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Original Research Article

Myocardial fibrosis detected by cardiac CT predicts ventricular fibrillation/ventricular tachycardia events in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: Myocardial fibrosis (MF) occurs in up to 80% of subjects with asymptomatic or mildly symptomatic hypertrophic cardiomyopathy (HCM) and can constitute an arrhythmogenic substrate for re-entrant, life-threatening ventricular arrhythmias in predisposed persons.

Objective: The aim was to investigate whether MF detected by delayed enhancement cardiac CT is predictive of ventricular tachycardia (VT) and fibrillation (VF) that require appropriate therapy by an implantable cardioverter defibrillator (ICD) in patients with HCM.

Methods: Twenty-six patients with HCM with previously (for at least 1 year) implanted ICD underwent MF evaluation by cardiac CT. MF was quantified by myocardial delayed enhanced cardiac CT. Data on ICD firing were recorded every 3 months after ICD implantation. Risk factors for sudden cardiac death in patients with HCM were evaluated in all patients.

Results: MF was present in 25 of 26 patients (96%) with mean fibrosis mass of 20.5 ± 15.8 g. Patients with appropriate ICD shocks for VF/VT had significantly greater MF mass than patients without (29.10 ± 19.13 g vs 13.57 ± 8.31 g; $P = .01$). For a MF mass of at least 18 g, sensitivity and specificity for appropriate ICD firing were 73% (95% CI, 49%–88%) and 71%

A.A.S. and T.S. contributed equally to this work.

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(95% CI, 56%–81%), respectively. Kaplan–Meier curves indicated a significantly greater VF/VT event rate in patients with MF mass ≥18 g than in patients with MF <18 g ($P = .02$). In the Cox regression analysis, the amount of MF was independently associated with VF/VT in ICD-stored electrograms.

Conclusion: The mass of MF detected by cardiac CT in patients with HCM at high risk of sudden death was associated with appropriate ICD firings.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac genetic disorder related to sudden cardiac death (SCD) in young people.[1–4] Clinical characteristics[5–12] and genetic findings[13–18] provide important diagnostic and prognostic information in patients with HCM. However, risk stratification for SCD remains a challenge because of the heterogeneity in HCM presentation.

Late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR) has emerged as the reference standard for noninvasive detection of myocardial fibrosis (MF) in HCM,[19–21] and it has been validated against pathology in humans.[22] MF occurs in up to 80% of asymptomatic or mildly symptomatic subjects with HCM[23] and can constitute an arrhythmogenic substrate for re-entrant, life-threatening ventricular arrhythmias in predisposed persons.[13,24–27] Bruder et al[28] and O'Hanlon et al[29] reported significantly increased all-cause mortality and cardiac mortality in a follow-up of largely asymptomatic patients with HCM. Rubinshtein et al[30] showed a higher prevalence of ventricular arrhythmias in the follow-up of >400 patients with HCM and that LGE was strongly associated with arrhythmia, SCD, or implantable cardioverter defibrillator (ICD) discharge. Recent studies have indicated that MF demonstrated by LGE is associated with a high likelihood of appropriate ICD firing.[31,32]

CMR is generally contraindicated for patients with ICDs, even though, with several precautions, magnetic resonance imaging (MRI) might be done safely for selected cardiac devices.[33] Patients with HCM and ICDs constitute a subgroup of HCM with high risk of SCD.[34] An alternative to CMR is cardiac CT, because MF detection has been validated in patients and animals with infarcts.[35,36] Our group also demonstrated the ability of detecting MF in a patient with HCM by cardiac CT. MF areas by cardiac CT matched the MF areas by CMR.[37] More recently, Berliner et al[38] showed a reasonable correlation between cardiac CT and CMR areas of delayed enhancement in patients with HCM.

The purpose of this prospective study was to detect and evaluate the extent of MF by cardiac CT in patients with HCM with previously implanted ICDs.

2. Methods

The study was approved by our institutional review board, and all patients provided written informed consent for the study. Patients with HCM followed in our HCM/arrhythmia clinic and with previously implanted ICD for at least 1 year were invited to undergo cardiac CT if they had at least 12 months of clinical follow-up at our institution and no history of septal ablation or surgical myectomy. From the 800 patients of our HCM clinic, 28 patients met these criteria, 1 patient was excluded because of renal dysfunction (creatinine >1.5 mg/dL), and another patient declined to participate. We included all available patients in our HCM clinic that had these inclusion criteria during the time of the study protocol. Patients were followed prospectively after the CT examination; however, for the follow-up analysis, the time after ICD implantation was also considered as follow-up time; that is, the time zero for follow-up was the date of ICD implantation. Therefore, our prospective study on MF by cardiac CT has both retrospective and prospective follow-up. All patients had ICD implanted as primary prevention (no prior sudden death, but presenting ≥2 classic risk factors[4]) or secondary prevention (after an aborted SCD).

2.1. ICD therapy data

ICDs were examined every 3 months or if ICD firing occurred. Two experienced investigators (C.G.P. and M.M.F.) blinded to knowledge of the CT results categorized the rhythm-prompting shock or antitachycardia pacing with the use of all stored electrograms since ICD implantation, including events before the CT examination. Appropriate ICD therapy was defined as any shock or antitachycardia pacing delivered during an episode of ventricular fibrillation (VF) or ventricular tachycardia (VT; defined as heart rate of >180 beats/min for 30 seconds or more associated with atrioventricular dyssynchrony and wide QRS complexes). The shock-free period was defined as the time between (1) the ICD implant and the first life-threatening arrhythmia (VF/VT) appropriately treated by the ICD or (2) the last ICD interrogation in patients with no history of appropriate therapy.

2.2. Risk factors for SCD and other exploratory factors

Evaluation of risk factors for SCD in patients with HCM before ICD implantation was performed according to previously published criteria.[3] Risk factors included history of syncope, defined as episodes of unexplained loss of consciousness within the previous 12 months[39]; prior cardiac arrest[40]; familial history of SCD in first-degree relatives younger than 40 years old[41,42]; 24-hour ambulatory electrocardiogram monitoring for detection of nonsustained VT,[8,10,43,44] defined as ≥3 consecutive ventricular beats at a rate of ≥120 beats/min, lasting <30 seconds; end-diastolic myocardial thickness of >30 mm[12,45] by 2-dimensional echocardiography.

2.3. *Multidetector CT*

Patients underwent cardiac CT scans with the use of a 64 detector-row scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) for MF evaluation. Delayed enhancement images for MF were obtained 7 minutes after intravenous administration of 150 mL of iodine contrast (Iopamiron 370; Shering AG, Berlin, Germany) with the use of a retrospective electrocardiogram-gating cardiac helical protocol with detector collimation of 64 × 0.5 mm, tube voltage of 120 kV, tube current adjusted for body mass index of 270 to 500 mA, helical pitch of −14.4, pitch factor of 0.225, and scanning field of view of 220 mm. Estimated radiation dose was 10 to 15 mSv.

Images were reconstructed at 1-mm thick intervals at 75% of the R-R interval (diastolic phase). One-millimeter thick axial CT images acquired 7 minutes after contrast injection were processed by multiplanar reformat with the use of a commercially available workstation (Vitrea 2; Vital Images, Minnetonka, MN) to obtain true LV long axis and short axis. The short-axis images were then displayed as a 10-mm thick average image and then exported as a stack of short-axis images. The stack of 10-mm thick short-axis images covered the entire LV and was then analyzed on Image J software. Endocardial and epicardial contours were performed to extract the myocardial area. Then, using Image J software (NIH Image), we used a threshold technique whereby the level of thresholding could be manually modified by a sliding bar, and the pixels above this specific threshold are colored in red. Once our single observer with 6 years of experience in cardiac CT (A.A.S.) and blinded to the ICD data reached a threshold level that corresponded to the same area of myocardial delayed enhanced area on the CT image by his visual inspection, the software calculated the number of pixels above that threshold, which was then converted into area in square centimeters and multiplied by 1-cm slice thickness to obtain the volume of MF of that specific slice. The total LV MF volume was simply obtained by the summation of all short-axis slices. To obtain MF mass, the MF volume was multiplied by myocardial-specific density, that is, 1.05 g/mL.[46] Percentage of MF was calculated as MF divided by LV mass. Basal and mid inferoseptal segments had significant metal artifacts in all patients and were excluded from analysis (Fig. 1). Measurements were repeated in random order by the same observer after 2 months. Image analysis was performed with Image J software (NIH Image). One additional analysis was the qualitative visual classification of MF patterns, based on previously published patterns initially describe by CMR.[47]

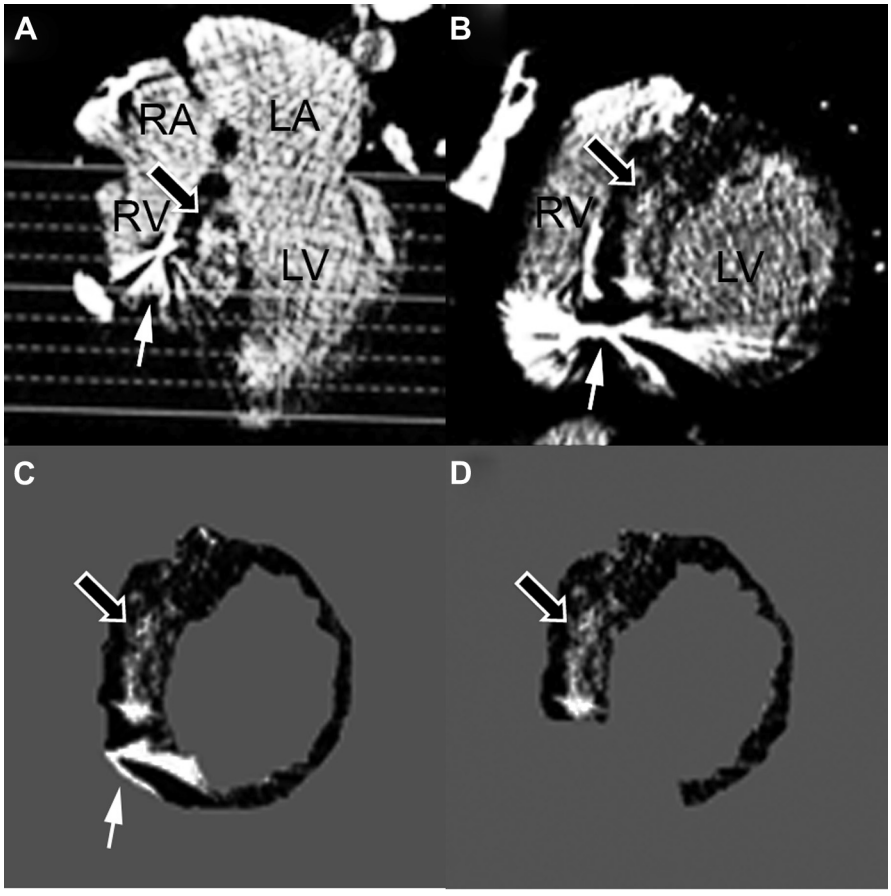

Figure 1 – Image analysis for determination of myocardial fibrosis. Delayed cardiac CT images in 4-chamber (A) and short-axis (B) views show septal hypertrophy associated with myocardial hyperenhancement (*black arrow*). Metal artifact caused by implantable cardioverter defibrillator lead (*white arrow*) precludes the analysis of inferoseptal left ventricular segment. (C) Segmentation of the LV is shown in the short-axis view. (D) Exclusion of the inferoseptal left ventricular segment. LA, left atrium, LV, left ventricle, RA, right atrium, RV, right ventricle.

2.4. Statistical analysis

Continuous variables are expressed as mean ± SD, and discrete variables are expressed in proportions. Continuous variables were compared with Student *t* test, and categorical variables were compared with Fisher exact test. The MF value with best accuracy to predict VF/VT occurrence was obtained by logistic regression. The ability of MF to predict ICD-appropriate therapy for VF/VT was evaluated by the area under the receiver-operating characteristic curve. Kaplan–Meier curves were used to express the shock-free period in relationship to degree of MF. Differences in shock-free survival curves were assessed by the log-rank test. Two Cox multivariate regression models were performed: one that included all variables with $P < .10$ in the univariate analysis and the other that included all clinically relevant factors, independent of their statistical significance on univariate analysis. In addition, we performed 2 backward stepwise Cox regression models (with the significance level for removal from the model of 0.1) that included MF by CT and all relevant SCD risk factors. Significance threshold was $P < .05$, and confidence intervals were 95%.

Intra-observer variability for MF was measured as the percentage of mean difference.

3. Results

Appropriate ICD therapy for VF/VT occurred in 13 patients (12 with VF and 1 with VT), whereas 13 patients had no appropriate ICD therapy. The mean follow-up was 38.5 ± 25.5 months. A longer follow-up was observed in the group without appropriate ICD therapy (56.5 ± 21.0 months vs 20.4 ± 14.7 months; $P < .001$). No missing patient or follow-up loss until the end of study period was observed. Only 1 patient died in the VF/VT group. Representative delayed cardiac CT scans are shown in Figures. 2 and 3 for patients with and without VF/VT events, respectively.

Table 1 shows demographic data, risk factors for SCD, and cardiovascular characteristics of the study population. Twenty-one patients had ICD implanted as primary prevention (no prior sudden death, but presenting 2 or more classic risk factors), and 5 patients had ICD implantation after an aborted SCD. More frequent antiarrhythmic therapy was observed in the appropriate ICD therapy group ($P = .04$). A trend toward increased septal wall thickness was present in the VF/VT group compared with the no VF/VT event group (26.4 ± 6.7 mm vs 21.5 ± 6.2 mm, respectively; $P = .06$).

Myocardial fibrosis by cardiac CT was detected in 25 of 26 patients (96.1%). The mean MF mass for all patients was 20.5 ± 15.8 g. The intra-observer variability for MF mass was 3.2% ± 1.5%.

Patients with VF/VT events had approximately 2-fold greater MF mass than patients without VF/VT events (29.1 ± 19.1 g vs 13.6 ± 8.3 g, respectively; $P = .01$; Table 2, Figures. 2 and 3). The percentage of MF was also greater in the VF/VT event group (21.0% ± 10.5% vs 11.9% ± 8.1%, respectively; $P = .02$). A MF mass of 18 g yielded the optimal cutoff for predicting the occurrence of VF/VT events, with area under the receiver-operating characteristic curve of 0.75 (95% CI, 0.56–0.95). The 18-g MF cutoff yielded a sensitivity of 73% (95% CI, 49%–88%), specificity of 71% (95% CI, 56%–81%), positive predictive value of 61% (95% CI, 42%–75%), and negative predictive value of 80% (95% CI, 63%–92%) to predict VF/VT events. Kaplan–Meier curves indicated a significantly greater VF/VT event rate in patients with MF mass ≥18 g than in patients with MF <18 g ($P = .02$; Fig. 4).

No differences in risk factors were observed for sudden death (syncope, prior cardiac arrest, familial history of SCD, nonsustained VT) for the groups with MF <18 g and MF ≥18 g. A trend was observed for a higher proportion of septal thickness >30 mm within the group with MF ≥18 g than in the group with MF <18 g ($P = .06$). In addition, specific patterns of MF by cardiac CT, defined by visual analysis, did not correlate to VF/VT in this high-risk group of patients with HCM.

Multivariate analysis with the use of the Cox model showed MF mass ≥18 g was the only independent variable associated with VF/VT appropriately treated by ICD firing, with a hazard ratio of 3.46 (95% CI, 1.12–10.66; $P = .03$). For each 10-g increase in MF mass, we found a 47.6% increase in

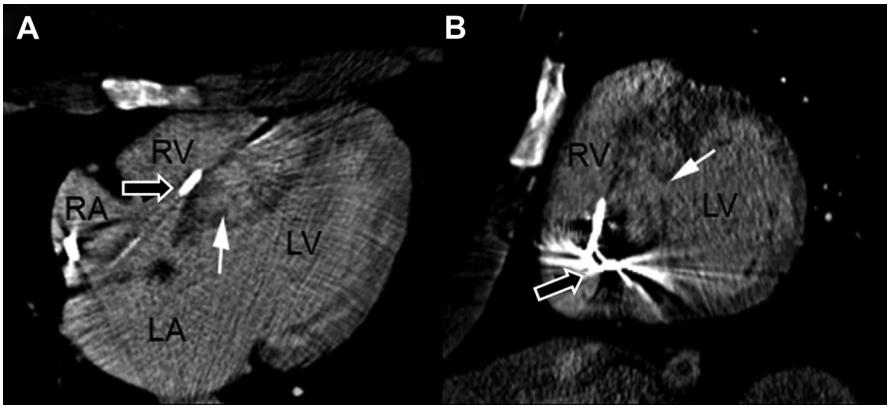

Figure 2 – Delayed cardiac CT scan of a 26-year-old female patient with 55.1 g ofmyocardial fibrosis and appropriated shock by implantable cardioverter defibrillator shown in 4-chamber (A) and short-axis (B) views. Extensive myocardial fibrosis is present in the interventricular septum (white arrows). An implantable cardioverter defibrillator lead artifact is present (*black arrows*). LA, left atrium, LV, left ventricle, RA, right atrium, RV, right ventricle.

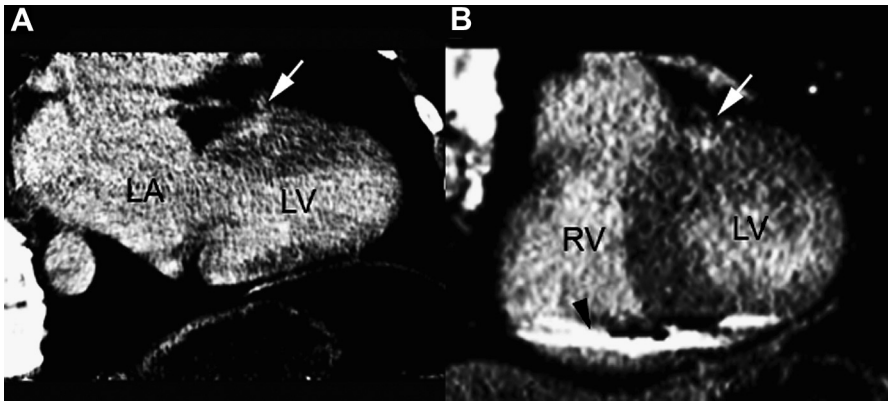

Figure 3 – Delayed cardiac CT scan of an 18-year-old male patient with 8.3 g of myocardial fibrosis and no ventricular fibrillation or ventricular tachycardia event shown in 2-chamber (A) and short-axis (B) views. A small area of myocardial fibrosis is present in the anteroseptal region of the left ventricle close to the right ventricular junction (*arrows*). LA, left atrium, LV, left ventricle, RV, right ventricle.

the probability of having VF/VT detected by ICD in patients with HCM (hazard ratio, 1.48; 95% CI, 1.10–1.99; $P = .01$). These results remained unchanged in all Cox regression models, including MF by CT with 18-g cutoff and all relevant SCD risk factors.

4. Discussion

A greater extent of MF in patients with HCM has been related to an increased probability of VF/VT as studied by CMR.[28–30] However, after ICD placement, CMR is generally contraindicated, except in selected cases and with specific protocols.[33] In selected patients who have undergone CMR with an ICD, the ability to analyze myocardial detail is usually greatly compromised because of the lack of MRI signal in the region of the ICD leads. Cardiac CT represents an alternate and potentially safer alternative in these cases.[48] To our knowledge, this is the first study to evaluate the prognostic significance of MF detected by cardiac CT in high-risk patients with HCM with ICD. We demonstrated that patients with greater MF detected by cardiac CT were more likely to have VF/VT events appropriately treated by the ICD. MF mass >18 g had a sensitivity and specificity of 73% and 71%, respectively, for predicting VF/VT events.

Precise identification of patients at high risk of SCD has not been achieved by the currently known risk factors, possibly because of the heterogeneity of disease presentation, low prevalence in cardiologic practice, and the occurrence of SCD as the initial manifestation of HCM.[4,5,7,12,39–42,49] MF has been proposed as the anatomic substrate for malignant life-threatening arrhythmias in several cardiomyopathies,[24,25,27,50–53] particularly in ischemic and dilated cardiomyopathy. In HCM, VF/VT is believed to be the main cause of SCD.[54] However, until recently, no strong evidence has associated MF and prognosis in patients with HCM,[28-30] and some experts will still consider that there is no direct evidence between MF and VF/VT in HCM. In that regard, current guidelines do not recommend MF evaluation by CMR as a tool for risk stratification, except in selected cases.[55] In addition, specific patterns of MF by cardiac CT as previously described[47] did not correlate to VF/VT in this high-risk group of patients with HCM.

Our study has the unique characteristic of performing MF measurements by cardiac CT. Compared with MRI, cardiac CT is generally thought to have much lower risk in patients with ICD. Recently, some reports have been issued about a potential electromagnetic signal around the bore of the CT scanners that could interact with the electronics in a pacemaker or ICD. However, these appear to be rare, and similar findings have not been observed in our center. Because CMR is generally contraindicated in this patient population, the natural history and potential of MF in these patients with HCM could be evaluated in the future by cardiac CT. Although radiation doses were somewhat high in the present study, cardiac CT scans in this longitudinal study were obtained before the current generation of dose-reduction cardiac CT techniques.

Our findings are in agreement with recent data[29] that indicated that the risk of ventricular arrhythmogenic events increases with the magnitude of the MF and also in agreement with earlier data that indicated that patients who died suddenly had larger amount of MF than patients with noncardiac death.[56] Similarly, previous work has suggested that MF extent correlates with VF/VT inducibility in electrophysiology studies in ischemic patients.[50] Previous reports suggested that the presence of MF in HCM may be a marker of increased arrhythmic risk independent of its extent.[24,25,27] We evaluated a high-risk group with ICD and with high prevalence of MF (96%), compared with approximately 60% prevalence of MF in patients undergoing CMR reported in the literature.[57]

Although the sensitivity and positive predictive value of MF >18 g showed a wide 95% CI, the specificity and negative predictive value of MF <18 g was high. Therefore, <18 g of scar is a good indicator of low risk of VF/VT, even in patients with clinical risk factors. Another important conclusion is that it is critical to quantify MF and to define a threshold, given that MF is found in a most patients with HCM.

In our study, the rate of antiarrhythmic drug use was significantly greater in the group with VF/VT, most likely

Table 1 – Patient characteristics.

	All patients (n = 26)	Patients with VF/VT (n = 13)	Patients without VF/VT (n = 13)	P value
Age (y), mean ± SD	39.7 ± 17.0	43.4 ± 18.3	35.9 ± 15.5	.27*
Male sex, n (%)	12 (46.1)	6 (46.1)	6 (46.1)	<.999†
Familial history of SCD, n (%)	21 (80.8)	11 (84.6)	10 (76.9)	<.999†
Syncope, n (%)	18 (69.2)	9 (69.2)	9 (69.2)	<.999†
Prior cardiac arrest, n (%)	5 (19.2)	2 (15.4)	3 (23.1)	<.999†
NYHA functional class, n (%)				.48‡
I	15 (57.7)	7 (53.8)	8 (61.5)	
II	10 (38.5)	5 (38.5)	5 (38.5)	
III	1 (3.8)	1 (7.7)	0	
Atrial fibrillation, n (%)	8 (30.8)	4 (30.8)	4 (30.8)	<.999†
NSVT, n (%)	9 (34.6)	5 (38.4)	4 (30.8)	<.999†
LVEF (%), mean ± SD	70.9 ± 12.4	68 ± 0.1	73 ± 0.1	.29*
LV EDD (cm), mean ± SD	4.1 ± 0.5	4.1 ± 0.4	4.2 ± 0.6	.46*
Left atrium (cm), mean ± SD	4.3 ± 0.6	4.4 ± 0.5	4.4 ± 0.7	.80*
LV mass (g), mean ± SD	128.2 ± 50.5	130.4 ± 44	126.3 ± 58.5	.84*
LV septal wall thickness (mm), mean ± SD	23.9 ± 7.0	26.4 ± 6.7	21.5 ± 6.2	.06*
LV septal wall thickness ≥30 mm, n (%)	6 (23)	4 (30.8)	2 (15.4)	.64†
LVOT gradient >30 mm Hg, n (%)	12 (46.1)	5 (38.5)	7 (53.8)	.64†
Antiarrthymics, n (%)	14 (53.8)	10 (76.9)	4 (30.8)	.04†
β-Blockers, n (%)	22 (84.6)	12 (92.3)	10 (76.9)	.59†
Calcium antagonists, n (%)	8 (30.8)	4 (30.8)	4 (30.8)	<.999†
ACE inhibitors, n (%)	1 (3.8)	1 (7.7)	0	<.999†
ARBs, n (%)	8 (30.8)	4 (30.8)	4 (30.8)	<.999†
Spironolactone, n (%)	4 (15.4)	2 (15.4)	2 (15.4)	<.999†
Statins, n (%)	3 (11.4)	3 (23.1)	0	.22†
ASA/oral anticoagulation, n (%)	7 (26.9)	4 (30.8)	3 (23.1)	<.999†

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; EDD, end-diastolic diameter; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Fisher exact test.

† likelihood ratio test.

‡ Student *t* test.

because of the need to clinically control more frequent arrhythmic events. This observation may highlight the influence of MF in the genesis of VF/VT, even under effect of antiarrhythmic drugs.

The present study was small in size and limits our ability to adjust for clinically relevant cardiovascular parameters that may also be associated with VF/VT or may modify the predictive value of MF. Yet statistically significant group differences were noted, despite the small sample size. This suggests good predictive power for MF in our high-risk HCM cohort. Interestingly, the high-density streak-like artifacts were restricted to the mid inferoseptal segment in all patients, whereas all the other segments were free of significant artifact and could be evaluated for MF. In addition, ICD wire artifacts on CT images did not allow quantification of MF in the LV mid inferoseptal region, leading to underestimation of MF in both groups. This is a limitation that probably cannot be overcome by current CT technology, and the exclusion of this segment would be the rule for any scientific investigation that used the same method nowadays. However, the fact that we have removed LV inferoseptal region in all patients with HCM, regardless of presenting records of VF/VT on ICD, we believe it may have mitigated this limitation, at least for the current group comparison presented in our study. Delayed enhancement of cardiac CT has previously been shown to present a fair comparison with CMR for MF evaluation[26,27,35,36]; however, we did not compare cardiac CT and CMR in this study. A disadvantage of cardiac CT is additional radiation

Table 2 – Myocardial fibrosis by cardiac CT.

	All patients (n = 26)	Patients with VF/VT (n = 13)	Patients without VF/VT (n = 13)	P value
Presence of DE cardiac CT, n (%)	25 (96.1)	13 (100)	12 (92.3)	<.999*
Myocardial fibrosis mass (g), mean ± SD	20.5 ± 15.8	29.1 ± 19.3	13.6 ± 8.3	.01
Myocardial fibrosis (%), mean ± SD	16.5 ± 10.3	21 ± 10.5	11.8 ± 8.1	.02

DE, myocardial delayed enhancement; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Fisher exact test.

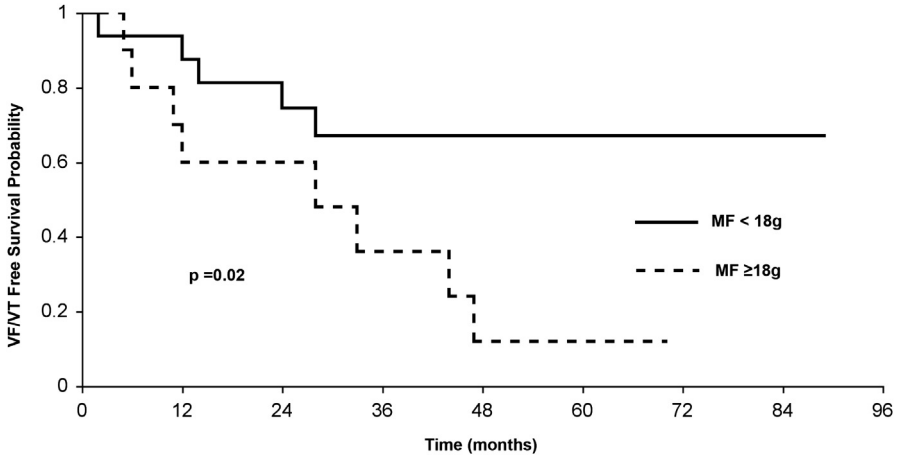

Figure 4 – Kaplan–Meier curve indicating VF/VT event-free survival for patients with myocardial fibrosis (MF) ≥18 g (*dotted line*) and < 18 g (*continuous line*). VF, ventricular fibrillation; VT, ventricular tachycardia.

exposure for patients who are young and who may otherwise have frequent diagnostic or therapeutic x-ray exposure as a result of their HCM diagnosis.

The purpose of this study was to establish a relationship between amount of MF by CT and ventricular arrhythmias in patients with HCM. For that purpose we have chosen a patient population that could be continuously monitored, in this case, by ICD. Thus, our study group was the patients with HCM with previously implanted ICD, but we did not investigate the clinical utility of using CT specifically for this subgroup. Nonetheless, we clearly not only established the relationship between MF and VF/VT but also defined a threshold of the amount of MF, beyond which, the risk for VF/VT is significantly increased. If that relationship and threshold will hold true for other subgroups of patients with HCM, it will require further studies.

In conclusion, we found a significant relationship between MF extent and life-threatening arrhythmias appropriately treated by an ICD in a high-risk group of patients with HCM.

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