Significant Delayed Conduction and Characteristic Ventricular Tachycardias in Patients with Cardiac Sarcoidosis and Electrical Storm

Running title: Electrical storm in cardiac sarcoidosis

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Abstract

(**Background**) Electrical storm (ES) of ventricular tachyarrhythmias (VTAs) is an important cause of sudden death in patients with cardiac sarcoidosis (CS). VTAs in CS are associated with myocardial scarring and inflammation. However, little is known about the risk factors of ES in patients with CS and VTAs. The objective of this study is to clarify the characteristics and risk factors for development of ES in patients with CS.

(**Methods**) The study population included a consecutive 52 patients with CS and sustained VTA. Twenty-five out of 52 patients experienced ES. We evaluated clinical characteristics, imaging modalities, and electrocardiogram (ECG) parameters to determine the risk factors associated with ES.

(**Results**) Half of the patients experienced VTAs as the initial symptom of sarcoidosis, and eight patients had ES as the initial VTA episode. There were no differences in cardiac imaging abnormalities between patients with and without ES. Among ECG markers, significant QRS fragmentation (odds ratio [OR]: 7.9, p=0.01) and epsilon waves (OR: 12.24, p=0.02) were associated with ES. Among the ventricular tachycardia (VT) characteristics, multiple morphologies of monomorphic VTs (OR: 10.9, p<0.01), short VT cycle lengths (OR: 12.5, p<0.01), and polymorphic VT (OR: 13.5, p<0.01) were associated with ES. Bidirectional VTs were detected in 10 patients with ES and one patient without ES. Immunosuppressive therapy relieved ES in some patients.

(**Conclusions**) ES was common in patients with CS and VTAs. Significant depolarization abnormalities that appeared as QRS fragmentation, epsilon waves, and specific VT characteristics were associated with ES.

Key Words: cardiac sarcoidosis, ventricular tachycardia; sudden cardiac death; electrical storm, ventricular fibrillation

Introduction

Sarcoidosis is a systemic granulomatous disease that affects multiple organs[1]. Granulomatous involvement of the heart is a major determinant of patient prognosis. Cardiac sarcoidosis results in atrioventricular (AV) block, ventricular tachyarrhythmias (VTAs), and heart failure. Ventricular tachycardias (VTs) and ventricular fibrillation (VF) can lead to sudden cardiac death (SCD)[2, 3].

Risk stratification modalities have been proposed for predicting VTAs and SCD in patients with cardiac sarcoidosis. Myocardial inflammation can be detected using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or ^{67}gallium (Ga) single-photon emission computed tomography (SPECT)[4, 5]. Cardiac magnetic resonance (CMR) imaging using late gadolinium enhancement (LGE) reveals fibrosis after inflammation[6, 7]. Myocardial inflammation and fibrosis act as substrates for VTAs. Programmed electrical stimulation (PES) enables prediction of the occurrence of reentrant VTs[8]. These modalities are useful for predicting the risk of VTAs in patients with cardiac sarcoidosis.

Electrical storm (ES) is the most severe form of VTAs and is associated with the poor prognosis of various heart diseases[9]. Frequent anti-tachycardia pacing or cardioversion by an implantable cardioverter defibrillator (ICD) can aggravate cardiac dysfunction. However, risk factors for predicting ES have not been fully evaluated in patients with cardiac sarcoidosis.

This study aimed to clarify the characteristics of patients with ES and identify the risk factors for the development of ES in patients with cardiac sarcoidosis and VTAs.

Materials and Methods

Study subjects

A total of 52 patients who visited our hospital between January 1992 and June 2022 with cardiac sarcoidosis and VTAs were included. This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University. We retrospectively assessed the patients and their clinical courses. Diagnosis of cardiac sarcoidosis was determined according to the Japanese Circulation Society Guidelines for the Diagnosis and Treatment of Cardiac Sarcoidosis[10,11].

VTA events were defined as the occurrence of sustained VT/VF or appropriate therapy with an ICD or cardiac resynchronization therapy and defibrillator (CRT-D). ES was defined as three or more VTAs that required an intervention, such as direct current shock, administration of an intravenous antiarrhythmic agent, or appropriate ICD/CRT-D therapies, for termination of the VTAs within a 24-hour period. We compared the clinical data of patients with ES (ES group) with those without ES (non-ES group).

Evaluation of the clinical data

We assessed 12-lead ECGs, signal-averaged electrograms (SAECGs), electrophysiological study results, and images from various modalities.

We evaluated the 12-lead ECG at the time of the first VTA episode (PR, QRS, and QTc intervals; QRS morphology; fragmented QRS [fQRS]; epsilon wave; and early repolarization). We measured the PR, QRS, and QT intervals of lead II. The QRS interval was measured during sinus rhythm or pacing rhythm. Wide QRS morphologies

included right or left bundle branch block (RBBB and LBBB, respectively) and ventricular pacing. fQRS was defined as a QRS complex with >2 positive spikes in the R or S wave in at least two contiguous leads (Figure 1) [12]. The extent of the fQRS area was determined by the number of leads with fQRS in the 12-lead ECG[13]. For quantification of fQRS, we evaluated the number of positive spikes in leads I, aVF, V1, V3, and V5. The epsilon wave was defined as the low-amplitude signal between the end of the major QRS complex and the onset of the T wave (Figure 2)[14]. The presence of early repolarization was defined as ST elevation at the J point with a slurring or notched J wave ≥ 0.1 mV in at least two contiguous leads[15]. If a coved-type J-point elevation (≥ 0.2 mV) was observed in the right precordial leads, it was considered a Brugada ECG pattern[15]. The severe AV blocks included the Mobitz type II second-degree AV block, paroxysmal AV block, and third-degree AV block.

For each patient, we evaluated the characteristics of VTs, measured their minimum cycle length, and counted the number of monomorphic VT morphologies. Polymorphic VT was defined as VT with various changes in QRS morphology. Bidirectional VT is a polymorphic VTs and is defined as a VT with 2:1 alternative change in QRS morphology. ECGs and VT patterns were reviewed blindly by three cardiologists (HM, SA, and SO).

We used SAECGs to evaluate late potentials. Patients with ventricular pacing were excluded. The filtered QRS duration, root-mean-square voltage of the terminal 40 ms in the filtered QRS complex (RMS40), and duration of the low-amplitude signals <40 μV in the terminal filtered QRS complex (LAS40), were measured. LPs were positive when more than two of the following criteria were met: filtered QRS complex >120 ms, RMS40 <20 μV, and LAS40 >38 ms. In patients with wide QRS complexes,

LP was positive when both RMS40 and LAS40 met the criteria. The Supplemental Methods section describes the imaging modalities.

An electrophysiological study was performed after written informed consent was obtained. Induction of VTAs was attempted using PES with up to three extra stimuli from the right ventricular apex and right ventricular outflow tract. The endpoint of the PES was either the induction of sustained VTAs or completion of the protocol.

Statistics

Continuous data are expressed as mean ± SD values. Comparisons between the two groups were made using Student's *t*-test or a non-parametric test for paired and unpaired data, as appropriate. Fisher's exact test or the χ^2 test was used for categorical variables. Survival and event rates were determined using the Kaplan-Meier method and compared between groups using a 2-sample log-rank test. Clinical markers were used in logistic regression analyses to assess risk factors for ES. Odds ratios (ORs) and confidence intervals (CIs) are presented for univariate analysis.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed using JMP version 14.3.0 (SAS Institute Inc., Cary, North Carolina, USA). All authors have full access to and take full responsibility for the data integrity.

Results

Characteristics of patients with cardiac sarcoidosis and VTAs

The patient clinical characteristics are shown in Table 1. Among the patients with cardiac sarcoidosis and VTAs, approximately half (48%) experienced ES. Cardiac symptoms (such as VTAs, AV block, and heart failure) frequently appeared in both groups as the initial manifestations of sarcoidosis. The age at onset of sarcoidosis and first VTAs did not differ between the two groups. Half of the patients without ES experienced a severe AV block before the first VTA, whereas patients with ES frequently had VTAs as the initial symptoms of cardiac sarcoidosis. ES occurred as the first VTA episode in one-third of the patients with ES.

Electrical devices were used for 51 patients. A pacemaker was initially implanted in 16 patients and later upgraded to an ICD or CRT-D in 14 patients. CRT-D was frequently implanted in patients without ES, and an ICD was frequently implanted in patients with ES at the final follow-up.

Supplemental Table 1 shows the patient imaging data. There were no significant differences in the imaging modalities between the two groups. The patients in both groups frequently showed reduced left ventricular function, a wide area of LGE and myocardial inflammation.

Twelve-lead ECG parameters and characteristics of VTAs

Table 2 shows ECG parameters and characteristics of VTAs. PR, QRS (Figure 3A) and QTc intervals did not differ between the two groups. Incidences of ventricular pacing and BBB were not different between the two groups. Fragmented QRS frequently appeared in both groups, and the ES group had more leads with fQRS and multiple spikes in QRS complex than the non-ES group (Figures 1 and 3B–D). Epsilon wave was more frequently observed in the ES group than in the non-ES group and was

associated with prominent late potentials (Figures 2 and 3E). There was no difference in the incidence of J wave between the two groups. Brugada-type ECG appeared in one patient with ES. Late potential was frequently positive in both groups; however, there were no differences in the incidence and parameters of late potentials.

Generally, the ES group had more severe forms of VTAs than the non-ES group; the ES group exhibited additional morphologies of monomorphic VTs than the non-ES group. The cycle lengths of VTs were shorter in the ES group than in the non-ES group. Bidirectional VT (Figure 4), polymorphic VTs, and VF occurred frequently in the ES group. The medication administered at the onset of VTAs did not differ between the groups (Supplemental Table 2), and the characteristics of VT were not influenced by pharmacotherapies. Amiodarone was initiated in three patients in the non-ES group due to frequent premature ventricular contractions or non-sustained VT. The incidence and number of PES-induced VTs did not differ between the two groups, and PES did not induce bidirectional VTs.

Immunosuppressive therapy

Prednisolone was used before the first VTA episodes in 18 patients (non-ES: 11; ES: 7), and methotrexate was used with prednisolone in only one patient in the non-ES group. After the first VTA episode, prednisolone therapy was initiated in 19 patients (non-ES: 8, ES: 11; p=0.0681). VTA occurrence was reduced or eliminated after the administration of prednisolone in 12 patients (no ES: five, ES: seven, p=0.9606). However, seven patients still experienced VTAs, and the occurrence of VT was aggravated in three. Prednisolone had been initiated in 17 patients (68%) before ES, and high-dose prednisolone was initiated in three at the time of ES; prednisolone did not

affect VT in two patients receiving 30 mg/day of prednisolone and 1 g/day of methylprednisolone, while the ES was treated in one patient after starting 1 g/day of methylprednisolone. In the later patient, beta-blocker was already administrated, and amiodarone was terminated due to QT prolongation before the occurrence of ES. We scheduled ablation therapy for this patient, but Ga^{67}-Scintigraphy revealed active inflammation, so we initially started 1g of prednisolone per day. Bidirectional VT occurred in five patients during the administration of prednisolone, and prednisolone was newly administered in two patients; prednisolone was effective in one patient but did not reduce VTAs in the other. Prednisolone was administered in 39 (75%) patients (non-ES: 19, ES: 20) at the last follow-up (Supplemental Table 2). Methotrexate was administered to a patient in the non-ES group in addition to prednisolone.

Prognosis and risk factors for ES

Thirteen patients died during follow-up (Table 1). Cardiac death occurred in three patients without ES and six patients with ES. All cardiac deaths in the non-ES group were caused by heart failure. In the ES group, four patients died of heart failure and three patients died of VTAs. Among the three patients who died from VTAs, one died of heart failure with ES. The second patient, in whom ICD implantation was performed, died from a VF storm. The third patient, in whom a pacemaker was implanted and scheduled to undergo an upgrade to ICD, died suddenly from VT/VF.

Recurrence of VTAs > 1 month after the initial VTA episode was observed in 18 patients without ES and 22 patients with ES (p=0.0136). Recurrence of ES was observed in 7 out of 23 patients after an average of 4.8±3.5 years (range: 0.2–9.3 years) from the first ES episodes.

Table 3 shows the results of the logistic regression analysis of the risk factors associated with ES. The first VTA episode preceding a severe AV block was associated with ES. An increasing number of leads with fQRS, number of QRS spikes, and the presence of epsilon waves were significant risk factors for ES. Multiple morphologies of monomorphic VTs, bidirectional VT, polymorphic VT, and VT with short cycle lengths were associated with ES.

Discussion

New observations

Approximately half of patients with cardiac sarcoidosis and sustained VTAs experience ES and ES can occur as the initial symptom of sarcoidosis. The substrates of the VTAs did not differ between the patients with and without ES. Significant depolarization abnormalities detected by the extension and severity of fQRS and epsilon waves are associated with ES. Rapid multiple types of monomorphic and polymorphic VTs are predictors of ES. Bidirectional VTs were observed in 21% of the patients and were associated with ES. Immunosuppressive therapy relieved ES in some patients.

VTA substrates and risk markers associated with ES in cardiac sarcoidosis

Cardiac sarcoidosis is a malignant form of sarcoidosis that affects patient prognosis. Cardiac involvement has been found in 2.3–25% of patients with systemic sarcoidosis[1, 16]. Cardiac sarcoidosis manifests as heart failure, AV block, and VTAs, and is associated with significant morbidity and mortality[1, 16]. ES is a severe form of VTAs and previous studies have shown the incidence of ES in patients with cardiac

sarcoidosis to be 3–24% [17-20]. The ES is a significant factor leading the application of catheter ablation therapy in patients with cardiac sarcoidosis and VTAs, affecting 56–81% of these patients[2, 21]. SCD is common, occurring in 10–14% of patients with cardiac sarcoidosis[16, 22]. Fibrosis and inflammation detected using CMR and FDG-PET are powerful predictors of VTAs and SCD[3, 4, 6, 7]. ECG signs indicating conduction abnormalities, such as AV node dysfunction, BBB, and fQRS, are also associated with VTA events and SCD[19, 23, 24]. PES can be used to identify high-risk patients for VTs, appropriate ICD therapies, and SCD[8].

Since the present study focused on patients with VTAs, most previously determined risk factors associated with VTAs were present in our patient population. The arrhythmogenic substrates of VTAs detected by imaging modalities, such as low cardiac function, area of fibrosis, and incidence of inflammation, were similar in patients with and without ES. Extended and significant QRS fragmentation, and epsilon waves were unique ECG findings representing remarkable depolarization abnormalities in patients with ES. Patients with fQRS experienced more frequent VTA episodes compared to those experienced by patients without fQRS[24]. The present study focused on patients with VTAs, and the incidences of fQRS and positive late potentials did not differ between the two groups. However, the extent and severity of fragmented QRS, which had been determined by the number of leads with fQRS and number of positive spikes within the QRS complex, respectively, were more significant in patients with ES than in those without ES. A fragmented QRS represents changes in the wavefront of ventricular activation caused by an inexcitable scar. Extended and significant QRS fragmentations can represent multiple dispersed scar islands in the ventricle, which cause many changes in the direction of the excitation wavefront. The myocardium

between multiple scar islands could be the channels of the reentrant circuits of the VTAs. While epsilon waves are typically observed in patients with right ventricular cardiomyopathy, there have been reported cases of cardiac sarcoidosis[25, 26]; although, there are no data on the relationship between epsilon waves and ES. The present study showed that epsilon waves frequently appeared in patients with ES. The epsilon waves represent some extent of the myocardium with delayed conduction surrounded by an inexcitable scar. The entrance and exit of the myocardium within excitable areas may form part of the reentrant circuits. The myocardial area in the inexcitable scar that generates an epsilon wave also causes changes in the excitation wavefront and can result in fQRS. As epsilon waves and significant fQRS reflect the existence of a significantly conduction abnormality that could be a substrate for ES[25]. These ECG changes should be associated with a more advanced arrhythmogenic substrate.

Among the characteristics of VTAs, rapid and multiple types of monomorphic and polymorphic VT were high-risk VTAs associated with ES. Observation of results of PES and imaging modalities may help elucidate the mechanisms of these VTAs. Based on the PES results and existence of a wide area of fibrosis, the major mechanism of VT may be reentry. However, myocardial inflammation was observed in approximately 90% of the patients during the follow up. Inflammation can induce abnormal automaticity and triggered activity by altering the ion channel function, intracellular calcium handling, and autonomic nerve activity[27]. Thus, the mechanism of some VTAs is non-reentry. We also found that bidirectional VT is common in patients with cardiac sarcoidosis and VTAs. Bidirectional VT was initially reported in patients with digitalis poisoning and was caused by a triggered activity. Bidirectional VT in cardiac sarcoidosis can be explained by alternate changes in the exit site because of a

conduction block within the reentrant circuit; however, it can occur from the triggered activity induced by myocardial inflammation. High-dose steroids suppressed VT occurrence in one of three patients with ES and one of two patients with bidirectional VT. Although not all patients respond to immunosuppressive therapy, some may develop non-reentrant VT because of inflammation. Immunosuppressive therapy can be considered an optional therapy to reduce VTAs. In patients with active inflammation, ablation of VT foci can be useful, but substrate mapping of the low-voltage area can change with the appearance/disappearance of inflammation. Subsequently, substrate mapping should be performed after the resolution of myocardial inflammation.

The CRT-D implantation was more frequent in the non-ES group than in the ES group. Cardiac function was not different between two groups (Supplemental Table 1). Approximately half of the patients experienced severe AV block as the first heart symptoms, such patients frequently exhibit all ventricular pacing rhythm, leading to dyssynchronous motion of the left ventricle. Therefo implantation of CRT-D would be more frequent in the non-ES group than in the ES group.

Clinical perspectives

In patients without VT episodes, the appearance of fQRS should be monitored because it may be a warning sign of VT[24]. Ambulatory ECG, cardiac MR and PET/Ga-scintigram should be recorded to detect VTAs and expansion of fibrosis and inflammation. In patients with sustained VT, an increase in fQRS, the appearance of epsilon waves, and the occurrence of AV block during the follow-up could be risk markers for the progression of the VT substrate that can induce ES. Although 15% of the patients experienced ES as the first VTA episode, the characteristics of the initial

VTs, including rapid, multiple monomorphic or polymorphic VT, including bidirectional VT, are also associated with the occurrence of ES. In patients with myocardial inflammation, immunosuppressive therapy is a treatment option for VTAs.

Limitations

There were limitations to the current study. This retrospective study was conducted at a single center and the patient inclusion duration was long. The number of patients included in this study was small, and the results of the present study should be validated in a larger cohort though a multicenter study. In addition, remarkable progress was made in the diagnostic methods, the treatment of heart failure and arrhythmias during the study period, and advances in therapeutic methods may have influenced patient prognosis. Therefore, we deemed it inappropriate to present detailed prognostic data, such as survival curves and the efficacy of ablation.

Conclusions

ES frequently occurs in patients with cardiac sarcoidosis and sustained VTAs. There were significant depolarization abnormalities and characteristic VTAs in patients with ES.

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Tables

Table 1. Characteristics of patients

		Overall	Non-electrical storm	Electrical storm	*p* value
Number of patients		52	27 (52%)	25 (48%)	
Age (years)	The first symptoms associated with sarcoidosis	56.0 ± 16.5	58.9 ± 14.0	52.9 ± 16.7	0.1620
	The first VTAs	62.4 ± 14.6	65.6 ± 14.0	59.0 ± 14.7	0.1017
	Electrical storm	-	-	61.8 ± 14.2	
Sex (Male)		32 (62%)	17 (63%)	15 (60%)	1.0000
NYHA (at the time of the first VTA)		1.9 ± 0.8	1.9 ± 0.8	2.0 ± 0.9	0.4174
The initial manifestation of sarcoidosis					
	Cardiac	39 (75%)	20 (74%)	19 (76%)	1.0000
	Extracardiac	13 (25%)	7 (26%)	6 (24%)	
The initial heart manifestations					
	VTAs	24 (46%)	9 (33%)	15 (60%)	0.0563
	Severe AVB	19 (36%)	14 (52%)	5 (20%)	0.0183
	Heart Failure	12(23%)	5 (19%)	7 (28%)	0.4220
	AVB+VTAs (<1 month)	3 (9%)	1 (4%)	2 (8%)	0.5109
First VTA episode					
	Non-electrical storm	43 (83%)	27 (100%)	16 (64%)	-
	Electrical storm	8 (15%)	0 (0%)	8 (32%)	-
	Ventricular fibrillation	2 (4%)	0 (0%)	2 (8%)	0.2262
The other heart complications					
	Admission by heart Failure	26 (50%)	14 (52%)	12 (48%)	0.7665
	Severe AVB	28 (54%)	14 (52%)	14 (56%)	0.7880
Cause of death					
	Overall	13 (25%)	4 (15%)	9 (36%)	0.0809

Heart Failure	7 (14%)	3 (11%)	4 (16%)	0.6093
VTAs	3 (6%)	0 (0%)	3 (12%)	0.0663
Cancer	2 (4%)	1 (4%)	1 (4%)	0.9562
Pneumonia	1 (2%)	0 (0%)	1 (4%)	0.2987
Intracranial hemorrhage	1 (2%)	0 (0%)	1 (4%)	0.2987
Implantable devices				
Overall	51 (98%)	26 (96%)	25 (100%)	0.3359
Pacemaker	16 (31%)	11 (41%)	5 (20%)	0.1088
ICD/CRT-D	49 (94%)	26 (96%)	23 (92%)	0.6029
Number of ICD/CRT-D/PM at the last follow-up	21/28/2	6/20/0	14/9/2	0.0057
Preventive therapy of defibrillator: Primary / Secondary	22/27	15/11	11/12	0.5722
CRT-D upgrade from ICD	4 (8 %)	1 (4%)	3 (13%)	0.2455
ICD/CRT-D upgrade from PM	14 (29%)	11 (42%)	3 (13%)	0.0251

AVB: atrioventricular block, CRT-D: cardiac resynchronization therapy defibrillator, ICD: implantable cardioverter defibrillator, PM: pacemaker, VTA: ventricular tachyarrhythmia

Table 2. Parameters of 12-lead ECG and ventricular tachycardia

		Overall	Non-electrical storm	Electrical storm	*p* value
ECG parameters at the time first VT					
PR interval		211.8 ± 60.3	206.1 ± 32.9	215.4 ± 3.4	0.7111
QRS interval		152.2 ± 43.2	145.0 ± 31.0	146.8 ± 32.7	0.8263
QTc interval		461.4 ± 61.1	463.1 ± 56.4	454.3 ± 53.9	0.5678
QRS morphology					
Ventricular pacing rhythm		25 (48%)	16 (59%)	9 (40%)	0.0967
Right bundle branch block		12 (23%)	4 (15%)	8 (32%)	0.1456
Left bundle branch block		2 (4%)	2 (7%)	0 (0%)	0.1777
Normal QRS interval		12 (23%)	5 (28%)	7 (28%)	0.4220
Fragmented QRS		48 (92%)	23 (85%)	25 (100%)	0.0495
Number of spikes	Lead				
	I	1.9 ± 0.8	1.9 ± 0.8	2.0 ± 0.8	0.4035
	aVF	2.7 ± 1.3	2.4 ± 1.3	3.0 ± 1.2	0.1297
	V1	2.8 ± 1.2	2.5 ± 1.3	3.1 ± 1.1	0.0994
	V3	2.6 ± 1.3	2.1 ± 1.2	3.2 ± 1.3	0.0055
	V5	2.5 ± 1.2	2.2 ± 1.1	2.9 ± 1.4	0.0657
Number of sum of spikes		12.6 ± 3.7	11.1 ± 3.2	14.1 ± 3.5	0.0026
Sum of spikes ≥10 spikes		39 (75%)	16 (59%)	23 (92%)	0.0096
Number of leads with fQRS		5.4 ± 3.3	3.3 ± 2.5	7.6 ± 2.4	<0.0001
Leads with fQRS > 5 leads		23 (44%)	5 (19%)	18 (72%)	0.0001
ε wave		8 (15%)	1 (4%)	7 (28%)	0.0163
Early repolarization		7 (13%)	2 (4%)	5 (10%)	0.1880
Signal averaged electrogram (n)		36	14	22	

Positive late potential (n)	27 (75%)	9 (64%)	18 (82%)	0.2429
Filtered QRS duration	159.0 ± 32.9	162.9 ± 29.8	156.5 ± 35.1	0.5777
LAS40	54.2 ± 26.4	52.8 ± 27.5	55.1 ± 26.2	0.8011
RMS40	17.7 ± 17.2	20.5 ± 21.2	15.9 ± 14.3	0.4455
Spontaneous VTAs				
Number of monomorphic VT morphologies	2.1 ± 1.4	1.4 ± 0.8	2.8 ± 1.6	<0.0001
Minimum VT cycle length	328 ± 71	362 ± 78	292 ± 39	<0.0001
VT Cycle length ≤ 330ms	32 (62%)	10 (37%)	22 (88%)	0.0002
Polymorphic VTs	15 (29%)	2 (7%)	13 (52%)	0.0004
Bidirectional VTs	11 (21%)	1 (4%)	10 (40%)	0.0015
Ventricular fibrillation	4 (8%)	0 (0%)	4 (16%)	0.0322
Electrophysiological study	34 (69%)	13 (48%)	21 (84%)	0.0091
PES-induced VT	30/34 (88%)	11 (85%)	19 (90%)	0.6272
Number of induced VT	3.3 ± 2.0	2.5 ± 1.7	3.8 ± 2.1	0.1324

fQRS: fragmented QRS, LAS40: duration of low-amplitude signals <40 μV in the terminal filtered QRS complex, PES: programmed electrical stimulation, RMS40: root mean square voltage of the terminal 40 ms of the filtered QRS complex, SCD: sudden cardiac death, VF: ventricular fibrillation, VT: ventricular tachycardia

Table 3. Univariable analysis of risk factors associated with electrical storm

	Odds ratio	CI	*p* value
Clinical characteristics			
VT preceded the severe AV block	3.21	1.01 - 10.22	0.0479
ECG at the onset of the first VTA			
fQRS: sum of QRS spikes ≥10 spikes	7.91	1.54 - 40.60	0.0133
Leads with fQRS > 5 leads	11.31	3.07 - 41.76	0.0003
Epsilon wave	12.24	1.40 - 106.82	0.0235
Characteristics of VTAs			
Number of morphologies of monomorphic VTs ≥2	10.86	2.93 - 40.17	0.0004
Polymorphic VTs	13.54	2.63 - 69.81	0.0018
Bi-directional VT	17.33	2.02 - 149.04	0.0094
VT cycle length ≤ 330 ms	12.47	2.96 - 52.46	0.0006

AV: atrioventricular, fQRS: fragmented QRS, VTA: ventricular tachyarrhythmia, VT: ventricular tachycardia

Figure and figure legends

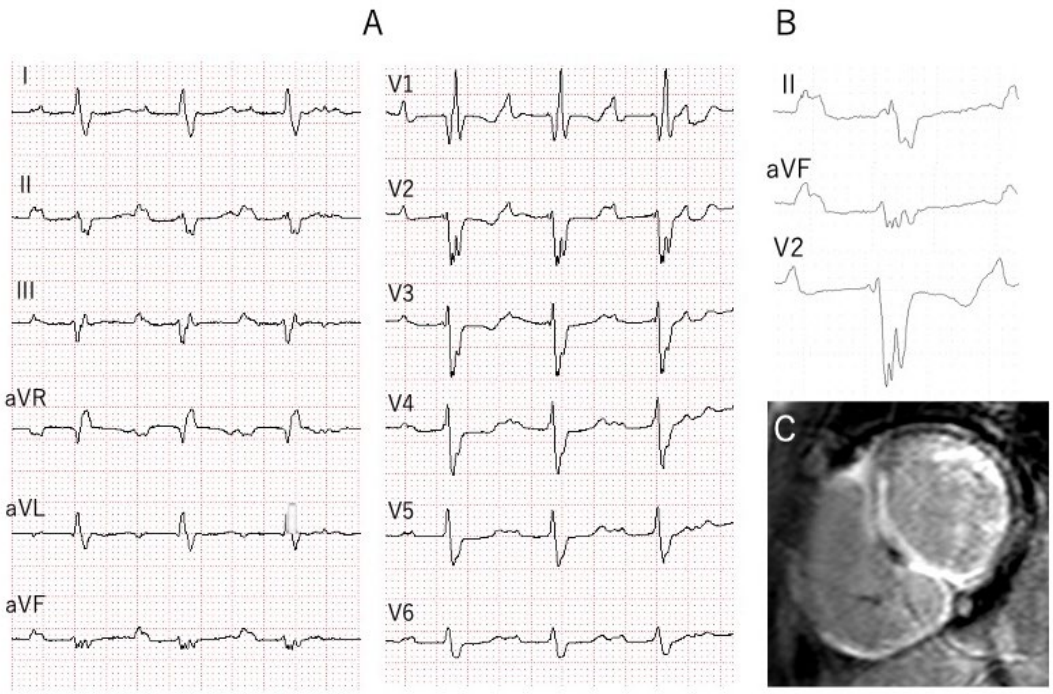


Figure 1. Fragmented QRS complex

A. 12-lead ECG in a patient with electrical storm. ECG shows PR and QRS prolongations with an intraventricular conduction disturbance. Fragmented QRS was observed in inferior and anterior leads. B. Magnification of leads II, aVF and V2. Fragmented QRS was observed. C. Late gadolinium enhancement by cardiac magnetic resonance imaging. Significant enhancement was observed in the intraventricular septum and inferior wall of both ventricles.

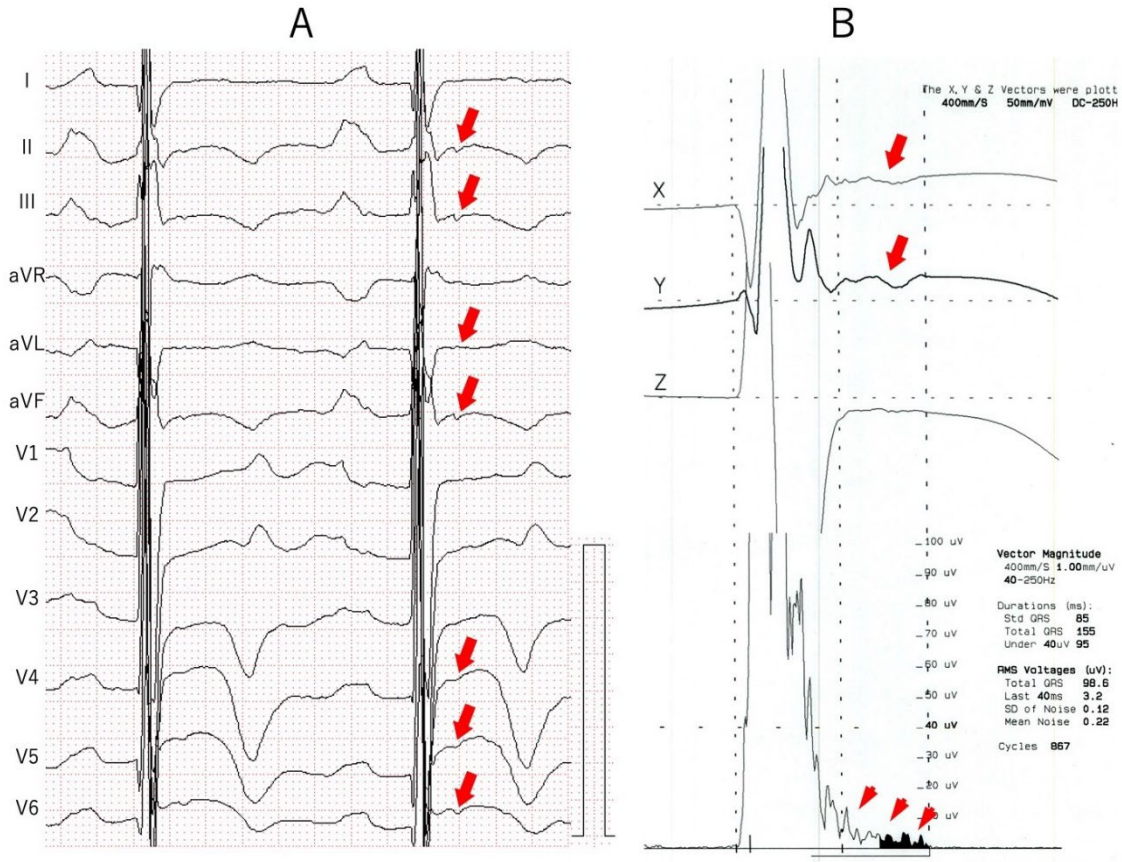


Figure 2. Epsilon waves in a patient with electrical storm.

A. Epsilon waves in a 12-lead ECG. Epsilon waves (arrows) were observed in inferolateral leads. B. Signal-averaged electrogram showed a remarkable late potential (arrowheads) that coincided with epsilon waves in leads X and Y (arrows).

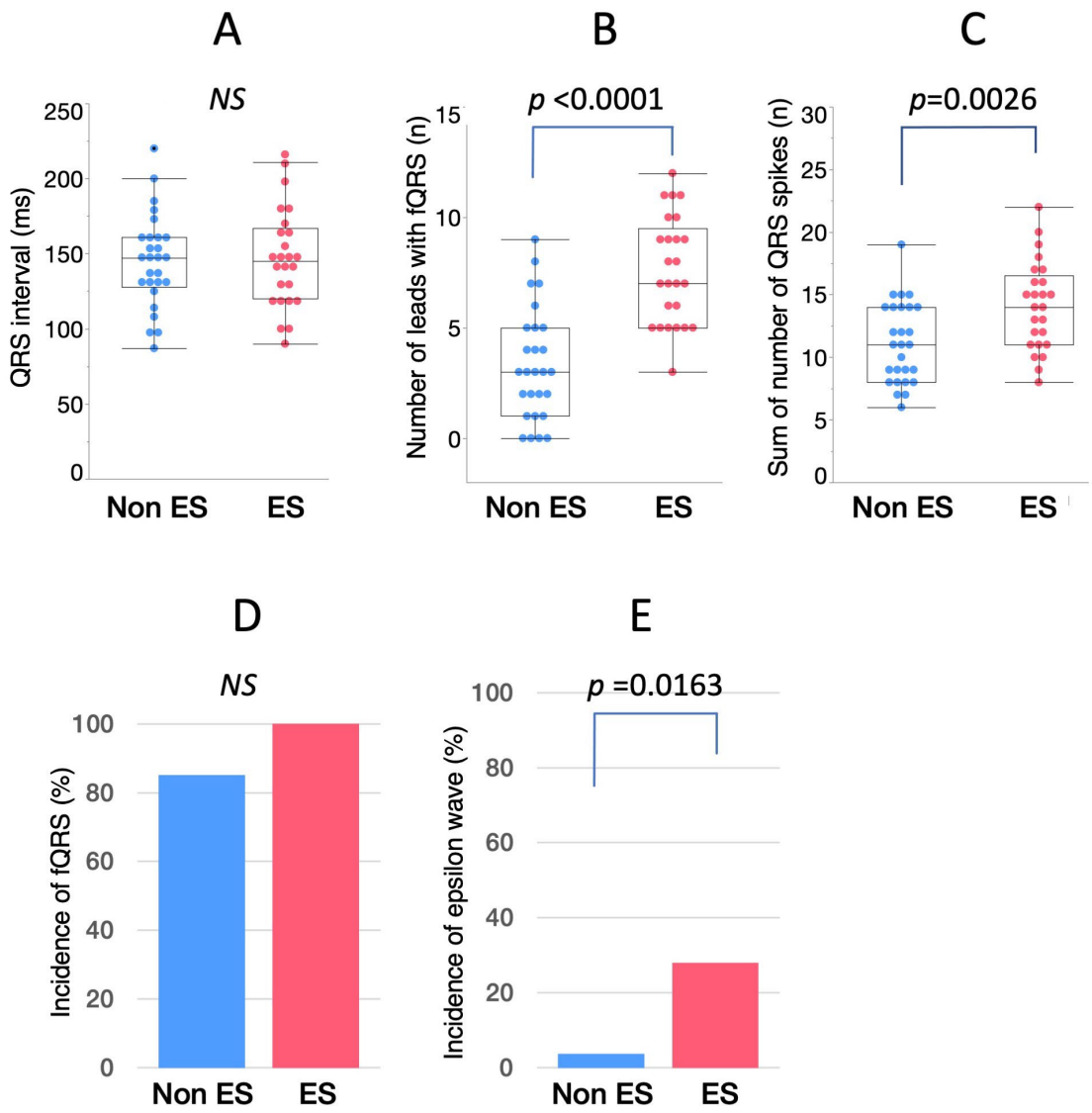


Figure 3. Depolarization ECG markers at the onset of the first ventricular tachyarrhythmias.

A. QRS interval. There was no difference in QRS interval between patients with electrical storm (ES) and patients without ES. B. Number of leads with fragmented QRS (fQRS). C. Sum of the positive spikes within QRS complex in leads I, aVF, V1, V3 and V5. D. Incidence of fQRS. Although incidence of fQRS was not different

between two groups, patients with ES frequently had many ECG leads with fQRS and QRS fragmentation. E. Incidence of epsilon wave . Epsilon wave frequently appeared in patients with ES.

ES, electrical storm; fQRS, fragmented QRS complex; NS, not significant.

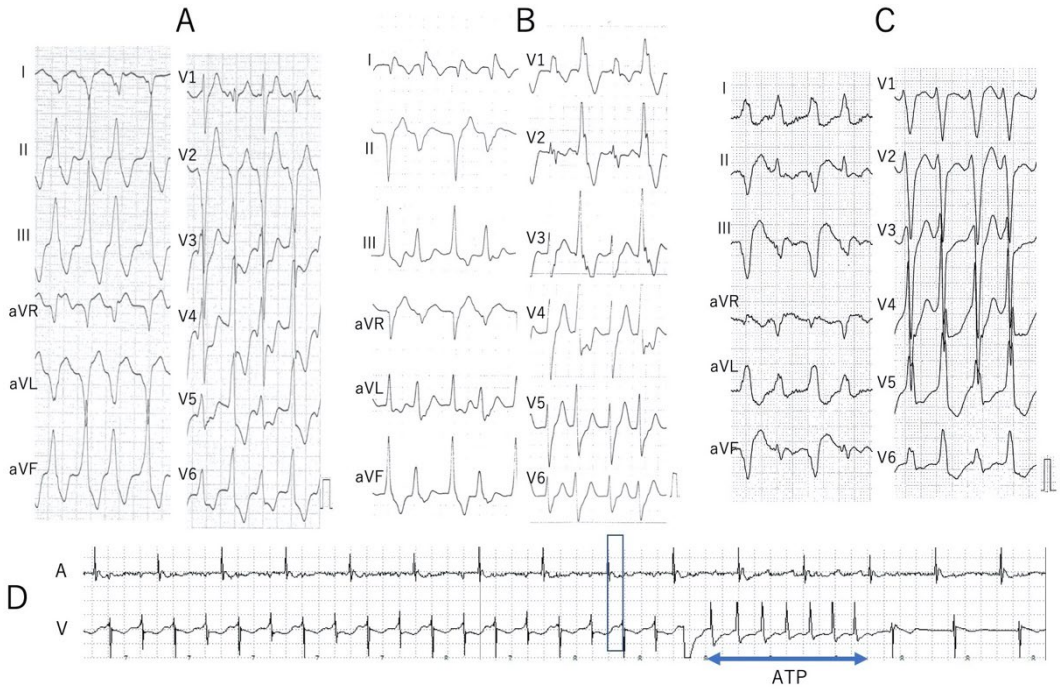
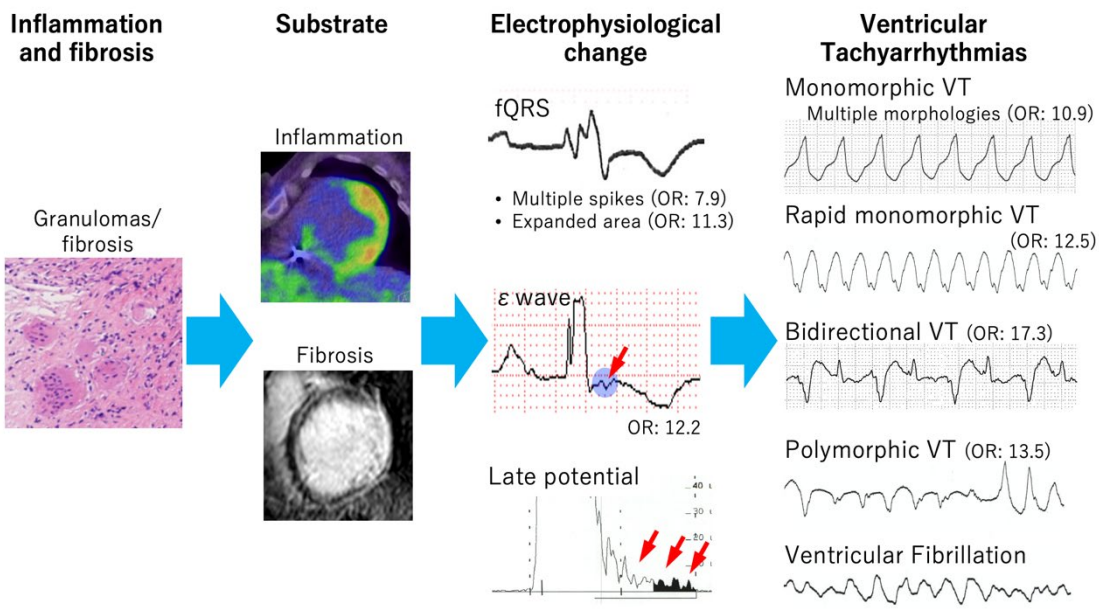


Figure 4. Bidirectional ventricular tachycardia.

Bidirectional ventricular tachycardia (VT) was recorded on 12-lead ECGs (A-C) and intracardiac electrograms of implantable cardioverter defibrillators (D). Beat-by-beat QRS alternans were observed during VTs. ATP: anti-tachycardia pacing.



Graphic Abstract