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Original article

Delayed enhancement on cardiac magnetic resonance imaging is a poor prognostic factor in patients with cardiac sarcoidosis

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ABSTRACT

Background: Predictors of ventricular arrhythmias (VA) in patients with cardiac sarcoidosis (CS) remain unclear.
Methods and results: We examined 61 consecutive CS patients who were admitted to our hospital from April 2002 to March 2012 with a mean follow-up period of 45 ± 31 months for the relationship between delayed enhancement on cardiac magnetic resonance imaging (DE-MRI) and VA or a composite endpoint, including VA, heart failure hospitalization, and cardiovascular mortality. Although there was no significant difference in baseline clinical characteristics between patients with VA and those without it, the former group was characterized as compared with the latter by lower left ventricular (LV) ejection fraction ($p < 0.05$), larger LV systolic/diastolic dimensions (both $p < 0.05$), and a significant association with DE-MRI ($p < 0.05$). Furthermore, the patients with DE-MRI ($n = 26$), as compared with those without it ($n = 11$), had a significantly higher composite endpoint event rate (41% vs. 0%, $p < 0.05$) and a trend toward higher VA (29% vs. 0%, $p = 0.12$). Univariate analysis also showed that impaired LV systolic function was significantly associated with composite events on follow-up.
Conclusions: These results indicate that the presence of DE-MRI is a significant predictor of VA events and poor outcome in CS patients.

Introduction

Sarcoidosis is a multisystem disease that is histologically characterized by non-caseating granuloma formation in various organs [1]. Although sarcoidosis could affect any organ, including the lungs, skin, eyes, liver, and lymphatics [1,2], cardiac involvement is the most important prognostic factor [3,4]. The incidence of cardiac sarcoidosis (CS) has been reported to be ~2% among patients with sarcoidosis, however, previous autopsy studies demonstrated that cardiac involvement is relatively high (20–25%) [4,5], which has been recently confirmed by cardiac imaging [6].

CS frequently presents as asymptomatic cardiac involvement and is only evident by abnormalities on electrocardiography (ECG), echocardiography, or magnetic resonance imaging (MRI) [2]. Clinically, CS commonly presents with congestive heart failure and dilated cardiomyopathy (DCM)-like manifestations associated with electrical abnormalities, including conduction disturbances [4] and serious ventricular arrhythmias (VA), including ventricular tachycardia (VT) and ventricular fibrillation (VF) [7]. Indeed, sustained or non-sustained VT (NSVT) has been noted in 23% of patients with CS, where re-entry is the most common mechanism involving myocardial scarring and fibrosis areas [8]. Indeed, VF could account for the majority of cases of sudden cardiac death (SCD) in CS patients [4].

Although CS in general and VA in particular are predictors of poor outcome [3], predictors of VA and adverse outcome in CS patients remain to be identified.

In the present study, we thus addressed this clinically important issue in our CS patients, with focus on the role of delayed enhancement on magnetic resonance imaging (DE-MRI) as a marker of poor prognosis in general, and of this serious arrhythmia in particular in this subset of patients.

Methods

Patient selection

We examined 61 consecutive patients who were diagnosed as having CS at our hospital or other referring hospitals in the Tohoku

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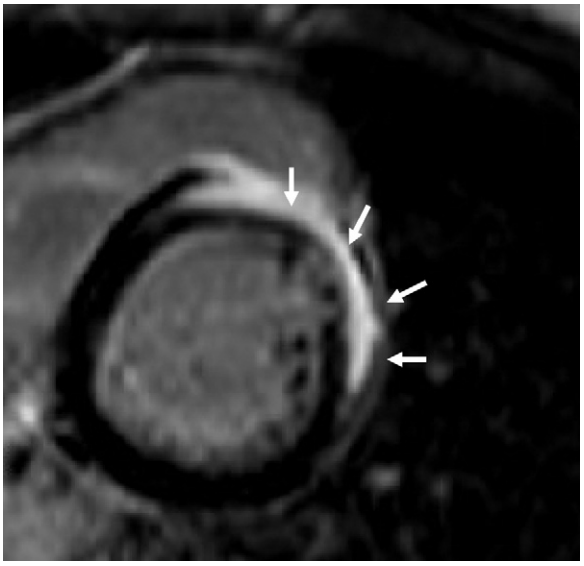

Fig. 1. Delayed enhancement on cardiac magnetic resonance imaging (MRI) in a cardiac sarcoidosis (CS) patient. Evidence of delayed gadolinium enhancement on cardiac MRI in the sub-epicardial layer of the anterior left ventricular wall (multiple small white arrows) in a 41-year-old male patient with sustained ventricular tachycardia and diagnosed with CS on the background of a pre-existing pulmonary sarcoidosis.

area between April 2002 and March 2012. Their clinical data were obtained from the detailed database of our department at Tohoku University Hospital, including demographic, clinical, laboratory, imaging, procedural, and interventional data. We examined the association between baseline data and the presence of VA (NSVT, VT, and VF) at presentation and on follow-up.

Diagnostic criteria

The revised guidelines for diagnosis of CS from the Japanese Ministry of Health and Welfare were used [9]. The diagnosis of CS was made either directly by endomyocardial biopsy, or indirectly by detection of clinical CS manifestations in the presence of extra-cardiac sarcoidosis. Beside clinical history, ECG findings and cardiac imaging tests, including echocardiography, scintigraphy, and MRI were used for this purpose.

VA were detected either by ECG monitoring during admission or later diagnostic evaluation with 12-lead ECG or Holter ECG. VA were defined as 3 or more consecutive beats of ventricular origin, at a rate of more than 100 beats/min [10], detected by any of the modalities mentioned above, and thus including NSVT, VT, and VF. Beats of ventricular origin not fulfilling these conditions were not included.

Study outcomes

We retrospectively examined the baseline clinical variables, including age, gender, presence of extra-CS, heart rate, New York Heart Association (NYHA) class, brain natriuretic peptide level (BNP), and left ventricular ejection fraction (LVEF) of our CS population. The primary endpoint was the occurrence of VA and the secondary endpoint was a composite of VA, heart failure (HF) hospitalizations, and cardiovascular mortality.

MRI protocol

Cardiac MRI (Fig. 1) was performed before starting corticosteroid therapy and after patients had become clinically stable. We used the standard protocol for cardiac MRI in our institution [11], and ECG-gated magnetic resonance (MR) images were obtained in all patients during breath-holding on a 1.5-T imager (Magnetom Vision, Siemens Medical Solutions, Erlangen, Germany; Achiva, Philips Medical Systems, Best, The Netherlands) using a body array coil (Siemens) or a 5-channel cardiac coil (Philips). To evaluate LV anatomy, cine MR images of the LV in one horizontal, one vertical-long, and 5 short-axis slices were obtained. Images from DE-MRI using inversion-recovery-prepared gradient-echo sequence were acquired 10–15 min after the 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. The acquisition parameters of the DE-MRIs were 3.7–7.5/1.2–3.4; flip angle, 15°; field

Table 1
Patient characteristics at baseline.

Variables	All patients ($n = 61$)
Age (years)	57 ± 12
Gender (M/F)	18/43
Extra-cardiac sarcoidosis present	54 (89)
Hypertension	14 (23)
Diabetes mellitus	14 (23)
CAD	2 (3)
Dyslipidemia	23 (37)
Smoking	
Non-smoker	49 (80)
Ex-smoker	6 (10)
Current smoker	6 (10)
Cardiac phenotype (by echocardiography)	
Normal	29 (47)
Septal thinning	25 (41)
DCM-like	17 (28)
Clinical data	
Heart rate (beats/min)	71 ± 14
NYHA class	
I	33 (54)
II	17 (28)
III	9 (15)
IV	2 (3)
Electrical abnormalities	
Ventricular arrhythmias	14 (23)
Non-sustained VT	11 (18)
VT/VF	8 (13)
Advanced heart block	24 (39)
Sick sinus syndrome	1 (2)
AF	7 (11)
Supraventricular tachycardia	1 (2)
Laboratory data	
Hemoglobin (g/dl)	13 ± 1.7
Serum creatinine (mg/dl)	0.8 ± 0.3
Triglyceride (mg/dl)	138 ± 72
Total cholesterol (mg/dl)	205 ± 35
Brain natriuretic peptide (pg/ml)	325 ± 515
Echocardiographic parameters	
LVEF (%)	50 ± 16
LVDs (mm)	37 ± 12
LVDd (mm)	52 ± 8
LAD (mm)	35 ± 6
Positive cardiac biopsy	10 (16)
Ga scintigraphy (positive/negative)	18/16
DE-MRI (yes/no)	26/11
Drugs	
β-Blockers	27 (44)
ACE-I/ARBs	33 (54)
Statins	17 (28)
Amiodarone	4 (7)

Results are presented as either mean ± SD or number of patients (%). ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BNP, brain natriuretic peptide; CAD, coronary artery disease; DCM, dilated cardiomyopathy; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, gallium; LAD, left atrial dimensions; LVDs/LVDd, end-systolic/end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia. The results on Ga scintigraphy were obtained from 34 patients only. The results on DE-MRI were obtained from 37 patients without device therapy.

of view, 380 mm; matrix, 182–224 × 139–256; and slice thickness, 5 mm. The inversion time (200–300 ms) was adjusted to null signal from normal myocardium. MRI was performed in 37 patients as the remaining 24 patients had implanted metal devices. DE-MRIs were confirmed by the consensus of 2 experienced radiologists blinded to patient outcome.

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are presented as percentage and frequency. Differences between groups were compared by Student *t*-test (for normally distributed variables) and Mann–Whitney test (for non-normally distributed variables) for continuous variables. The chi-square test was used for categorical variables and the Fisher exact test for those instances in which the expected cell count was <5. Event rates of endpoints are expressed as unadjusted Kaplan–Meier estimates and a Cox proportional hazard test was used for the interaction between patient characteristics and endpoints. All statistical tests were 2-tailed, and a p-value < 0.05 was considered to be statistically significant. All analysis was performed using SPSS software (version 18, SPSS, Chicago, IL, USA).

Results

The clinical characteristics of the 61 patients with CS are shown in Table 1. They were characterized by middle-age with majority of them being females, and 89% of them had extra-cardiac involvement of sarcoidosis, with the rest being diagnosed based on histological criteria of endomyocardial biopsy. The prevalence of hypertension, diabetes mellitus, coronary artery disease, and smoking was relatively low. No clinical or echocardiographic evidence of structural heart disease was noted in approximately half of the patients (47%), with evidence of characteristic septal thinning noted in 41% of patients and DCM-like phenotype noted in 28% of them.

Most of the patients were in NYHA class I (54%) or II (28%), but some patients were in class III (15%) or IV (3%). Advanced heart block was the most common electrical abnormality encountered at baseline (39%), and VA collectively was the second most common electrical abnormality (23%), where NSVT was noted in 18% and VT/VF in 13%. Laboratory and echocardiographic data were within normal range except for mildly elevated BNP level (Table 1). Importantly, DE-MRI was noted in 70% of the 37 CS patients tested, whereas a positive gallium (Ga) scintigraphy was noted in 50% of the 34 patients tested at presentation and finally only 16% of patients had a positive cardiac biopsy. Amiodarone was administered to 7% of the patients.

Table 2 shows the baseline characteristics of the 37 patients with MRI data according to presence or absence of DE-MRI. There was no significant difference in baseline characteristics between the 2 groups despite the expected trends of a higher NYHA class, a higher BNP level, and a larger LV in patients with DE-MRI. Interestingly, in this sub-population LVEF was preserved and showed no difference in LVEF between the 2 groups.

The variables of interest for possible association with VA at baseline are shown in Table 3. Age, gender, the presence of extra-CS, heart rate, worse NYHA class, and BNP were not significantly associated with VA. In contrast, echocardiographic parameters of impaired systolic LV function, as assessed by LVEF and end-systolic/end-diastolic dimensions (LVDs/LVDd), were significantly associated with VA (p = 0.01, 0.02, and 0.04, respectively). Importantly, the presence of DE-MRI also showed a significant association (p < 0.05) and its absence carried 100% negative predictive value for VA at baseline.

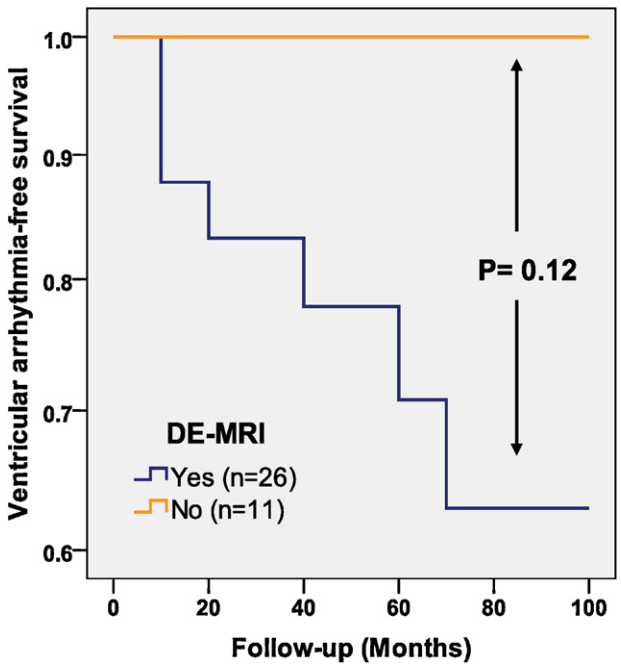

Fig. 2. Ventricular arrhythmia-free survival. Ventricular arrhythmia-free survival rate tended to be worse in cardiac sarcoidosis patients with delayed enhancement on cardiac magnetic resonance imaging (DE-MRI) compared with those without it (log rank test, p = 0.12).

In the mean follow-up period of 45 months, VA-free survival rate tended to be worse in CS patients with DE-MRI compared with those without it (p = 0.12) (Fig. 2). Furthermore, composite endpoint-free survival rate was significantly worse in CS patients with DE-MRI compared with those without it (p < 0.05) (Fig. 3). Unadjusted Cox proportional hazard analysis showed that among multiple variables beside DE-MRI, only the presence of impaired LVEF carried a significant risk for the occurrence of composite

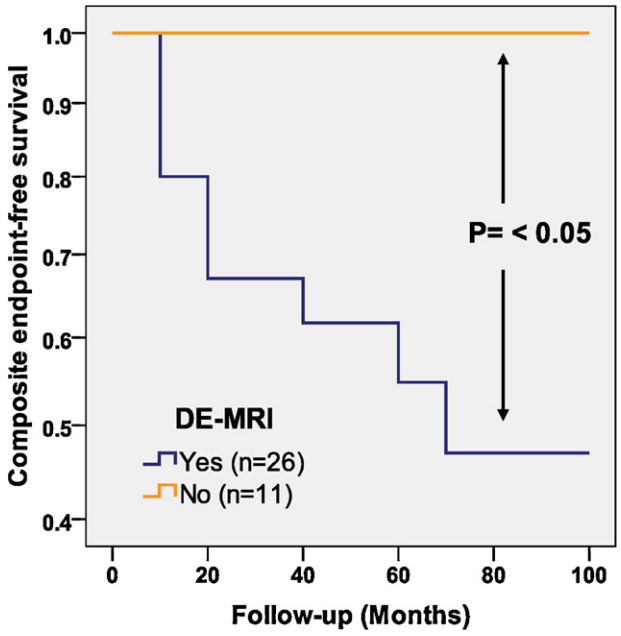

Fig. 3. Composite endpoint-free survival. Composite endpoint-free survival was significantly worse in cardiac sarcoidosis patients with delayed enhancement on cardiac magnetic resonance imaging (DE-MRI) compared with those without it (Log rank test, p = 0.03).

Table 2
Patient characteristics by the presence or absence of delayed enhancement on magnetic resonance imaging ($n = 37$).

Variables	DE-MRI ($n = 26$)	No DE-MRI ($n = 11$)	p-Value
Age (years)	56 ± 15	53 ± 12	0.64
Gender (M/F)	8/18	4/7	0.51
Extra-cardiac sarcoidosis	22 (84)	8 (72)	0.33
Heart rate (beats/min)	73 ± 12	65 ± 17	0.16
Septal thinning (present/absent)	7/14	0/7	0.09
DCM-like phenotype	5 (19)	0 (0)	0.15
NYHA class			
I	17 (65)	9 (82)	0.20
II	8 (31)	1 (9)	
III	0 (0)	1 (9)	
IV	1 (4)	0 (0)	
BNP (pg/ml)	133 ± 192	112 ± 178	0.76
Echocardiographic parameters			
LVEF (%)	56 ± 14	57 ± 8	0.88
LVDd (mm)	50 ± 8	47 ± 4	0.34
LVDs (mm)	34 ± 9	27 ± 10	0.052
Cardiac biopsy (positive/negative)	3/14	0/4	0.51
Ga scintigraphy (positive/negative)	6/7	0/4	0.13

Results are presented as either mean ± SD or number of patients (%). BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, gallium; LVDs/LVDd, end-systolic/end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. The results on Ga scintigraphy were obtained from 34 patients only.

endpoint [Hazard ratio (HR) 0.35; 95%CI, 0.16–0.75; $p = 0.01$], but not for that of VA (HR, 0.52; 95%CI, 0.20–1.34; $p = 0.17$) (Table 4). The long-term prognosis, including VA and composite endpoint, was comparable between the CS patients who underwent MRI test ($n = 37$) and those who did not ($n = 24$) ($p = 0.27$, and 0.21 respectively).

Discussion

The novel finding of the present study is that in addition to reduced LV systolic function, DE-MRI is a significant prognostic factor of serious VA and poor outcome in patients with CS.

Prevalence and diagnosis of CS

The prevalence of sarcoidosis is relatively high in Japan [2] and the incidence of cardiac involvement is also high [12], reaching ~60% of sarcoidosis patients in some series [13]. This offers a unique chance to study various unstudied aspects of this disorder. Although it was previously shown that the majority of western CS patients are young adults between the ages of 20–40 years without a definite sex predominance [5], the present study shows that the majority of the Japanese CS patients are middle-aged females, a consistent finding with the previous studies in Japan [3,14]. These results suggest some racial differences in demographic characteristics of CS patients that might extend to presentation and prognosis of the disorder. Most of the CS patients in the present study were diagnosed in conjunction with involvement of other organs, again, a consistent finding with a previous study in Japan [15].

Almost half of CS patients in the present study showed no evidence of structural cardiac abnormality when assessed by echocardiography with a similar prevalence rate as in western studies with 14–31% prevalence rate [16,17], thus highlighting the limited sensitivity of echocardiography in this subset of CS patients [18]. In CS patients, the usual echocardiographic abnormality in our study was characteristic septal thinning, which was a part of LV being globally affected, and depressed LVEF characteristic of a DCM-like picture noted in half of them. It was difficult to distinguish this abnormality from the idiopathic form [2,12,18], which was a common morphological finding in our cohort.

Indeed, echocardiography has a low specificity for diagnosis of CS [18], and its main value lies in its ability to predict poorer

Table 3
Patient characteristics by the presence or absence of ventricular arrhythmias at baseline.

Variables	Ventricular arrhythmia ($n = 14$)	No ventricular arrhythmia ($n = 47$)	p-Value
Age (years)	57 ± 13	57 ± 12	0.94
Gender (M/F)	6/8	12/35	0.31
Extra-cardiac sarcoidosis	10 (71)	39 (82)	0.44
Heart rate (beats/min)	71 ± 11	71 ± 15	0.95
Septal thinning (present/absent)	10/3	15/23	0.02
DCM-like phenotype	7 (50)	13 (27)	0.19
NYHA class			
I	7 (50)	26 (55)	0.82
II	4 (29)	13 (28)	
III	2 (14)	7 (15)	
IV	1 (7)	1 (2)	
BNP (pg/ml)	434 ± 656	291 ± 466	0.37
Echocardiographic parameters			
LVEF (%)	40 ± 17	52 ± 14	0.01
LVDd (mm)	57 ± 12	51 ± 7	0.04
LVDs (mm)	45 ± 12	35 ± 11	0.02
Ga scintigraphy (positive/negative)	7/14	11/12	0.31
DE-MRI (yes/no)	8/0	18/11	0.04

Results are presented as either mean ± SD or number of patients (%). BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; DE-MRI, delayed enhancement on magnetic resonance imaging; Ga, gallium; LVDs/LVDd, end-systolic/end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. The results on Ga scintigraphy were obtained from 34 patients only. The results on DE-MRI were obtained from 37 patients without device therapy.

Table 4
Unadjusted hazard ratios for ventricular arrhythmias and composite endpoint.

Variables	Ventricular arrhythmias		Composite endpoint	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age	1.01 (0.96–1.04)	0.79	1.01 (0.97–1.03)	0.87
Gender	1.04 (0.37–2.94)	0.93	0.91 (0.38–2.19)	0.84
LVEF	0.52 (0.20–1.34)	0.17	0.35 (0.16–0.75)	0.01
VA at baseline	2.24 (0.87–5.77)	0.09	1.69 (0.78–3.68)	0.18

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmias.

prognosis of CS patients, as LV dilatation is an established predictor of mortality [3]. Although an appearance similar to hypertrophic cardiomyopathy (HCM) has been described in some cases [19], we did not come across any patient with such a phenotype in the present study.

Ventricular arrhythmias in CS patients

It seems that the prevalence of VA in CS patients has tended to increase in recent registries and observation studies compared with previous ones. There may be two reasons for this. First, the number of survivors with out-of-hospital cardiac arrest (OHCA) has been increasing owing to early defibrillation intervention in many countries [20,21]. Second, the use of Holter ECG monitoring and exercise stress testing for CS patients has been increasing [22]. Although both advanced atrioventricular block and VT are postulated as major causes of OHCA in CS patients [23], it was reported that sustained VT associated with LV enlargement by echocardiography was an independent predictor of all-cause mortality in Japanese CS patients [3]. This highlights the importance of establishing risk-stratifying criteria for VT with a high-degree of sensitivity and specificity to prevent OHCA.

Patients with DE-MRI

In the sub-population with MRI data, it is interesting to see that there are no significant differences in baseline characteristics between patients with DE-MRI and those without it. More importantly, LVEF, which is the most important confounding factor associated with the presence of DE-MRI, was preserved and comparable between the 2 groups, suggesting that any detected value of DE-MRI is independent of the effect of LV function.

Factors associated with VA and poor outcome in CS patients

In the present study, in order to elucidate the prognostic factors that could predict the occurrence of VA and poorer outcome in CS patients, we first analyzed the association between various baseline characteristics with VA, both at presentation and longitudinally on follow-up, as our primary endpoint. Although higher resting heart rates are being studied extensively as a marker of poor outcome in ischemic patients [24], this has not been the case in our CS cohort. Also, despite that we found a significant association between the presence of VA at baseline and multiple surrogates for compromised LV systolic function (e.g. septal thinning, lower LVEF, and larger LVDs/LVDd), in agreement with previous studies [25–27], an impaired LV systolic function was not found to significantly predict VA incidence during the follow-up period of the study, despite an apparent trend. This may be related to both the limited number of patients with impaired LV function and the limited number of VA events on follow-up in the present study.

On the other hand, by using cardiac magnetic resonance imaging (CMRI) [28,29], we were able to demonstrate that DE-MRI was significantly associated with VA at baseline and showed a strong trend toward higher VA events on follow-up by Kaplan–Meier estimates. This finding also supports the role of CMRI as a risk stratification method for VA and adverse prognosis in various forms of structural heart disease, owing to its unique ability to accurately detect and delineate myocardial fibrosis, the presence and extent of which have become well-established markers of poorer prognosis [30–35]. Bello et al. reported that scar burden was a significant predictor of VT inducibility, whereas LVEF was not [30]. It has been recently shown that patients with advanced cardiomyopathy and implantable cardioverter-defibrillators (ICDs) with proven myocardial fibrosis by DE-MRI have a high likelihood of appropriate ICD therapy [36]. Although scar-based-reentry has been thought to account for VA only in patients with ischemic cardiomyopathy (ICM), accumulating evidence suggests that reentry appears to play a major role in the mechanism of sustained monomorphic VT in this patient population [37]. Furthermore, it has been recently demonstrated that programmed electrical stimulation predicts appropriate ICD therapy used for primary prevention of SCD only in patients with evidence of cardiac involvement on CMRI or positron emission tomography [38], suggesting the possible importance of DE-MRI for risk stratification for VA and SCD in CS patients.

The extent of myocardial fibrosis was also shown to predict poorer outcome, in terms of cardiovascular morbidity and mortality, in various forms of structural heart disease, whether detected by histopathology [39] or DE-MRI [32,33], and was even related to poor prognosis in the general population [40]. This notion is supported by the present finding that DE-MRI could predict poorer outcome for morbidity and mortality in CS patients.

It would be more important to point out that all CS patients without DE-MRI could have an uneventful course and that this perfect negative predictive value not only enforces the role of DE-MRI in prediction of adverse outcome in this population but also stands out as a unique diagnostic criterion for CS in patients with extracardiac involvement. The present findings may be useful for the revision of a major diagnostic criterion by the Japanese Ministry of Health and Welfare [9].

Study limitations

Several limitations should be mentioned for the present study. First, our study has the inherent limitations of retrospective analysis. Thus, the present findings should be confirmed in a future prospective study. Second, not all CS patients underwent CMRI test. This was inevitable as device implantation was the reason for contraindication in most cases without CMRI study. However, since the clinical characteristics and long-term prognosis were comparable between the patients who underwent CMRI study and those who did not, the present findings may not be biased on this point. Third, the number of CS patients who underwent the test was relatively small. Thus, the present finding remains to be confirmed in a future study with a large number of patients.

Fourth, the present study included the patients who had been diagnosed more than 10 years ago, when it was insufficient to search for extra-CS. This may have caused the slightly high rate of isolated CS. Thus, the present finding remains to be confirmed in a future study with a large number of patients.

Conclusions

In the present study, we were able to demonstrate that a primary presentation with VA is relatively common in Japanese CS patients and that the presence of DE-MRI is a strong and significant predictor of poor outcome in general and VA in particular in this patient population.

Disclosures

None.

Acknowledgments

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