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

Masato Segawa, MD; Koji Fukuda, MD, PhD; Makoto Nakano, MD, PhD; Masateru Kondo, MD, PhD; Hiroyuki Satake, MD, PhD; Michinori Hirano, MD; Hiroaki Shimokawa, MD, PhD

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 al5 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.3

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.

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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 institution13 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 Aichi; 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 18F-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.6,11

Steroid Therapy and VTs in CS
WHAT IS KNOWN
- 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 troponin T level were controversial.14
- 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.6,11

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.5 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.2,13

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).10 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 troponin T level were relatively high. Positive results of the PET or gallium scintigraphy tests before corticosteroid therapy
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

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

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Cardiac Sarcoidosis Cohort</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>57.0±11.2</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>18:50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (22)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>19 (28)</td>
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**Extracardiac sarcoidosis**

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<table>
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<tr>
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<tbody>
<tr>
<td>Lung</td>
<td>52 (76)</td>
</tr>
<tr>
<td>Eye</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Skin</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Liver, spleen, and pancreas</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Bone</td>
<td>3 (4)</td>
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<tr>
<td>Nervous system</td>
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**NYHA class**

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<table>
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<tbody>
<tr>
<td>I</td>
<td>30 (44)</td>
</tr>
<tr>
<td>II</td>
<td>28 (41)</td>
</tr>
<tr>
<td>III</td>
<td>9 (13)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (1)</td>
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**History of electrical abnormalities**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>VT/VF</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Advanced heart block</td>
<td>29 (43)</td>
</tr>
<tr>
<td>AF</td>
<td>7 (10)</td>
</tr>
<tr>
<td>NSVT</td>
<td>33 (49)</td>
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**Echocardiographic parameter**

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<tr>
<td>LVEF, %</td>
<td>50.5±16.3</td>
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<tr>
<td>LAD, mm</td>
<td>35.7±6.62</td>
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<tr>
<td>LVDd, mm</td>
<td>52.6±9.79</td>
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<tr>
<td>Thin ventricular septum</td>
<td>31 (46)</td>
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**Laboratory data**

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<table>
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<tr>
<td>BNP, pg/mL (Q1–Q3)</td>
<td>166 (30–385)</td>
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<tr>
<td>sIL-2R (U/mL)</td>
<td>742±558</td>
</tr>
<tr>
<td>ACE, IU/L</td>
<td>20.3±9.27</td>
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<tr>
<td>Cr, mg/dL</td>
<td>0.84±0.36</td>
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<tr>
<td>Hb, g/dL</td>
<td>13.3±1.59</td>
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<tr>
<td>TC, mg/dL</td>
<td>200±31.8</td>
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<tr>
<td>TG, mg/dL</td>
<td>134±73.9</td>
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**Imaging examination**

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<td>Ga scintigraphy</td>
<td>24 (46)</td>
</tr>
<tr>
<td>PET</td>
<td>55 (98)</td>
</tr>
<tr>
<td>DE-MRI</td>
<td>39 (87)</td>
</tr>
<tr>
<td>Perfusion defect on MIBI</td>
<td>51 (91)</td>
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**Histology**

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<tr>
<td>Positive histology</td>
<td>47 (69)</td>
</tr>
<tr>
<td>Heart</td>
<td>9 (30)</td>
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</tbody>
</table>

(continued)
the first 6 months after initiation of corticosteroid therapy. After 15 months, the number of a first VT event 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.
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).

**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 al5 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 trigeminal 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.10,26–30 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 event during the first 12 months. In contrast,
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,18,19,33,34} Cardiac PET has high sensitivity and specificity.\textsuperscript{14,18,35} In this
Table 4. Cox Regression Analysis for Electrical Storm After Initiation of Corticosteroid Therapy Among VT Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (0.96–1.14)</td>
<td>0.318</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.13 (0.03–0.57)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.85 (0.11–6.81)</td>
<td>0.877</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.48 (0.37–5.98)</td>
<td>0.579</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.39 (0.57–10.06)</td>
<td>0.234</td>
</tr>
</tbody>
</table>

**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; LV, left ventricular; LVEF, left ventricular ejection fraction; MIBI, methoxy-isobutylisonitrile; 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.

The healing of inflammation by corticosteroid could lead to unstable ventricular myocardial excitation and frequent abnormal automaticity with resultant increment of triggers for VTs. 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.

**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. The meta-analysis of ES also demonstrates that ES accounts for a 3-fold increased risk of death. 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%). 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.

The healing of inflammation by corticosteroid could lead to unstable ventricular myocardial excitation and frequent abnormal automaticity with resultant increment of triggers for VTs. 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 initia-
tion of steroid therapy, adjustment of maintenance dose of cor-
ticosteroid depended on each physician’s decision. Third, we
were unable to evaluate the effects of radiofrequency cath-
eter ablation to control VTs in CS. It was previously reported
that systematic comprehensive approach including radiofre-
cuency catheter ablation could suppress VTs recurrence in CS
patients.19 However, although we performed radiofrequency
cather ablotion in 5 CS patients with VTs, we failed to com-
pletely 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 es-
malliation 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. Fur-
ther 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 inflamma-
tory 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.

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Disclosures
None.

References
1. Ohira H, Tsujino I, Yoshinaga K. 18F-Fluoro-2-deoxyglucose posi-
tion emission tomography in cardiac sarcoidosis. Eur J Nucl Med Mol
JA. Sustained ventricular tachycardia associated with sarcoidosis: as-
essment of the underlying cardiac anatomy and the prospective utility
of programmed ventricular stimulation, drug therapy and an implantable
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, Creeger MA, Ettenger SM, Faxon DP, Halperin JR, 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
5. Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE,
Garcia FC, Cooper JM. Long-term follow-up of patients with cardiac sar-
coidosis and implantable cardioverter-defibrillators. Heart Rhythm.
6. Takada K, Ina Y, Yamamoto M, Satoh T, Morishita M. Prognosis after
pacemaker implantation in cardiac sarcoidosis in Japan. Clinical evalua-
T, Sekiguchi M; Central Japan Heart Study Group. Prognostic determi-
nants of long-term survival in Japanese patients with cardiac sarcoidosis
Noguchi T, Yasuda S, Ogawa H, Aunai T. Effect of corticosteroid therapy
on long-term clinical outcome and left ventricular function in patients with
CJ-14-1275.
of corticosteroid therapy on ventricular arrhythmias in patients with car-
11. Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis:
aplications of imaging in diagnosis and directing treatment. Heart.
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 sar-
13. Ichinose A, Otani H, Oikawa M, Takase K, Saito H, Shimokawa H,
Takahashi S. MRI of cardiac sarcoidosis: basal and subepicardial localiza-
tion of myocardial lesions and their effect on left ventricular function. AJR
K, Yokoyama T, Suzuki T, Kurabayashi M. Usefulness of fasting 18F-FDG PET in
15. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H, Baba
AM COLL CARDIOL. Cardiovasc Imaging. 2010;3:1219–1228. doi:
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 sar-
coidosis in patients presenting with monomorphic ventricular tachycardia,
18. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakae K, Kamigaki I, Ito N,
Ohira H, Ikeda T, Tamaki N, Nishimura M. Focal uptake on 18F-fluoro-2-
deoxyglucose positron emission tomography images indicates cardiac in-
eurheartj/ehi180.
Aonuma K. Systematic treatment approach to ventricular tachycardia in
cardiac sarcoidosis. Circ Arrhythm Electrophysiol. 2012;5:707–714. doi:
10.1161/CIRCEP.111.007334.
ML, Hall WJ, McClintick B, Huang DT; MADIT-II Research Group.
Ventricular arrhythmia storm in postinfarction patients with implantable
defibrillators for primary prevention indications: a MADIT-II substudy.
21. Uusimaa P, Ylitalo K, Anttonen O, Kerola T, Virtanen V, Pääkkö E,
Betensk Y, Voskoboinik A, Taylor AJ. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in


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Supplemental Figure 1

(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.