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Original article

Increased extent of myocardial fibrosis in genotyped hypertrophic cardiomyopathy with ventricular tachyarrhythmias

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ABSTRACT

Background: Occurrence of malignant ventricular tachyarrhythmias such as ventricular tachycardia and fibrillation (VT/VF) in hypertrophic cardiomyopathy (HCM) can be related to the extent of myocardial fibrosis. Although late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) imaging has been used to detect myocardial fibrosis, few data exist regarding relationships between CMR-determined myocardial fibrosis and VT/VF in genotyped HCM populations.
Objective: We retrospectively investigated whether the extent of LGE can be increased in HCM patients with VT/VF compared to those without VT/VF in the genotyped HCM population.
Methods and results: We studied 35 HCM patients harboring sarcomere gene mutations (*TNNI3* = 22, *MYBPC3* = 12, *MYH7* = 1) who underwent both CMR imaging and 24-h ambulatory electrocardiographic monitoring. VT/VF were identified in 6 patients (2 men, mean age 55.0 years). The extent of LGE was significantly increased in patients with VT/VF ($n = 6$) compared with those without VT/VF ($n = 29$) ($18.6 \pm 14.4\%$ vs. $8.3 \pm 11.4\%$, $p = 0.04$), although the LGE extent was not an independent predictor for the occurrence of VT/VF. Applying a cut-off point $\geq 3.25\%$, episodes of VT/VF were identified with a sensitivity of 100%, specificity of 51.7%, positive predictive value of 30%, negative predictive value of 100%, and the area under the curve of 0.767 (95% confidence interval: 0.590–0.944).
Conclusion: These results demonstrate that myocardial fibrosis determined by CMR imaging may be increased in genotyped HCM patients with episodes of VT/VF. A further prospective study will be needed to clarify the association between the LGE extent and arrhythmic events in HCM patients harboring sarcomere gene mutations.

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disease, and mutations in 11 or more genes encoding proteins of the cardiac sarcomere (>1400 variants) are associated with HCM [1,2]. Although the overall prognosis of HCM may not be unfavorable, hereditary HCM with sarcomere gene mutations may be associated with increased cardiovascular events [3,4]. Moreover, in some cases sudden death associated with malignant ventricular tachyarrhythmias such as ventricular tachycardia and fibrillation (VT/VF) may occur, particularly in young adults [5–7]. Under these conditions, the occurrence of these arrhythmias may be related to the extent of myocardial fibrosis [8]. However, few clinical data exist regarding the relationship between myocardial fibrosis and occurrence of ventricular tachyarrhythmia particularly in HCM with sarcomere gene mutations.

Evaluation of late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) imaging enables us to detect myocardial fibrosis and to examine whether LGE is associated with

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the occurrence of VT/VF in HCM [9,10]. In the present study, using CMR imaging we investigated the correlation between the extent of myocardial fibrosis and VT/VF in HCM patients in whom sarcomere gene mutations were identified.

Methods

Study patients

The diagnosis of HCM was based on the guidelines of the American College of Cardiology Foundation/European Society of Cardiology [11]. Patients with coronary artery disease, intrinsic valve dysfunction, and idiopathic pulmonary artery hypertension were excluded from the study. We screened for mutations in sarcomere genes in 488 unrelated HCM probands (377 men) who were diagnosed at Kanazawa University Hospital and affiliated hospitals [12]. Sarcomere gene mutations were identified in 69 of the 488 probands. Family studies of these 69 probands revealed an additional 88 mutation carriers; thus in total 157 mutation carriers were identified. Of these, 35 HCM patients harboring sarcomere genes' mutations who underwent both CMR and 24-h Holter electrocardiogram (ECG) monitoring were included in this study. All clinical evaluations for the 35 patients were performed from 2005 to 2009 at the Kanazawa University Hospital, and data were retrospectively collected. Informed consent for genetic analysis and use of clinical data for research was obtained from all subjects or their guardians. The study was approved by the Bioethical Committee on Medical Research, School of Medicine, Kanazawa University.

Genetic analysis

Mutations in translated exons of the 8 common sarcomere genes were screened: cardiac myosin binding protein C (*MYBPC3*), cardiac myosin heavy chain (*MYH7*), cardiac regulatory and essential myosin light chains (*MYL2* and *MYL3*), cardiac troponin I (*TNNI3*), cardiac troponin T (*TNNT2*), cardiac tropomyosin (*TPM1*), and cardiac actin (*ACTC1*). Mutations were screened using the polymerase chain reaction (PCR) and the single-strand conformational polymorphism (SSCP) technique or high resolution melting (HRM) analysis (LightScanner System, Idaho Technology, Salt Lake City, UT, USA). For the abnormal SSCP or HRM patterns, PCR products were directly sequenced to identify mutations [4].

Clinical evaluations

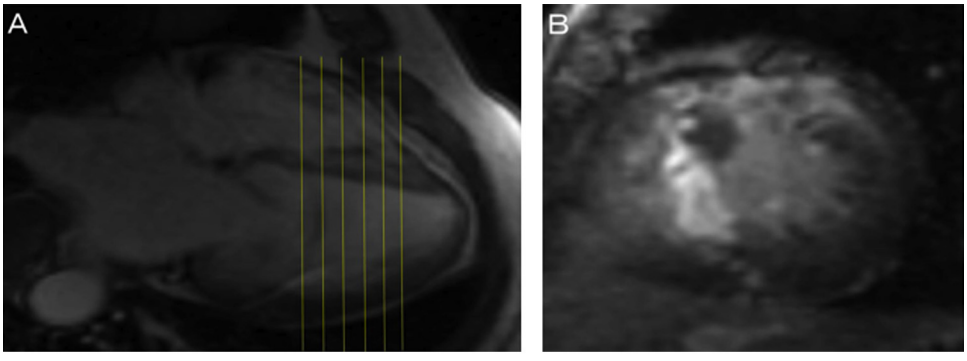
The 35 HCM patients underwent 12-lead standard ECG, 24-h ambulatory ECG monitoring, echocardiography, and CMR. All clinical evaluations were performed from 2005 to 2009 at the Kanazawa University Hospital, and data were retrospectively collected.

Standard M-mode and 2-dimensional echocardiographic studies were performed by sonographers with knowledge of HCM diagnosis but without knowledge of CMR parameters to avoid potential measurement bias. Measured parameters included thicknesses of the interventricular septum and left ventricular (LV) posterior wall at the level of the tips of the mitral valve leaflets. Fractional shortening was calculated as (end-diastolic dimension–end-systolic dimension)/end-diastolic dimension. LV ejection fraction was calculated with Simpson's method [13]. Impaired systolic LV function was defined when LV ejection fraction was $<50\%$ [14].

CMR images were acquired by using a 1.5-T Signa MR unit (Echo speed CVi) with a cardiac coil (GE Medical Systems, Milwaukee, WI, USA). Fast spoiled gradient recalled acquisition cines were acquired during 8-second breath-holds (the echo time/repetition time 1.3/5.0 ms, flip angle 30°) in long-axis planes and sequential 8-mm short-axis slices (2 mm gap between slices) from the apex to the atrioventricular ring. Intravenous gadolinium with diethylenetriamine pentaacetic acid was given (0.2 mmol/kg) and contrast-enhanced images were acquired after 10–15 min in 8–10 identical short-axis planes and 4-chamber view planes by using an inversion-recovery segmented gradient echo. Inversion times were adjusted to null normal myocardium (230–350 ms) with voxel sizes of 2.0 mm $\times$ 1.6 mm $\times$ 8.0 mm [15]. Hyperenhanced areas were calculated by manual planimetry in all short-axis slices and the total areas of hyperenhancement are expressed as a percentage of total myocardium (Fig. 1) [16,17]. All imaging studies were analyzed separately by two observers without knowledge of clinical findings. In patients with VT/VF, the areas of LGE were indicated in the American Heart Association/American College of Cardiology 17-segment model nomenclature [18].

Evaluation of arrhythmic events

Arrhythmic events were defined as sudden cardiac death, non-sustained VT, sustained VT, and VF. Documentation of these events was based on records of VT/VF on an automated external defibrillator, 24-h Holter ECG, continuous ECG monitoring, the use of an implantable defibrillator, or the occurrence of sudden



$$\text{The extent of LGE (\%)} = \frac{\text{The areas of total hyperenhancement (cm}^2\text{)}}{\text{The areas of total myocardium (cm}^2\text{)}}$$

Fig. 1. Methods for evaluation of the extent of late gadolinium enhancement (LGE). (A) Areas of LGE were measured in short-axis slices. (B) The total areas of LGE were measured by manual planimetry and were expressed as a percentage of total myocardium.

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cardiac death. Non-sustained VT was defined as a minimum of three consecutive ventricular beats with a rate of more than 120 beats/min. These arrhythmic events which occurred after the CMR examination were retrospectively collected using the electric medical record system. Thus, the observation period began on the date of the CMR examination and ended on the date of clinical data collection.

Statistical analysis

Data are presented as the mean ± standard deviation for continuous variables. Continuous variables between the two groups were compared using the Mann–Whitney *U*-test. Categorical frequencies were compared using Fisher's exact test. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was estimated to establish a cut-off of the extent of LGE with appropriate sensitivity and specificity to detect VT/VF. The optimum cut-off point was determined as the value corresponding to the greatest accuracy (*i.e.* highest summed value for sensitivity plus specificity values, with sensitivity and specificity weighted equally). Variables associated with VT/VF were analyzed with univariate and multivariate logistic regression analysis to examine the association between patients with and without VT/VF and to calculate odds ratio and 95% confidence intervals after controlling simultaneously for potential confounders. A linear regression analysis was used to analyze the relationship between the extent of LGE and plasma brain natriuretic peptide (BNP). A p value <0.05 was considered statistically significant. Data were analyzed using SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' profiles

Of the 35 HCM patients (12 men, mean age 54.9 years), 22 had a *TNNI3* mutation, 12 had a *MYBPC3* mutation, and one had a *MYH7* mutation (Table 1). Plasma BNP levels were 224.9 ± 245.8 pg/mL. As for medication, 22 patients were treated with β-blockers, 17 with angiotensin-converting enzyme inhibitors/angiotensin II receptor inhibitors, and 8 with amiodarone. No patients were implanted with implantable cardioverter-defibrillators or cardiac resynchronization therapy with defibrillator on the date of the CMR examination, which was the start date of the observation period. Interventricular septal wall thickness was 15.2 ± 3.8 mm, LV posterior wall thickness 10.4 ± 2.4 mm, and maximal LV wall thickness 16.3 ± 4.7 mm. LV end diastolic dimension was 46.1 ± 7.2 mm and systolic dimension 30.3 ± 8.2 mm. LV ejection fraction was 63.2 ± 14.3%. There were six patients with impaired systolic LV function (LV ejection fraction <50%). Left atrial dimension was 43.1 ± 7.2 mm. LGE was found in 30 of the 35 patients (85.7%). The mean extent of LGE was 10.1 ± 12.4%.

Occurrence of VT/VF and imaging parameters

With either conventional or continuous ECG recording, VT/VF was retrospectively identified in 6 (17%) of the 35 HCM patients. Of these six patients, VF was identified in four patients, and non-sustained VT was recorded on 24-h Holter ECG or continuous ECG monitoring in two patients. Sudden cardiac death was not identified, although one death from aggravated heart failure was identified. The mean observation periods of the total 35 patients, 29 patients without VT/VF, and 6 patients with VT/VF were 92.7 ± 13.1 months, 93.6 ± 13.0 months, and 88.5 ± 14.1 months, respectively. The six patients with VT/VF developed arrhythmic events 28 ± 25.6 months after the starting date of the observation period. In the six patients with VT/VF, LGE was observed more frequently in the inferolateral area than in the anteroseptal area ($p = 0.003$) (Supplement Fig. S1).

Supplementary Fig. S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2014.10.002.

The clinical characteristics of patients with or without VT/VF are shown in Table 1. Plasma BNP levels, the LV end-diastolic and

Table 1
Clinical characteristics of the HCM patients according to the presence or absence of VT/VF.

Variable	All patients ($n=35$)	VT/VF (+) ($n=6$)	VT/VF (−) ($n=29$)	p value
Clinical characteristics				
Age (years)	54.9 ± 16.1	55.0 ± 20.4	54.9 ± 15.5	0.915
Male, *n* (%)	12 (34.3)	2 (33.3)	10 (34.5)	1.000
Systolic blood pressure (mmHg)	116.7 ± 19.1	108.0 ± 5.3	118.1 ± 20.2	0.464
Diastolic blood pressure (mmHg)	71.2 ± 11.7	64.7 ± 9.2	72.2 ± 11.9	0.308
Mean blood pressure (mmHg)	86.3 ± 14.2	79.1 ± 7.9	87.5 ± 14.7	0.265
BNP (pg/ml)	224.9 ± 245.8	458.7 ± 436.1	174.8 ± 154.5	0.037
Echocardiographic and CMR data				
LAD (mm)	43.1 ± 7.2	46.7 ± 12.0	42.3 ± 5.9	0.312
IVST (mm)	15.2 ± 3.8	14.8 ± 3.2	15.3 ± 3.9	0.717
PWT (mm)	10.4 ± 2.4	11.3 ± 2.9	10.2 ± 2.3	0.356
MWT (mm)	16.3 ± 4.7	15.3 ± 4.1	16.5 ± 4.9	0.593
LVDd (mm)	46.1 ± 7.2	52.5 ± 8.2	44.8 ± 6.3	0.035
LVDs (mm)	30.3 ± 8.2	38.2 ± 10.5	28.7 ± 6.8	0.031
LVEF (%)	63.2 ± 14.3	53.5 ± 15.5	65.2 ± 13.5	0.076
LGE on CMR, *n* (%)	30 (85.7)	6 (100.0)	24 (82.8)	0.561
the extent of LGE on CMR (%)	10.1 ± 12.4	18.6 ± 14.4	8.3 ± 11.4	0.040
Disease-causing gene				
TNNI3, *n* (%)	22 (62.8)	4 (66.7)	18 (62.1)	0.893
MYBPC3, *n* (%)	12 (34.3)	2 (33.3)	10 (34.5)	
MYH7, *n* (%)	1 (2.9)	0	1 (3.4)	
Medication				
β-blockers, *n* (%)	22 (62.8)	3 (50.0)	19 (65.5)	0.649
RAAS inhibitors, *n* (%)	17 (48.6)	4 (66.7)	13 (44.8)	0.402
Amiodarone, *n* (%)	8 (22.9)	3 (50.0)	5 (17.2)	0.117

HCM, hypertrophic cardiomyopathy; VT/VF, ventricular tachycardia/ventricular fibrillation; BNP, plasma B-type natriuretic peptide; CMR, cardiovascular magnetic resonance; IVST, interventricular septum thickness; LAD, left atrial dimension; LGE, late gadrinium enhancement; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MWT, maximal left ventricular wall thickness; PWT, posterior left ventricular wall thickness; RAAS, renin-angiotensin-aldosterone system.

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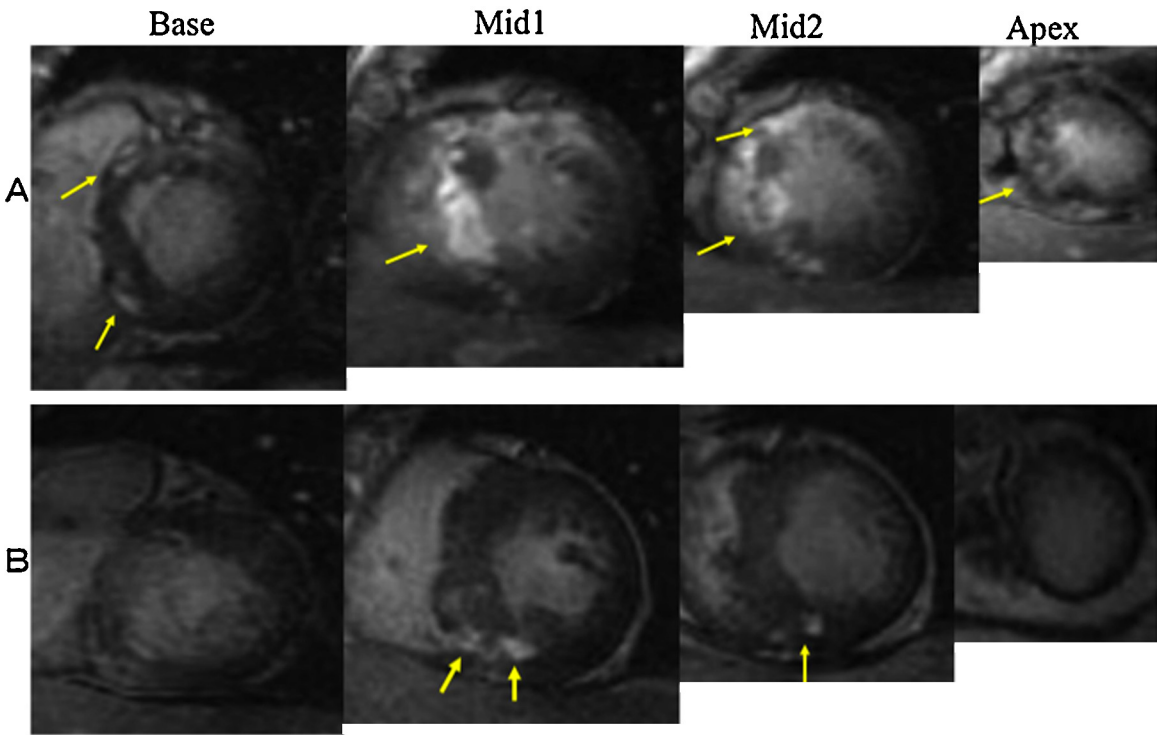

Fig. 2. Representative magnetic resonance imaging in patients with hypertrophic cardiomyopathy (HCM) with (A) or without (B) ventricular tachyarrhythmias. (A) The image was obtained from a 52-year-old female with the late gadolinium enhancement (LGE) (arrows) extent of 37.6%. The thickness of interventricular septum was 14 mm. (B) The image was obtained from a 35-year-old female with the LGE (arrows) extent of 6.5%. The thickness of interventricular septum was 15 mm.

LV end-systolic dimensions were significantly increased in patients with VT/VF compared to those without VT. Representative CMR images of a patient with VT/VF or a patient without VT/VF are shown in Fig. 2A and B, respectively. Further, the extent of LGE was significantly increased in patients with VT/VF compared with those without VT/VF (18.6 ± 14.4% vs. 8.3 ± 11.4%, $p = 0.04$) (Fig. 3). There was no difference in frequency of the disease-causing gene or in echocardiographic LV thickness and ejection fraction between two groups.

We next tested whether the LGE extent predicts the occurrence of VT/VF in the 35 HCM patients; logistic regression analyses revealed that the LGE extent was not an independent predictor for the occurrence of VT/VF. Nonetheless, it may be intriguing to examine the diagnostic values of the LGE extent for predicting the occurrence of VT/VF in the study population. ROC curve analysis demonstrated that applying a cut-off point ≥3.25%, episodes of VT/VF were identified with a sensitivity of 100%, specificity of 51.7%, positive predictive value of 30%, negative predictive value of 100%, and the area under the curve of 0.767 (95% confidence interval: 0.590–0.944) (Fig. 4).

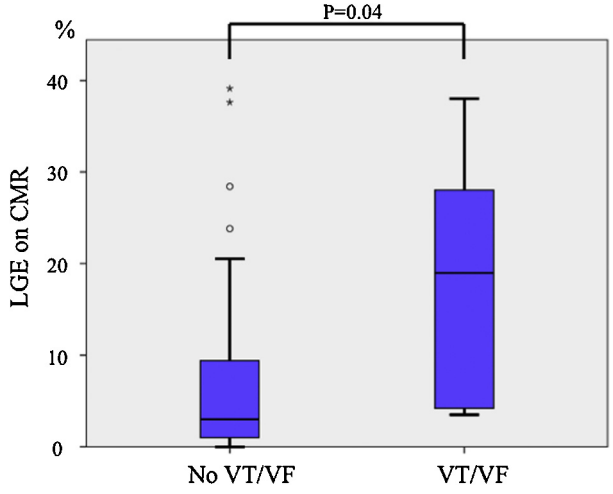

Fig. 3. Comparison of the extent of late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) in hypertrophic cardiomyopathy patients with vs. without ventricular tachycardia and fibrillation (VT/VF). There was a significant difference in the extent of LGE between patients with and without VT/VF (18.6 ± 14.4% and 8.3 ± 11.4%, respectively, $p = 0.04$).

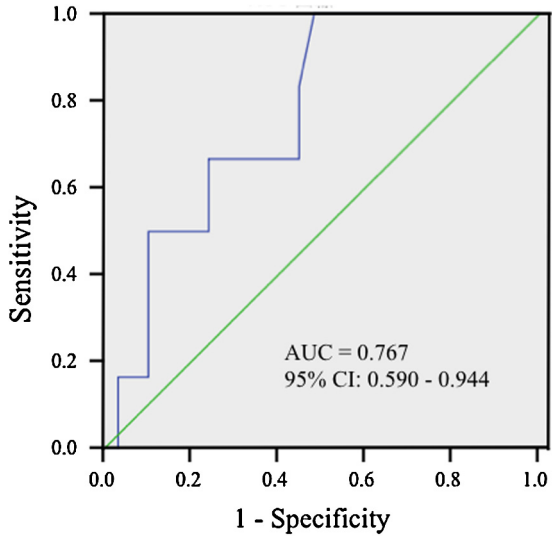

Fig. 4. Receiver operating characteristic (ROC) curve for the extent of late gadolinium enhancement (LGE) and the occurrence of ventricular tachycardia and fibrillation (VT/VF). ROC curve analysis demonstrated that applying a cut-off point ≥3.25%, episodes of VT/VF were identified with a sensitivity of 100%, specificity of 51.7%, positive predictive value of 30%, negative predictive value of 100%, and the area under the curve (AUC) of 0.767 [95% confidence interval (CI): 0.590–0.944].

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Discussion

The clinical manifestations of HCM can be remarkably variable, ranging from near-normal life expectancy with no symptoms to sudden cardiac death in youth [5–7]. Histopathologic abnormalities of HCM include myocyte hypertrophy, disarray, and increased interstitial and/or focal fibrosis [19,20]. Myocardial fibrosis contributes to diastolic and/or systolic dysfunction, and the occurrence of arrhythmic events in HCM [21–29]. Although little has been known whether CMR-determined myocardial fibrosis is associated with arrhythmic events in genotyped HCM, we demonstrated that the extent of LGE was increased in HCM patients with VT/VF in whom sarcomere gene mutations were identified (Table 1, Fig. 3).

Early studies regarding genotype–phenotype correlations of HCM showed some significant differences between phenotypes observed at various disease-causing genes [2,30,31]. However, taken as a whole, the value of genetic testing in HCM is often criticized as being unable to predict the clinical course of mutation carriers [2,12,32]. Indeed, no difference in frequency of disease-causing genes was observed between HCM patients with VT/VF and those without VT/VF (Table 1), indicating limitations of genetic testing as a tool for risk stratification in HCM. Together with evidence in associations between LGE and cardiac events in HCM [8–10,16,33,34], our findings indicate that it may be practical to determine the extent of myocardial fibrosis by LGE techniques in HCM harboring sarcomere gene mutations.

Regarding prediction of fatal arrhythmias, LGE was not an independent factor associated with occurrence of VT/VF in our genotyped Japanese HCM population, while Hen et al. recently reported that LGE may predict the occurrence of fatal arrhythmias in a non-genotyped Japanese HCM population [35]. We have previously reported that the presence of sarcomere gene mutation may be associated with the increased occurrence of cardiac events in HCM [4], suggesting that different genetic backgrounds of the study populations could affect prognostic values of LGE in HCM.

The increased LGE extent in HCM patients with VT/VF raises important issues regarding mechanisms of arrhythmogenicity in HCM. Despite the correlations between CMR-determined fibrosis and arrhythmic events in HCM patients [8–10,16,22–29,33,34], Wolf et al. have demonstrated that the extent of fibrosis was not correlated with *ex vivo* signal conduction properties or *in vivo* electrophysiologically stimulated ventricular arrhythmias in genetically engineered HCM mice harboring a sarcomere gene mutation [36]. Further, associations between patterns of fibrosis and ventricular arrhythmias (Fig. S1) were not reproduced in their HCM mice, together indicting that distinct somatic events contribute to variable HCM pathology [36]. Indeed, elevated BNP levels in HCM patients with VT/VF (Table 1) and the correlation between the LGE extent and BNP levels (Fig. S2) indicate the presence of modifying factors because multiple intrinsic and extrinsic myocardial stress stimulate BNP production [37,38]. Future studies will be needed to determine somatic factors that modify arrhythmogenicity in HCM.

Supplementary Fig. S2 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2014.10.002.

Study limitations

The present study has several limitations. First, the number of patients was relatively small in this single-center study. However, the findings do suggest that the extent of myocardial fibrosis could be increased in HCM patients with VT/VF harboring sarcomere gene mutations. Second, some patients with non-sustained VT could have been overlooked in the intermittent monitoring process. This disadvantage could potentially be minimized by interviewing carefully regarding the occurrence of arrhythmias. Third, there is no standard protocol for the use of therapeutic medicines, and pharmacologic treatment depended upon each doctor's judgment because of the retrospective nature of this study. However, therapy was administered according to the guidelines of the American College of Cardiology Foundation/American Heart Association [7] and the Japanese Circulation Society [39]. Finally, HCM progresses slowly and a prospective long-term follow-up study is required to determine whether the LGE extent predicts the occurrence of VT/VF.

Conclusion

CMR imaging-determined myocardial fibrosis could be increased in HCM patients harboring sarcomere gene mutations with ventricular arrhythmias. We suggest that careful attention to antiarrhythmic treatment for these hereditary HCM patients with extensive myocardial fibrosis may be needed.

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Disclosures

None declared.

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