon et al[11] reported the historical criteria to distinguish syncope from seizures; patients with seizures often experience tongue biting, déjà vu, hallucinations, and convulsive movements, whereas patients with syncope may experience presyncope, chest pain, and nausea. However, in their study, 60% of patients with syncope had vasovagal syncope. Although it may be useful for differentiating vasovagal syncope from epilepsy, it may be difficult to differentiate syncope caused by specific ventricular

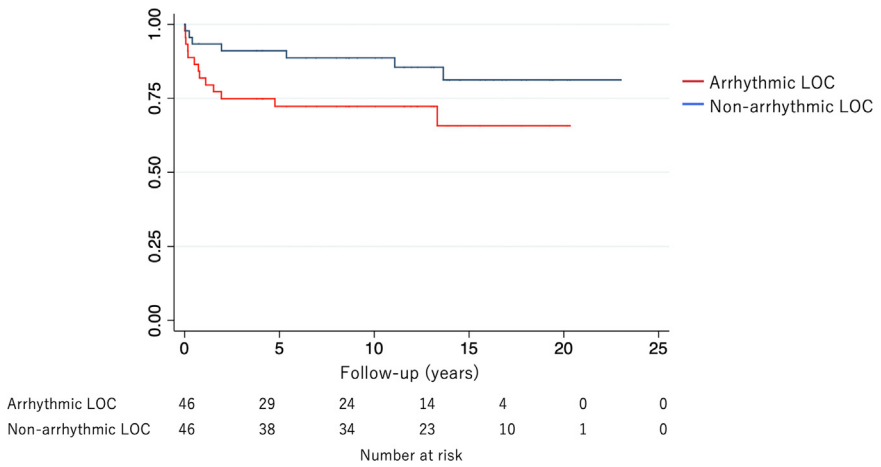

Figure 3 Event-free survival curve for arrhythmic and nonarrhythmic loss of consciousness (LOC) in patients with an initial LOC event.

arrhythmias, such as BrS, which often occur during sleep. Moreover, the patients with epilepsy in our study did not experience prodromes and concomitant symptoms indicative of epilepsy.

Table 4 lists the characteristics of patients with epilepsy in our study. Only 1 patient had spontaneous type 1 ECG, but typical type 1 ECGs were induced by sodium channel blocker administration in all patients. Three of the 4 patients were not diagnosed with epilepsy at the time of ICD implantation and experienced LOC during rest or sleeping, which was the most frequent situation of VF in BrS. Moreover, abnormal EEGs were not recorded during nonseizure periods, and VF was frequently induced by EPS. After repeated EEGs and other neurological examinations, the patients were diagnosed with epilepsy-related LOC. Convulsions were observed in 75% of the patients with epilepsy. However, convulsions were also observed in 30% of the patients with arrhythmic LOC due to VTA. There is a wide range of estimates of the prevalence of convulsive activity during syncope (4%–40%), and distinguishing epileptic convulsions from convulsive syncope usually is difficult.[12]

There is an ongoing debate on whether episodes of LOC caused by epilepsy in patients with BrS are benign. Previous case reports have described the incidental discovery of BrS in patients with a history of epilepsy, suggesting the coexistence of epilepsy and cardiac channelopathy.[13,14] Furthermore, some reports have described familial cases of genetic abnormalities that combine hereditary epilepsy and BrS.[15,16] Both epilepsy and BrS have been linked to abnormalities in the sodium channel Na_V, which consists of 9 different alpha subtypes ($Na_V1.1$, $Na_V1.9$). Mutations in these channels can cause diseases known as channelopathies.[17] However, there is no definitive evidence to suggest that cardiac channelopathy causes true epilepsy.[13] Mutations in Na_V channels expressed in cardiac tissues, namely, $Na_V1.4$ (SCN4A), $Na_V1.5$ (SCN5A), $Na_V1.8$ (SCN10A), and $Na_V1.9$ (SCN11A), have not been correlated with epilepsy.[18] None of the patients with epilepsy in our study experienced VF episodes, suggesting that the coexistence of epilepsy and BrS may be rare in clinical practice, except in some familial cases. Further research with larger sample sizes, prospective designs, and comprehensive data collection methods is required. Determining the underlying cause of LOC in patients with BrS can be time-consuming, thus highlighting the importance of long-term follow-up studies such as ours.

Regarding late complications, the rates of lead fractures and early battery depletion were higher than previously reported (2.5% vs 1.6%, 4.2% vs 3.7%, respectively).[19,20] Higher lead fracture rates may be due to longer-term follow-up (occurring at an average of 9.6 years), and the higher early battery depletion rate in S-ICDs might be attributed to a small sample size (12 patients).

Study limitations

Study limitations included a small sample size, low event rates of nonarrhythmic LOC, a retrospective study design, reliance on chart information for medical history collection, potential lack of important details from structured interviews, and missing initial medical histories in 3 cases. Additionally, we assume that similar symptoms and situations have the same cause, but there is a possibility that different underlying causes may lead to similar episodes. These limitations may have affected the completeness, accuracy, and precision of the findings.

Conclusion

Nonarrhythmic LOC similar to the initial episode was observed after ICD implantation in 13% of patients with a history of LOC before ICD implantation. Accurate classification of LOC based on detailed medical history is important for risk stratification; however, in some cases, especially in patients with epilepsy, it may be difficult to distinguish LOC from arrhythmic LOC. For repeated episodes of LOC after ICD implantation, it is important to consider epilepsy as a differential diagnosis and perform further neurological evaluations.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Written informed consent was obtained from each patient before the study.

Ethics Statement: This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University. Analysis of the *SCN5A* gene was performed in 78 patients in compliance with the guidelines for human genome studies of the Ethics Committee of Okayama University.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2023.09.007.

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