# Time Course and Factors Correlating With Ventricular Tachyarrhythmias After Introduction of Steroid Therapy in Cardiac Sarcoidosis

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***Background***—The time course and factors correlating with ventricular tachyarrhythmias (VTs) after introduction of corticosteroid therapy in patients with cardiac sarcoidosis remain to be elucidated.

***Methods and Results***—We examined 68 consecutive patients with cardiac sarcoidosis in the Tohoku University Hospital from October 1998 to September 2014 (age: 57±11 years old; male:female 18:50) and evaluated VTs after initiation of steroid therapy. VTs were defined as documented ventricular tachycardia or ventricular fibrillation lasting for more than 30 seconds or resulting in cardiovascular collapse, or appropriate implantable cardioverter defibrillator therapy. During a mean follow-up of 5.5 years, 20 out of 68 patients (29%) experienced VTs after initiation of corticosteroid therapy, especially in the first 12 months in 14 patients (70%). A multivariable analysis revealed that positive gallium scintigraphy had a significant correlation with VTs (hazard ratio, 11.33; 95% confidence interval, 3.22–39.92; $P<0.001$), in addition to reduced left ventricular ejection fraction (hazard ratio, 0.94; 95% confidence interval, 0.90–0.97; $P=0.001$). Furthermore, electrical storm was noted in 10 patients (14.7%), 8 within the first 12 months of treatment, whereas the recurrence of electric storm was relatively less.

***Conclusions***—These results indicate that VTs and electric storm frequently occur in the first 12 months after initiation of corticosteroid therapy, presumably because of inflammatory conditions, and that the positive gallium scintigraphy is a significant and independent predictor of VTs. The present findings may be useful to further improve the management of VTs in patients with cardiac sarcoidosis. **(*Circ Arrhythm Electrophysiol*. 2016;9:e003353. DOI: 10.1161/CIRCEP.115.003353.)**

**Key Words:** inflammation ■ prevalence ■ risk factor ■ sarcoidosis ■ ventricular fibrillation



Sarcoidosis is a heterogeneous, noncaseating, granulomatous disorder of unknown cause that can involve any organs within the body.[1] Clinical presentation of cardiac sarcoidosis (CS) seems to differ among various countries. In Japan, cardiac involvement is noted in 20–30% of patients,[1] and more than two thirds of deaths are attributed to cardiac involvement.[2]

Ventricular tachyarrhythmias (VTs) are often noted in patients with CS and could be fatal in some cases. VTs frequently recur and are difficult to control with antiarrhythmic drug therapy alone even when guided by electrophysiological test.[3] Predictive factors of VTs are not clear. The 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for device-based therapy in patients with CS indicate that it is a reasonable indication for implantable cardioverter defibrillator (ICD) implantation. However, the guidelines do not offer more specific recommendations regarding ICD therapy.[4] Additionally, there are few reports on the natural course of VTs. Betensky et al[5] examined the frequency of VTs requiring ICD in a series of 45 patients with CS. Appropriate ICD therapies for ventricular tachycardia or ventricular fibrillation (VF) were noted in 37.8% during a mean follow-up of 2.6 years after implantation.[5]

Corticosteroid therapy is a mainstay of CS treatment because it slows the progression of myocardial inflammation and fibrosis.[6–8] In contrast, the effects of corticosteroid therapy on VTs have been controversial,[3,9,10] and no information is available on the time course of VTs after initiation of corticosteroid therapy. In this study, we thus examined the effects of corticosteroid therapy on the prevalence and time course of VTs in patients with CS.

## Methods

This study and retrospective data use were approved by the University of Tohoku Institutional Review Board (2015-1-152). The study subjects gave their informed consent or were informed of the study by posted information in our institution.

Received July 7, 2015; accepted May 9, 2016.

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**The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.115.003353/-/DC1.**

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### WHAT IS KNOWN

- Ventricular tachyarrhythmias (VTs) are often noted in patients with cardiac sarcoidosis and could be fatal in some cases.
- Corticosteroid therapy is a mainstay of CS treatment, but the effects of corticosteroid therapy on the VTs have been controversial.

### WHAT THE STUDY ADDS

- The first VT events and the frequency of VT events in patients with cardiac sarcoidosis are frequently recognized early after the initiation of corticosteroid therapy.
- The time course of the occurrence of ventricular tachycardia electric storms has 2 peaks: during the early and the very late phase, and relatively few events between them.
- A positive gallium scintigraphy is the significant correlates of VTs, suggesting that corticosteroid therapy could modify the inflammation and calm down the VTs.



## Study Population and Diagnostic Criteria

We retrospectively examined 68 consecutive patients with CS in the Tohoku University Hospital from October 1998 to September 2014 (age: 57±11 years; male:female 18:50). CS was defined according to the original guidelines for diagnosis of CS from the Japanese Ministry of Health and Welfare.[11] The patients' data were collected from the time point of the initial CS diagnosis. The diagnosis of CS was made either directly by endomyocardial biopsy or indirectly by detection of clinical CS manifestations in addition to extracardiac sarcoidosis. Beside clinical history, ECG findings and cardiac imaging tests, including echocardiography, scintigraphy, and magnetic resonance imaging (MRI) findings were also used for this purpose.[12] ICD therapy was defined as the primary prevention when the patients had no history of VT/VF, sudden cardiac arrest, or syncope of unknown cause before device implantation and as the secondary prevention when they had a history of those events before the implantation.

## Imaging Examination and Biopsy

Cardiac MRI scans were performed by using the standard protocol in our institution[12] and ECG-gated magnetic resonance images were obtained in all patients during breath-holding on a 1.5-T imager (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany and Achiva; Philips Medical Systems, Best, The Netherlands) using a body array coil (Siemens) or a 5-channel cardiac coil (Philips). Delayed contrast-enhanced magnetic resonance images using inversion recovery-prepared gradient-echo sequence were acquired 10 to 15 minutes after injection of gadopentetate dimeglumine (0.15 mmol/kg) in the same plane as cine imaging with the Siemens Scanner or in 10 horizontal, 10 vertical long, and 20 short-axis slices with the Philips scanner.[13]

We routinely checked inflammation in almost all patients with CS except for in one patient during the admissions before introduction of corticosteroid therapy, using positron emission tomography (PET), gallium scintigraphy, or both. Patients underwent cardiac PET imaging in a fasting state (>12 hours), with images acquired 1 hour after the injection of 0.1 mCi/kg body weight of $^{18}$F-fluoro-2-deoxyglucose.[14,15] A positive PET scan was defined as a focal or focal-on-diffuse pattern of increased tracer uptake in the myocardium. Cardiac MRI, cardiac PET, gallium uptake, and perfusion defect of methoxy-isobutyl-isonitrile scintigraphy were confirmed by the consensus of experienced radiologists at the Tohoku University Hospital or were performed at outside institutions.

All patients were encouraged to have a biopsy examination of more than one organ. The cardiac biopsy was performed on the right ventricular septum in 30 patients. The diagnosis of sarcoidosis was made when tissue biopsy specimens exhibited noncaseating granulomas verified by experienced pathologists.[16,17]

## Steroid Therapy Protocol

Corticosteroid therapy was started in almost all patients during the hospitalization at the time point of the CS diagnosis, according to the Japanese guidelines for sarcoidosis treatment.[2] We performed a fixed steroid treatment protocol that started the dose at 30 mg for 4 weeks in all patients except for 6 patients (40 mg in 5 patients and 10 mg in 1 patient), followed by a stepwise reduction of 5 mg every 2 weeks until achieving 20 mg/d during hospitalization. After the 20 mg/d dose was achieved, the steroid dose was gradually decreased by 5 mg every 2 to 4 weeks until the maintenance dose of 5 to 10 mg/d was achieved according to each physician's decision. The steroid dose after reaching 20 mg/d was gradually decreased by 5 mg/d every 2 to 4 weeks until a maintenance dose of 5 to 10 mg/d was reached according to each physician's decision. One patient started with 10 mg/d and maintenance dose of 5 mg/d because of old age.

An increase in corticosteroid therapy was considered when reactivation of CS was suspected by PET, gallium scintigraphy, ultrasound echocardiography, or blood examination including soluble interleukin-2 receptor, brain natriuretic peptide, and troponin T level.[2,18]

## Definition of Events

VTs were defined as documented VT or VF lasting for >30 seconds or resulting in cardiovascular collapse and appropriate ICD therapy (antitachycardia pacing or shock).[19] Electrical storm (ES) was defined as the occurrence of 3 episodes of VTs including an appropriate ICD therapy, separated by 5 minutes during a 24-hour period.[20]

## Statistical Analysis

Continuous variables are expressed as mean±SD or median (interquartile range) for brain natriuretic peptide, and categorical variables are presented as number and percent. To explore the association between time to VT event outcomes and covariates, univariable and multivariable Cox proportional hazard models were applied. To select the optimal subset of the covariates in the multivariable analysis, the stepwise variable selection was adopted with forward selection that optimized Bayesian Information Criterion. In Kaplan–Meier analysis, event times were measured from the time of corticosteroid beginning (time zero) to the first documented VTs (appropriate ICD therapy or ECG recording including monitor ECG). The log-rank test was used to assess the significance of differences in VT events. All analyses were performed with the SPSS statistical software (version 21; SPSS, IBM) and R (version 3.2.4).

# Results

## Patient Characteristics

Patient characteristics are shown in Table 1. The mean age was 57±11 years, and 50 (74%) were women. The prevalence of hypertension, diabetes mellitus, and dyslipidemia was relatively low. Most of the patients were in New York Heart Association class I (44%) or II (41%), but some patients in class III (13%) or IV (1%). The average of left ventricular ejection fraction (LVEF) was slightly reduced, and left ventricular (LV) dimension was within normal range. The levels of brain natriuretic peptide, soluble interleukin-2 receptor, and angiotensin-converting enzyme were relatively high. Positive results of the PET or gallium scintigraphy tests before corticosteroid therapy

**Table 1. Patient Characteristics at Baseline (n=68)**

| Patient Characteristics | Cardiac Sarcoidosis Cohort |
|---|---|
| Age, y | 57.0±11.2 |
| Sex, male:female | 18:50 |
| Hypertension | 15 (22) |
| Diabetes mellitus | 12 (18) |
| Dyslipidemia | 19 (28) |
| Extracardiac sarcoidosis | |
| Lung | 52 (76) |
| Eye | 27 (40) |
| Skin | 10 (15) |
| Liver, spleen, and pancreas | 8 (12) |
| Bone | 3 (4) |
| Nervous system | 1 (1) |
| NYHA class | |
| I | 30 (44) |
| II | 28 (41) |
| III | 9 (13) |
| IV | 1 (1) |
| History of electrical abnormalities | |
| VT/VF | 17 (25) |
| Advanced heart block | 29 (43) |
| AF | 7 (10) |
| NSVT | 33 (49) |
| Echocardiographic parameter | |
| LVEF, % | 50.5±16.3 |
| LAD, mm | 35.7±6.62 |
| LVDd, mm | 52.6±9.79 |
| Thin ventricular septum | 31 (46) |
| Laboratory data | |
| BNP, pg/mL (Q1–Q3) | 166 (30–385) |
| sIL-2R (U/mL) | 742±558 |
| ACE, IU/L | 20.3±9.27 |
| Cr, mg/dL | 0.84±0.36 |
| Hb, g/dL | 13.3±1.59 |
| TC, mg/dL | 200±31.8 |
| TG, mg/dL | 134±73.9 |
| Imaging examination | |
| Ga scintigraphy | 24 (46) |
| PET | 55 (98) |
| DE-MRI | 39 (87) |
| Perfusion defect on MIBI | 51 (91) |
| Histology | |
| Positive histology | 47 (69) |
| Heart | 9 (30) |
| Medication | |
| β-Blockers | 38 (56) |
| ACE-I/ARBs | 45 (66) |
| Statins | 17 (25) |
| Amiodarone | 10 (15) |
| Device therapy | |
| PM | 22 (32) |
| ICD | 25 (43) |
| Primary prevention | 9 |
| Secondary prevention | 16 |
| CRT | 12 |

Results are presented as either mean±SD or number of patients (%) and median (Q1–Q3) for BNP. We defined advanced heart block as Mobitz type II or complete atrioventricular block. The results on DE-MRI, Ga scintigraphy, MIBI scintigraphy and PET were obtained in 45, 52, 56, 56 patients, respectively. ACE indicates angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BNP, brain natriuretic peptide; Cr, serum creatinine; CRT, cardiac resynchronization therapy; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, Gallium scintigraphy; Hb, hemoglobin; ICD, implantable cardioverter defibrillator; LAD, left atrial dimensions; LVDd, end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; MIBI, methoxy-isobutyl-isonitrile; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; PM, pacemaker; sIL-2R, soluble interleukin-2 receptor; TC, total cholesterol; TG, triglyceride; VF, ventricular fibrillation; and VT, ventricular tachyarrhythmia.

were noted in 60 patients (90%), who were defined as in active inflammatory state. Delayed enhancement on MRI was noted in 87% of the 45 CS patients tested. The positive biopsy results were noted more frequently in extracardiac specimens (56%) than in cardiac specimens (30%). β-Blockers and angiotensin-converting enzyme inhibitors were administrated to more than half of the patients, whereas amiodarone was administered to 15% of them. A total of 47 patients received a pacemaker or ICD; pacemaker for atrioventricular block in 22 and ICD for VTs in 25 (primary prevention in 9 and secondary prevention in 16) at baseline. Twelve patients were implanted with an ICD with an LV lead (cardiac resynchronization–defibrillator therapy) because of severe LV dysfunction and dyssynchrony (Table 1). In addition, 4 patients were upgraded from pacemaker to ICD, and 8 patients from pacemaker or ICD to cardiac resynchronization–defibrillator therapy during the follow-up period.

During a mean follow-up of 5.5 years, 4 patients died. The cause of death included circulatory failure, sudden death, esophageal cancer, and disaster (because of tsunami). Sixty-one patients were followed up for >1 year, and 44 had PET or gallium scintigraphy after 1 year. Eight out of the 44 patients experienced recurrence of inflammation and the dose of the corticosteroid therapy was increased to 20–30 mg/d.

## Time Course of VTs

Twenty out of the 68 patients (29%) experienced VTs during the follow-up period and 13 (65%) had a first event in

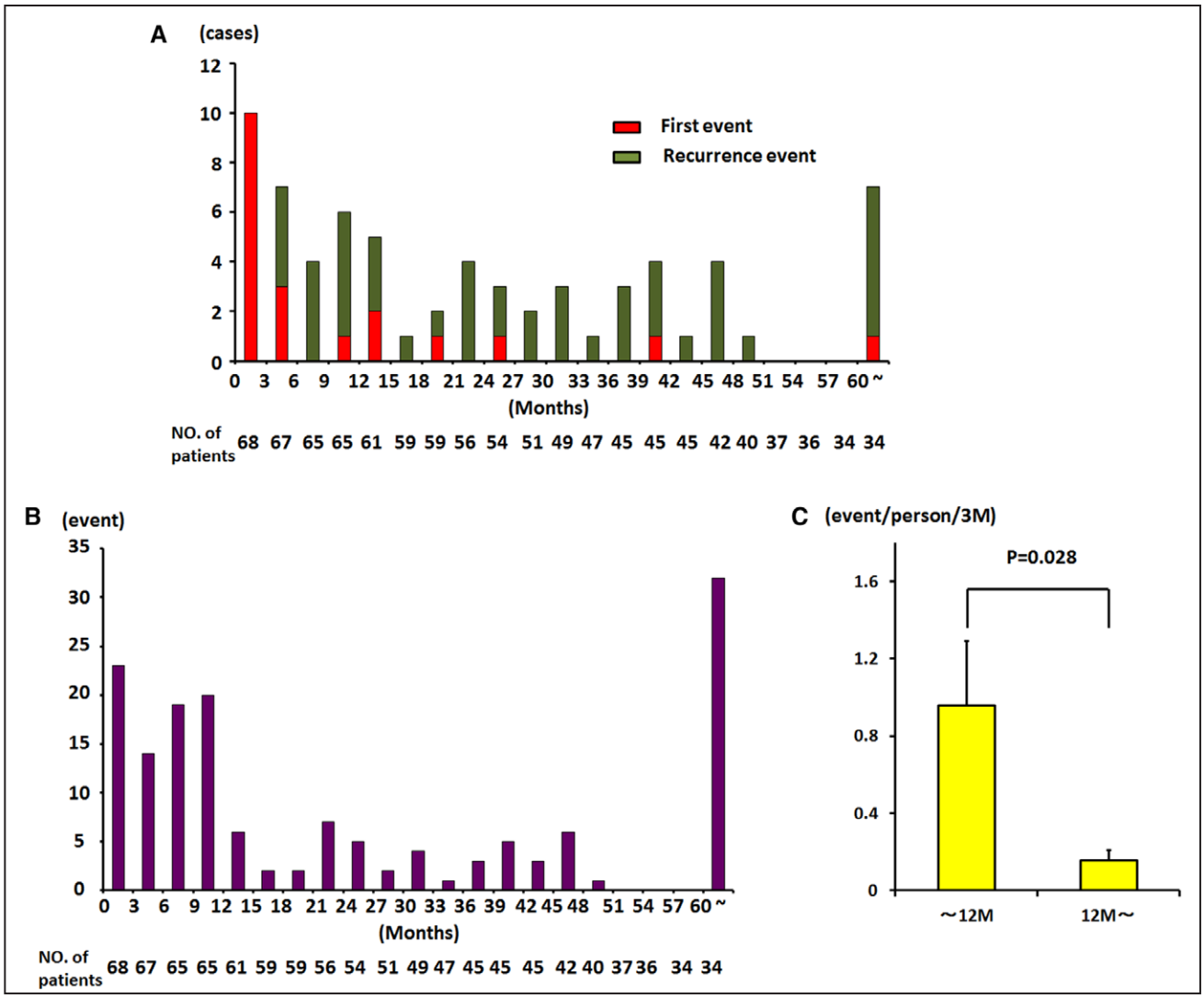


**Figure 1. A**, The time course of the number of patients with ventricular tachyarrhythmias (VTs). First event: number of patients with the first VT event after the initiation of corticosteroid therapy. Recurrent event: number of patients with any VT recurrence event after the initiation of corticosteroid therapy. **B**, The time course of the number of VT events including first and all recurrent events. **C**, The comparison of the frequency of VT events between in the early 12 months and beyond 12 months after the beginning of corticosteroid therapy.

the first 6 months after initiation of corticosteroid therapy. After 15 months, the number of a first VT events decreased although recurrent VTs were noted distributed evenly during follow-up (Figure 1A). Eighteen patients (90% of the 20 patients with VT events after the initiation of steroid therapy) experienced recurrent VTs. The frequency of the VT events was higher in the first 12 months after initiation of corticosteroid therapy than during the late (after 12 months) period (Figure 1B and 1C).

## Factors Correlating With VTs

Patients with VTs were characterized by more nonsustained ventricular tachycardia and VT/VF events at baseline, lower LVEF, progressive heart remodeling, more frequent thin ventricular septum, and higher brain natriuretic peptide levels (Table 2). Furthermore, positive gallium scintigraphy at baseline was more frequently noted in patients with VTs than in those without it, in addition to the prevalence of positive histopathologic examination.

When we adopted stepwise variable selection with forward selection procedure, positive gallium scintigraphy had a significant correlation with VTs (hazard ratio, 11.3; 95% confidence interval, 2.32–39.92; $P<0.001$), in addition to reduced LVEF (hazard ratio, 0.94; 95% confidence interval, 0.90–0.97; $P=0.001$; Table 3). It suggested that inflammatory activity strongly contributes to the onset of VTs after introduction of steroid therapy in patients with CS. The survival rate free from VT events was significantly lower in the positive group than that in the negative group (log-rank $P<0.001$; Figure 2). Importantly, most of the events occurred in the first 1 year after initiation of corticosteroid therapy.

## ES in Patients With CS

The number of patients with ES showed the 2 peaks after initiation of corticosteroid therapy, including the first 12 months and the very late phase (after 60 months) with only 2 recurrences between them (Figure 3). In contrast, single recurrences of VTs occurred throughout the follow-up period

**Table 2. Cox Regression Analysis for Correlation With Ventricular Tachyarrhythmias After Initiation of Corticosteroid Therapy**

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age | 1.03 (0.99–1.07) | 0.195 |
| Sex (female) | 0.80 (0.31–2.09) | 0.649 |
| Hypertension | 0.35 (0.08–1.51) | 0.159 |
| Diabetes mellitus | 1.69 (0.61–4.67) | 0.308 |
| Dyslipidemia | 0.54 (0.18–1.61) | 0.269 |
| History of electrical abnormalities | | |
| VT/VF | 7.64 (3.05–19.14) | <0.001 |
| Advanced heart block | 0.69 (0.27–1.72) | 0.422 |
| AF | 1.60 (0.46–5.48) | 0.458 |
| NSVT | 7.63 (2.23–26.09) | 0.001 |
| Echocardiographic data | | |
| LVEF | 0.94 (0.91–0.97) | <0.001 |
| LA | 1.11 (1.03–1.20) | 0.006 |
| LVDd | 1.08 (1.04–1.13) | <0.001 |
| LVDs | 1.08 (1.04–1.12) | <0.001 |
| Thin ventricular septum | 8.65 (2.53–29.59) | 0.001 |
| Laboratory data | | |
| BNP* | 1.14 (1.06–1.22) | <0.001 |
| sIL-2R* | 0.96 (0.85–1.09) | 0.511 |
| ACE | 0.99 (0.94–1.04) | 0.605 |
| Hb | 0.95 (0.71–1.28) | 0.745 |
| Cr | 1.44 (0.62–3.35) | 0.393 |
| TC* | 0.47 (0.10–2.19) | 0.336 |
| TG* | 0.85 (0.44–1.65) | 0.641 |
| Imaging examination | | |
| Ga scintigraphy | 9.97 (2.89–34.46) | <0.001 |
| PET† | … | … |
| DE-MRI† | … | … |
| Perfusion defect on MIBI† | 1.71 (0.23–12.81) | 0.602 |
| Histology | 4.49 (1.04–19.40) | 0.044 |

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BNP, brain natriuretic peptide; CI, confidence interval; Cr, serum creatinine; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, Gallium scintigraphy; Hb, hemoglobin; HR, hazard ratio; LA, left atrium; LVDd, end-diastolic left ventricular dimensions; LVDs, end-systolic left ventricular dimensions; LVEF, left ventricular ejection fraction; MIBI, methoxy-isobutyl-isonitrile; NSVT, nonsustained ventricular tachycardia; PET, positron emission tomography; sIL-2R, soluble interleukin-2 receptor; TC, total cholesterol; TG, triglyceride; VF, ventricular fibrillation; and VT, ventricular tachyarrhythmia.

*HRs and CIs in BNP, sIL-2R, TC, and TG are expressed for a 100 U change.

†Estimation procedure was not converged.

after 12 months after initiation of the corticosteroid therapy (Figure 1A). Eight out of 10 patients with ES had VTs before corticosteroid therapy. The VTs were noted in 6 out of 8 patients immediately before the steroid therapy and were aggravated during the ESs after steroid therapy. In the remaining 2 patients, there was no relationship between previous VT episode and ES after steroid therapy. ES after corticosteroid therapy was more recognized in male patients (Table 4).

**Table 3. Multivariable Analysis for Possible Influencing Factors on Ventricular Tachyarrhythmias by Forward Selection Procedure Method**

| | HR | 95% CI | *P* Value |
|---|---|---|---|
| LVEF | 0.94 | 0.90–0.97 | 0.001 |
| Positive gallium scintigraphy | 11.3 | 3.22–39.9 | <0.001 |

CI indicates confidence interval; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

## Discussion

The major findings of this study were that (1) the number of patients with the first VT events and the frequency of VT events were higher during the first 12 months after the initiation of corticosteroid therapy, (2) a positive gallium scintigraphy was the significant correlate of VTs, and (3) the time course of the occurrence of ES had 2 peaks: during the early (during the first 12 months after the initiation of the corticosteroid therapy) and the very late (after 60 months) phase, and relatively few events between them. To the best of our knowledge, this is the first study demonstrating the time course of VTs in patients with CS after initiation of corticosteroid therapy.

### Time Course of VTs

VTs are one of the main manifestations of CS and could be associated with sudden death.[17,21–23] However, the time course of VTs has not been fully elucidated. Only a few reports are available on the time course of VTs in patient with CS.[5,24] Betensky et al[5] reported that appropriate ICD therapies for VT/VF were noted in 37.8% of CS patients with ICD implantation with the incident rate of 15% per year. In this report, most patients experienced treated VT events during the first 3 years after ICD implantation.[5] However, because ICD implantation could have influenced the prevalence and incidence of VTs, it is unclear whether it reflects the natural course of VTs in CS patients.[5] In this sense, this study is the first report on the time course of VTs after initiation of corticosteroid therapy, a mainstay of CS therapy. In this study, the first VT events were mainly noted during the first 12 months after initiation of the corticosteroid therapy. Furthermore, the frequency of VT events in each patient was also high in the first 12 months. Although the mechanisms of the VTs are mainly related to macro-reentry at scarred lesions,[25,26] triggered activity and automaticity because of inflammation may also be involved.[23,27] Previous studies showed the relationship between arrhythmic events and unstable inflammatory conditions after initiation of the corticosteroid therapy.[10,28–30] This inflammatory mechanism may play an important role in the VT events during the early phase after the initiation of corticosteroid therapy. In this study, positive gallium scintigraphy was noted in 12 out of 14 (86%) patients who had an initial VT events during the first 12 months. In contrast,

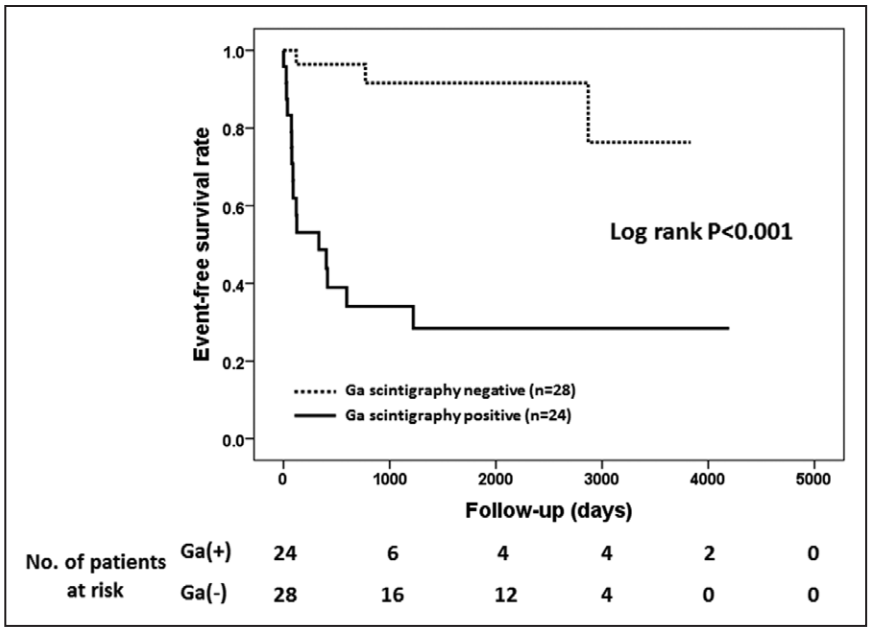


**Figure 2.** The Kaplan–Meier analysis of ventricular tachyarrhythmia events according to gallium (Ga) scintigraphy examination.

the number of the first VT events decreased after 12 months, whereas the recurrence events were constantly noted even after 15 months. The mechanisms of the VTs in the late phase may differ from those during the early phase. Crawford et al[31] reported the relationship between delayed enhancement on cardiac MRI and VTs recurrence. The recurrence events could be caused by the scar-related mechanisms after calming of inflammation, which is consistent with more frequent VT recurrences in patients with history of VTs as compared with those without it (Figure I in the Data Supplement). In addition, those patients were characterized by advanced diseased heart in this study (Table I in the Data Supplement). Thus, the VTs in CS patients may be caused by different mechanisms in different time course during the corticosteroid therapy. Steroid therapy has a potential to increase VTs during the early phase, which may be caused by unstable inflammation, but not during the late phase, because VTs during this phase may be caused by the scar-related mechanism. Further studies are needed to elucidate the detailed mechanisms involved.

## Positive Gallium Scintigraphy as a Factor Correlating With VTs

Risk stratification in CS patients for VTs has not been established yet. It has been reported that VTs are associated with reduced LVEF or a history of VTs in CS patients.[5,31,32] It was reported that delayed enhancement in the right ventricle on cardiac MRI is related to VTs in CS patients with preserved LV function and no history of VTs.[31] These findings may indicate the existence of the reentrant mechanisms for VTs. As mentioned above, inflammation is another potential mechanism for VTs in CS patients. Gallium scintigraphy and PET are now routinely used to detect inflammation of CS.[16,18,19,33,34] Cardiac PET has high sensitivity and specificity.[14,18,35] In this

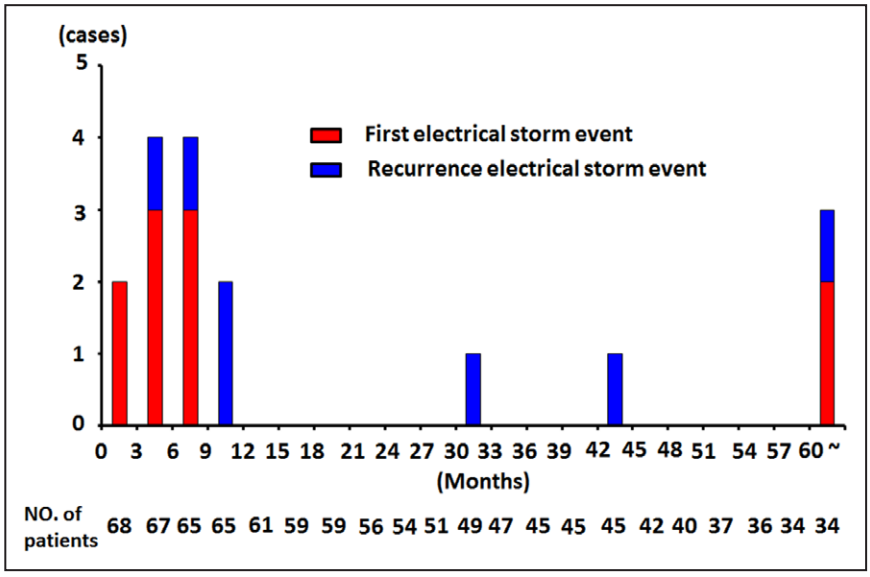


**Figure 3.** The time course of the number of patients with electrical storm (ES). First event: number of patients with the first ES event after the initiation of corticosteroid therapy. Recurrent event: number of patients with any ES recurrence event after the initiation of corticosteroid therapy.

**Table 4. Cox Regression Analysis for Electrical Storm After Initiation of Corticosteroid Therapy Among VT Patients**

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Age | 1.05 (0.96–1.14) | 0.318 |
| Sex (female) | 0.13 (0.03–0.57) | 0.007 |
| Hypertension | 0.85 (0.11–6.81) | 0.877 |
| Diabetes mellitus | 1.48 (0.37–5.98) | 0.579 |
| Dyslipidemia | 2.39 (0.57–10.06) | 0.234 |
| History of electric abnormalities | | |
| VT/VF | 2.74 (0.57–13.25) | 0.210 |
| Advanced heart block | 0.84 (0.21–3.35) | 0.799 |
| AF | 2.08 (0.41–10.48) | 0.377 |
| NSVT | 1.17 (0.14–9.55) | 0.882 |
| Echocardiographic data | | |
| LVEF | 0.96 (0.90–1.02) | 0.191 |
| LA | 1.08 (0.96–1.10) | 0.206 |
| LVDd | 1.03 (0.96–1.10) | 0.434 |
| LVDs | 1.03 (0.96–1.09) | 0.434 |
| Thin ventricular septum | 1.05 (0.13–8.52) | 0.967 |
| Laboratory data | | |
| BNP* | 0.86 (0.68–1.09) | 0.217 |
| sIL-2R* | 1.01 (0.80–1.28) | 0.921 |
| ACE | 0.95 (0.85–1.00) | 0.217 |
| Hb | 1.26 (0.91–1.73) | 0.165 |
| Cr | 1.00 (0.04–26.91) | 0.999 |
| TC* | 1.13 (0.23–5.64) | 0.885 |
| TG* | 2.74 (0.91–8.30) | 0.074 |
| Imaging examination | | |
| Ga scintigraphy† | … | … |
| PET† | … | … |
| DE-MRI† | … | … |
| Perfusion defect on MIBI† | … | … |
| Histology | 0.62 (0.08–5.08) | 0.656 |

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BNP, brain natriuretic peptide; CI, confidence interval; Cr, serum creatinine; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, gallium scintigraphy; Hb, hemoglobin; HR, hazard ratio; LVDd, end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; MIBI, methoxy-isobutyl-isonitrile; NSVT, nonsustained ventricular tachycardia; PET, positron emission tomography; sIL-2R, soluble interleukin-2 receptor; TC, total cholesterol; TG, triglyceride; VF, ventricular fibrillation; and VT, ventricular tachyarrhythmia.

*HRs and confidence intervals in BNP, sIL-2R, TC, and TG are expressed for a 100 U change.

†Estimation procedure was not converged.

study, almost all of the patients had positive PET examination. On the contrary, gallium scintigraphy has low sensitivity and high specificity because gallium scintigraphy has a feature of low-resolution image,[18] and positive gallium scintigraphy was noted in only 46% in this study. However, in this study, positive gallium scintigraphy, but not positive cardiac PET, had a significant correlation with VTs in CS patients, in addition to reduced LVEF. This may imply that positive gallium scintigraphy reflects the existence of enough substrate to develop sustained VTs. In contrast, Naruse et al[19] reported that absence of gallium-67 myocardial uptake before corticosteroid therapy was an independent predictor for VT recurrence, which is opposite to the present finding. This discrepancy could be explained by the difference in patient characteristics. Although Naruse et al[19] did not show the time course of VTs, their patients were likely to have advanced myocardial damage after inflammation was subsided with a resultant increment of VT recurrence.

## ES in CS Patients After Initiation of Steroid Therapy

Failure of ES control could lead to a poor prognosis in patients with structural heart diseases.[20,26] The meta-analysis of ES also demonstrates that ES accounts for ≈3-fold increased risk of death.[36] To the best of our knowledge, this study was the first report of the time course of ES in CS patients after initiation of corticosteroid therapy. In this study, ES was noted in 10 out of 68 patients with CS (14.7%), and the ES frequency was comparable to a previous report of ICD therapy in 112 CS patients (14.3%).[37] The time course of ES during the follow-up period had 2 peaks: the early phase (first 12 months after initiation of the corticosteroid therapy) and the very late phase (after 60 months). All the ES events calmed down during the follow-up period even if ablation therapy or antiarrhythmic agents were unable to completely control them. Furthermore, the time course of ES recurrence was different from that of VTs recurrence. In contrast to the recurrence of VTs, there were few recurrences of ES during the follow-up period, regardless of the presence or absence of history of VTs before corticosteroid therapy (Figure II in the Data Supplement). Importantly, no patients died because of worsening ES or congestive heart failure. These findings may imply that the mechanisms of ES in CS are different from those in other arrhythmic events, leading to poor prognosis if ES is unable to be treated properly.[20,26,36]

The healing of inflammation by corticosteroid could lead to unstable ventricular myocardial excitation and frequent abnormal automaticity with resultant increment of triggers for VTs.[29] In this study, patients with a history of VTs had a higher hazard ratio of the ES compared with those without it, although there was no significance between them. The triggers might invade into the pre-existing reentrant circuit and induce frequent VTs. Further studies are needed to elucidate the detailed mechanisms of ES in CS patients.

## Study Limitations

Several limitations should be mentioned for this study. First, in this study, the incidence of VTs or ES might not necessarily represent the true incidence because of the limited number of patients. In addition, the detection of VT and VT therapies via ICD programming may overestimate the incidence of VTs. In this study, however, the setting for ICD therapies was nominal or even longer detection protocol was used. Thus, we consider that this study excluded extremely short-lasting VTs. Second, the steroid therapy was not uniform in all patients.

Although almost all the patients had the same regime for initiation of steroid therapy, adjustment of maintenance dose of corticosteroid depended on each physician's decision. Third, we were unable to evaluate the effects of radiofrequency catheter ablation to control VTs in CS. It was previously reported that systematic comprehensive approach including radiofrequency catheter ablation could suppress VTs recurrence in CS patients.[19] However, although we performed radiofrequency catheter ablation in 5 CS patients with VTs, we failed to completely control VTs of suspected epicardial origins. Fourth, we did not always evaluate inflammation at the timing of the first VT events or VTs recurrence. In addition, we did not perform quantitative evaluation of inflammation. The quantitative estimation of gallium scintigraphy is difficult and physiological accumulation could be often a problem in PET examination. Preparative procedure with a fasting time (>12 hours) for PET examination in this study might be insufficient to reduce the physiological accumulation. Recently, several methods such as high-fat, low-carbohydrate diet and heparin administration before PET examination have been developed to overcome this issue. Finally, the present findings need to be confirmed in future studies with a large number of patients with VTs. Further studies are needed to elucidate the relationship between the extent of inflammation and VT in patients with CS.

## Conclusions

In this study, we were able to demonstrate that VTs and ES frequently occur during the first 12 months after the initiation of corticosteroid therapy, presumably because of inflammatory conditions and that the positive gallium scintigraphy had a significant correlation with VTs. The present findings may be useful to further improve the treatment of VTs in CS patients.

## Acknowledgments

We thank Satoshi Miyata for kind contribution.

## Disclosures

None.

## References

1. Ohira H, Tsujino I, Yoshinaga K. $^{18}$F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2011;38:1773–1783. doi: 10.1007/s00259-011-1832-y.
2. Tsuda T. Statement on the treatment of sarcoidosis. *Jpn J Sarcoidosis Granulomatous Disord*. 2003;23:105–114.
3. Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E, Gomes JA. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. *J Am Coll Cardiol*. 1991;18:937–943.
4. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;51:e1–62. doi: 10.1016/j.jacc.2008.02.032.
5. Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC, Cooper JM. Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. *Heart Rhythm*. 2012;9:884–891. doi: 10.1016/j.hrthm.2012.02.010.
6. Takada K, Ina Y, Yamamoto M, Satoh T, Morishita M. Prognosis after pacemaker implantation in cardiac sarcoidosis in Japan. Clinical evaluation of corticosteroid therapy. *Sarcoidosis*. 1994;11:113–117.
7. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi T, Sekiguchi M; Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol*. 2001;88:1006–1010.
8. Nagai T, Nagano N, Sugano Y, Asaumi Y, Aiba T, Kanzaki H, Kusano K, Noguchi T, Yasuda S, Ogawa H, Anzai T. Effect of corticosteroid therapy on long-term clinical outcome and left ventricular function in patients with cardiac sarcoidosis. *Circ J*. 2015;79:1593–1600. doi: 10.1253/circj.CJ-14-1275.
9. Belhassen B, Pines A, Laniado S. Failure of corticosteroid therapy to prevent induction of ventricular tachycardia in sarcoidosis. *Chest*. 1989;95:918–920.
10. Yodogawa K, Seino Y, Ohara T, Takayama H, Katoh T, Mizuno K. Effect of corticosteroid therapy on ventricular arrhythmias in patients with cardiac sarcoidosis. *Ann Noninvasive Electrocardiol*. 2011;16:140–147. doi: 10.1111/j.1542-474X.2011.00418.x.
11. Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. *Heart*. 2011;97:2078–2087. doi: 10.1136/hrt.2011.226076.
12. Shafee MA, Fukuda K, Wakayama Y, Nakano M, Kondo M, Hasebe Y, Kawana A, Shimokawa H. Delayed enhancement on cardiac magnetic resonance imaging is a poor prognostic factor in patients with cardiac sarcoidosis. *J Cardiol*. 2012;60:448–453. doi: 10.1016/j.jjcc.2012.08.002.
13. Ichinose A, Otani H, Oikawa M, Takase K, Saito H, Shimokawa H, Takahashi S. MRI of cardiac sarcoidosis: basal and subepicardial localization of myocardial lesions and their effect on left ventricular function. *AJR Am J Roentgenol*. 2008;191:862–869. doi: 10.2214/AJR.07.3089.
14. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, Endo K, Yokoyama T, Suzuki T, Kurabayashi M. Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med*. 2004;45:1989–1998.
15. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H, Baba K, Ishibashi M, Hayabuchi N, Narula J, Imaizumi T. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. *J AM COLL CARDIOL. Cardiovasc Imaging*. 2010;3:1219–1228. doi: 10.1016/j.jcmg.2010.09.015.
16. Doughan AR, Williams BR. Cardiac sarcoidosis. *Heart*. 2006;92:282–288. doi: 10.1136/hrt.2005.080481.
17. Nery PB, Mc Ardle BA, Redpath CJ, Leung E, Lemery R, Dekemp R, Yang J, Keren A, Beanlands RS, Birnie DH. Prevalence of cardiac sarcoidosis in patients presenting with monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol*. 2014;37:364–374. doi: 10.1111/pace.12277.
18. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M, Ito N, Ohira H, Ikeda D, Tamaki N, Nishimura M. Focal uptake on 18F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. *Eur Heart J*. 2005;26:1538–1543. doi: 10.1093/eurheartj/ehi180.
19. Naruse Y, Sekiguchi Y, Nogami A, Okada H, Yamauchi Y, Machino T, Kuroki K, Ito Y, Yamasaki H, Igarashi M, Tada H, Nitta J, Xu D, Sato A, Aonuma K. Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol*. 2014;7:407–413. doi: 10.1161/CIRCEP.113.000734.
20. Sesselberg HW, Moss AJ, McNitt S, Zareba W, Daubert JP, Andrews ML, Hall WJ, McClinitic B, Huang DT; MADIT-II Research Group. Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: a MADIT-II substudy. *Heart Rhythm*. 2007;4:1395–1402. doi: 10.1016/j.hrthm.2007.07.013.
21. Uusimaa P, Ylitalo K, Anttonen O, Kerola T, Virtanen V, Pääkkö E, Raatikainen P. Ventricular tachyarrhythmia as a primary presentation of sarcoidosis. *Europace*. 2008;10:760–766. doi: 10.1093/europace/eun110.
22. Nadel J, Lancefield T, Voskoboinik A, Taylor AJ. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in

sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death. *Eur Heart J Cardiovasc Imaging*. 2015;16:634–641. doi: 10.1093/ehjci/jeu294.
23. Kron J, Ellenbogen KA. Cardiac sarcoidosis: contemporary review. *J Cardiovasc Electrophysiol*. 2015;26:104–109. doi: 10.1111/jce.12552.
24. Mohsen A, Jimenez A, Hood RE, Dickfeld T, Saliaris A, Shorofsky S, Saba MM. Cardiac sarcoidosis: electrophysiological outcomes on long-term follow-up and the role of the implantable cardioverter-defibrillator. *J Cardiovasc Electrophysiol*. 2014;25:171–176. doi: 10.1111/jce.12302.
25. Jefic D, Joel B, Good E, Morady F, Rosman H, Knight B, Bogun F. Role of radiofrequency catheter ablation of ventricular tachycardia in cardiac sarcoidosis: report from a multicenter registry. *Heart Rhythm*. 2009;6:189–195. doi: 10.1016/j.hrthm.2008.10.039.
26. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, Riva S, Moltrasio M, Cireddu M, Veglia F, Della Bella P. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation*. 2008;117:462–469. doi: 10.1161/CIRCULATIONAHA.106.686534.
27. Bartlett ML, Bacharach SL, Voipio-Pulkki LM, Dilsizian V. Artifactual inhomogeneities in myocardial PET and SPECT scans in normal subjects. *J Nucl Med*. 1995;36:188–195.
28. Gropler RJ, Siegel BA, Lee KJ, Moerlein SM, Perry DJ, Bergmann SR, Geltman EM. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. *J Nucl Med*. 1990;31:1749–1756.
29. Hiramastu S, Tada H, Naito S, Oshima S, Taniguchi K. Steroid treatment deteriorated ventricular tachycardia in a patient with right ventricle-dominant cardiac sarcoidosis. *Int J Cardiol*. 2009;132:e85–e87. doi: 10.1016/j.ijcard.2007.08.029.
30. Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, Ogo KO, Nishii N, Watanabe A, Nagase S, Sakuragi S, Ohe T. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. *Heart Rhythm*. 2007;4:1292–1299. doi: 10.1016/j.hrthm.2007.06.006.
31. Crawford T, Mueller G, Sarsam S, Prasitdumrong H, Chaiyen N, Gu X, Schuller J, Kron J, Nour KA, Cheng A, Ji SY, Feinstein S, Gupta S, Ilg K, Sinno M, Abu-Hashish S, Al-Mallah M, Sauer WH, Ellenbogen K, Morady F, Bogun F. Magnetic resonance imaging for identifying patients with cardiac sarcoidosis and preserved or mildly reduced left ventricular function at risk of ventricular arrhythmias. *Circ Arrhythm Electrophysiol*. 2014;7:1109–1115. doi: 10.1161/CIRCEP.113.000156.
32. Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, Rosenfeld L, Mitiku TY, Cooper JM, Mehta D, Greenspon AJ, Ortman M, Delurgio DB, Valadri R, Narasimhan C, Swapna N, Singh JP, Danik S, Markowitz SM, Almquist AK, Krahn AD, Wolfe LG, Feinstein S, Ellenbogen KA. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. *Europace*. 2013;15:347–354. doi: 10.1093/europace/eus316.
33. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, Kazemian P, Kwong RY, Tokuda M, Skali H, Padera R, Hainer J, Stevenson WG, Dorbala S, Di Carli MF. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol*. 2014;63:329–336. doi: 10.1016/j.jacc.2013.09.022.
34. Tadamura E, Yamamuro M, Kubo S, Kanao S, Hosokawa R, Kimura T, Kita T, Togashi K. Images in cardiovascular medicine. Multimodality imaging of cardiac sarcoidosis before and after steroid therapy. *Circulation*. 2006;113:e771–e773. doi: 10.1161/CIRCULATIONAHA.105.594200.
35. Ohira H, Tsujino I, Ishimaru S, Oyama N, Takei T, Tsukamoto E, Miura M, Sakaue S, Tamaki N, Nishimura M. Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2008;35:933–941. doi: 10.1007/s00259-007-0650-8.
36. Guerra F, Shkoza M, Scappini L, Flori M, Capucci A. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis. *Europace*. 2014;16:347–353. doi: 10.1093/europace/eut304.
37. Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR, Sweiss NJ, Nguyen DT, Aleong RG, Varosy PD, Weinberger HD, Sauer WH. Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosis. *J Cardiovasc Electrophysiol*. 2012;23:925–929. doi: 10.1111/j.1540-8167.2012.02350.x.

# Time Course and Factors Correlating With Ventricular Tachyarrhythmias After Introduction of Steroid Therapy in Cardiac Sarcoidosis

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*Circ Arrhythm Electrophysiol.* 2016;9:
doi: 10.1161/CIRCEP.115.003353
*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084

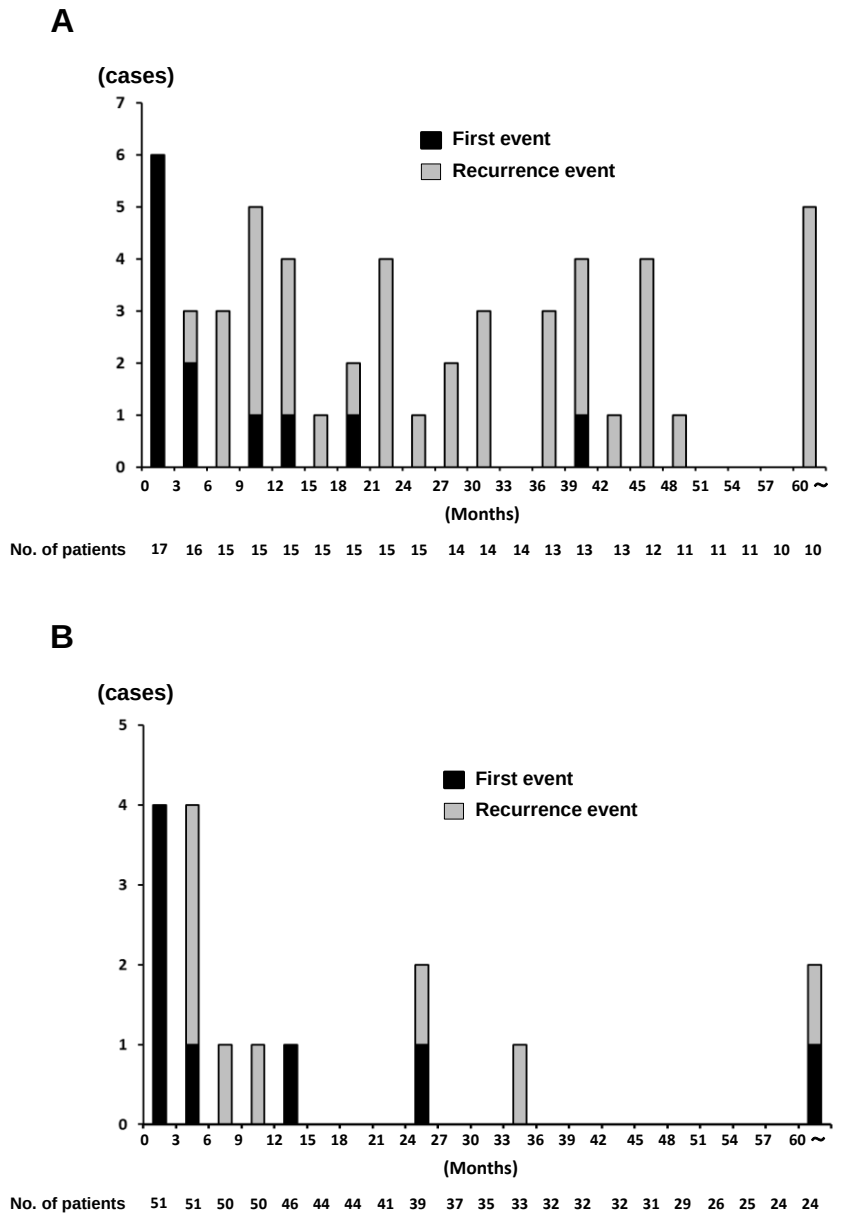
# SUPPLEMENTAL MATERIAL

## Supplemental Table

**Patient Characteristics by the Presence or Absence of Past History of VTs**

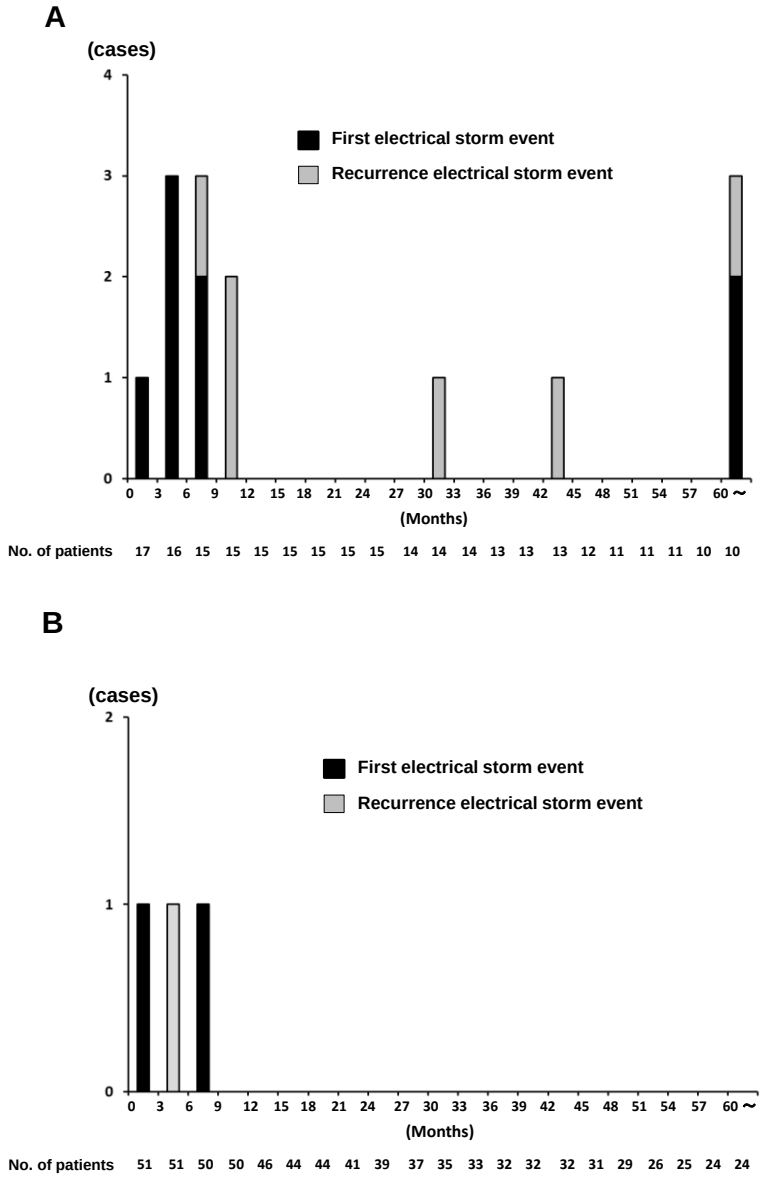
| | (+) History of VT/VF (N=17) | (-) History of VT/VF (N=51) | P-value |
|---|---|---|---|
| Age (y) | 58.5±9.41 | 56.5±11.9 | 0.526 |
| Gender (Male/Female) | 7/10 | 11/40 | 0.113 |
| Echocardiographic data | | | |
| LVEF (%) | 39.1±13.0 | 54.4±15.8 | 0.001 |
| LA (mm) | 38.2±6.11 | 34.9±6.70 | 0.076 |
| LVDd (mm) | 58.1±8.49 | 50.8±9.64 | 0.007 |
| LVDs (mm) | 47.1±8.86 | 36.5±12.2 | 0.002 |
| Thin ventricular septum | 13(76) | 18(35) | 0.003 |
| Laboratory data | | | |
| BNP (pg/ml) [IQR] | 240[85.8-425] | 118[27.9-367] | 0.797 |
| sIL-2R (U/ml) | 635±232 | 773±627 | 0.423 |
| ACE (U/L) | 17.1±7.03 | 21.2±9.75 | 0.144 |
| Imaging examination | | | |
| Ga scintigraphy | 13(81) | 11(31) | 0.001 |
| PET | 13(100) | 42(98) | 0.579 |
| DE-MRI | 6(100) | 33(85) | 0.302 |
| Perfusion defect of MIBI | 17(100) | 34(87) | 0.122 |
| Therapy | | | |
| ACE-I/ARB | 14(82) | 31(61) | 0.104 |
| β-blocker | 14(82) | 24(47) | 0.011 |
| Statin | 2(12) | 15(29) | 0.146 |
| Aldactone | 7(41) | 7(14) | 0.015 |
| Amiodarone | 8(47) | 2(4) | <0.001 |
| CRT | 11(65) | 9(18) | <0.001 |
| Histology | 12(71) | 35(69) | 0.880 |

## Supplemental Figure 1




Time-course of the number of patients with VTs according to the presence or absence of past history of VTs before the initiation of corticosteroid therapy. (**A**) Time-course of number of patients with past history of VTs. (**B**) Time-course of the number of patients without past history of VTs. First event; number of patients with the first VT event after the initiation of corticosteroid therapy. Recurrent event; number of patients with any VT recurrence event after the initiation of corticosteroid therapy.

## Supplemental Figure 2




Time-course of the number of patients with ES according to the presence or absence of past history of VTs before initiation of corticosteroid therapy. (**A**) Time-course of number of patients with past history of VTs. (**B**) Time course of the number of patients without past history of VTs. First electrical storm event; number of patients with the first VT event after initiation of corticosteroid therapy. Recurrent electrical storm event; number of patients with any VT recurrence event after initiation of corticosteroid therapy.