

Myocardial Fibrosis as a Predictor of Ventricular Arrhythmias in Patients With Non-ischemic Cardiomyopathy

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Abstract. *Background/Aim:* The aim of the study was to assess the relationship between myocardial fibrosis characteristics (percentage, localization, heterogeneity), evaluated by a non-invasive method such as cardiac magnetic resonance (CMR), with the extrasystolic ventricular arrhythmia in patients with non-ischemic cardiomyopathy. *Patients and Methods:* The study prospectively included 173 consecutive patients who underwent electrocardiogram Holter monitoring, transthoracic echocardiography and CMR with late gadolinium enhancement (LGE). *Results:* In univariate analysis, both the presence (OR=1.05, 95% CI=1.01-1.09; $p=0.015$), the percentage of fibrosis >15% ($p=0.018$), the septum size, the fibrosis in either lateral or septal walls ($p=0.004$), as well as fibrosis in the midwall ($p=0.019$) were statistically significant higher in the group with extrasystolic arrhythmia. After adjustment, the percentage of fibrosis >15%, had higher odds of extra systolic arrhythmia [OR=3.78 (95% CI=1.52-10.62, $p=0.007$)]. *Conclusion:* The presence, percentage, and localisation of left ventricle myocardial fibrosis characterized by LGE-CMR was associated with ventricular arrhythmias.

Non-ischemic cardiomyopathy is a common heart muscle disease, without significant coronary artery impairment. The condition is associated with significant morbidity and mortality due to progressive heart failure (HF) and sudden cardiac death (SCD) (1, 2).

This article is freely accessible online.

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Key Words: CMR, non-ischemic Cardiomyopathy, Sudden cardiac death, Implantable cardioverter-defibrillator.

Implantation of an implantable cardioverter-defibrillator (ICD) has significantly reduced mortality in these patients (3, 4), but most of the selected patients according to current guidelines do not really benefit from it (5). At present, the only structural abnormality provided in the practice guidelines for SCD prevention is left ventricular ejection fraction (LVEF), but it is not representative of the pathogenetic substrate, being insensitive and nonspecific (6). Cardiovascular magnetic resonance imaging (CMR) is accepted as the modality of choice for LVEF assessment, being able to classify more accurately patients who benefit from ICD implantation than echocardiography (7).

The arrhythmogenic substrate that produces lethal ventricular arrhythmia and thus SCD, is shown to be myocardial fibrosis, even in the absence of contractile dysfunction (8). It is involved through various mechanisms such as enhanced normal automaticity, abnormal automaticity, triggered activity, and re-entry (9).

The presence and pattern of myocardial fibrosis is highlighted by late gadolinium enhancement (LGE) using CMR, being presently the noninvasive method of choice (10). In patients with no LGE, histopathology confirms the absence or presence of fibrosis (11). The most important elements assessed include LGE by extent, pattern, number of transmural segments (12), existing several patterns and different aspects described depending on the pathogenetic type of cardiomyopathy (13, 14). The possibility to characterize the myocardial tissue by LGE adds incremental prognostic value (15).

There are only few studies assessing LGE with ventricular arrhythmia in patients with non-ischemic cardiomyopathy, and many have a limited number of subjects (16). Furthermore, there is a lack in evidences regarding whether the distribution, location or heterogeneity is predictive of arrhythmias. Finally, the LVEF value as quantified by CMR remains questionable regarding the prediction of arrhythmias, and as a criterion of ICD therapy.

Therefore, the objectives of this study were to assess the relationship between the myocardial fibrosis characteristics

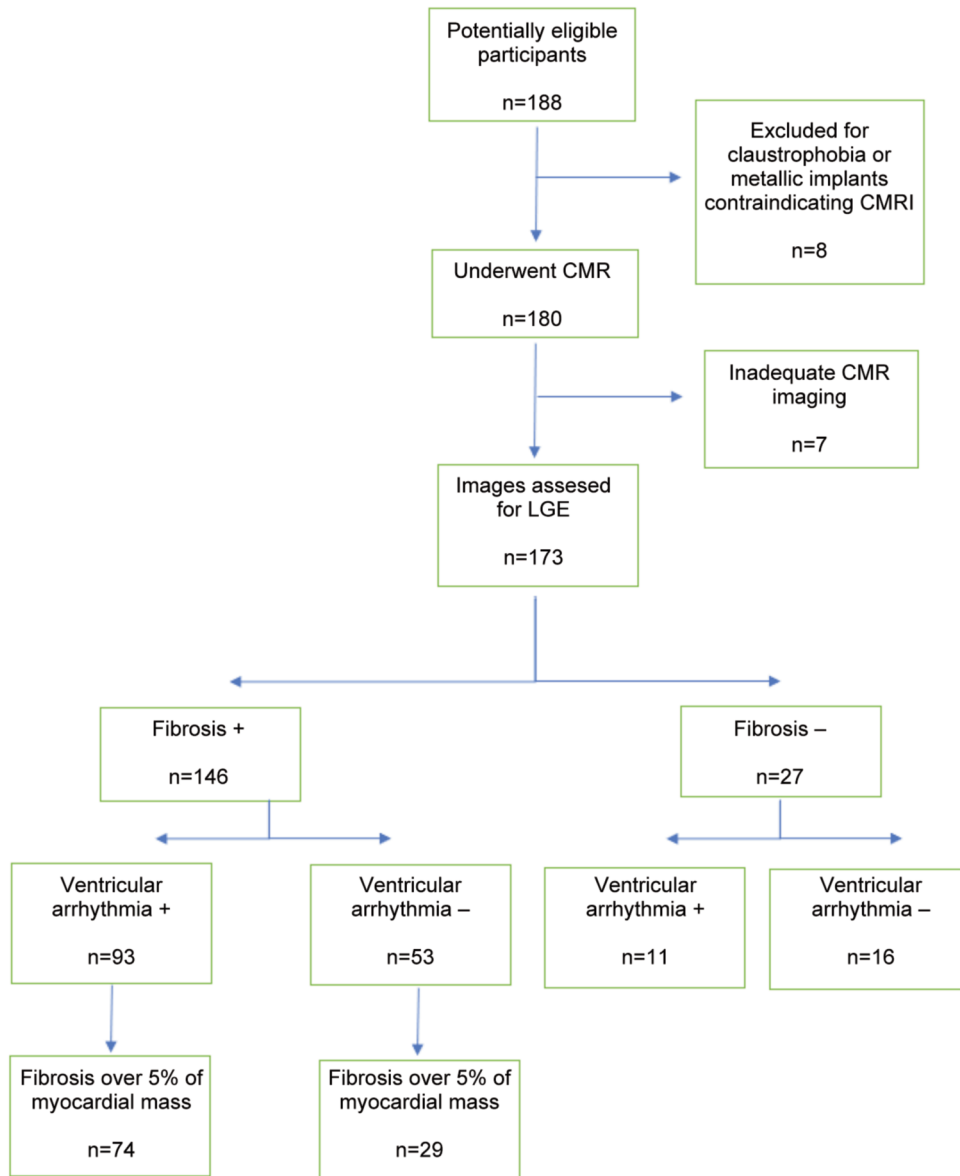


Figure 1. Flowchart showing the study cohort selection, and distribution of study outcomes.

(percentage, localization, heterogeneity), as well as of LVEF observed with the CMR with the extrasystolic ventricular arrhythmia in patients with non-ischemic cardiomyopathy.

Patients and Methods

Study design and setting. This prospective cohort study included 173 consecutive patients assessed in a regional Cardiology Institute between September 2017 and August 2019. Furthermore, we included patients from the hospital records between August 2016 and September 2017. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the

Ethics Committee of “Iuliu Hatieganu” University of Medicine and Pharmacy Cluj-Napoca (protocol code 154/02.04.2018).

Participants. The study included 173 subjects with magnetic resonance imaging (MRI) indication, suffering from cardiomyopathies of non-ischemic origin: dilated, hypertrophic and myocardial fibrosis of various non-ischemic etiologies including myocarditis. Inclusion criteria were: dilated cardiomyopathy, hypertrophic cardiomyopathy, myocardial fibrosis of various non-ischemic etiologies including myocarditis, availability of all clinical and lab data sustaining the diagnosis, Holter monitoring, complete cardiac MRI exam.

Subjects were excluded if they suffered from claustrophobia, had a history of a metallic prosthetic implant contraindicating CMR or

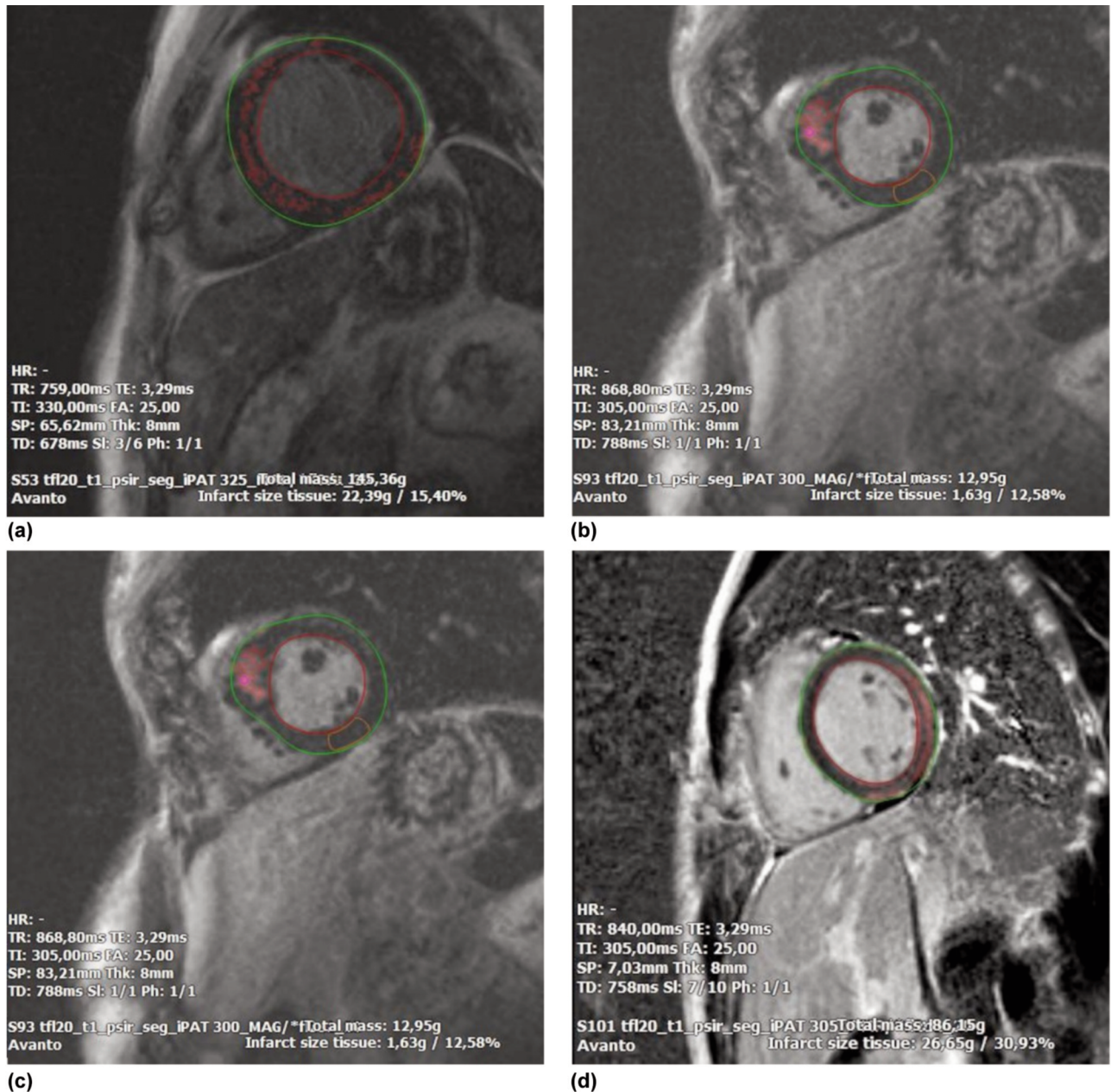


Figure 2. Example of contour tracing performed on Late Gadolinium Enhancement (LGE) imaging in a patient with (A) dilated cardiomyopathy, (B) hypertrophic cardiomyopathy, and (C-D) myocarditis. Endocardial border is shown in red, epicardial border shown in green, normal reference myocardium shown in an orange frame, a myocardial fibrosis reference contour is shown in pink circle. LGE volume analysis is shown by predefined signal thresholds using full-width-half-width (FWHW) approaches. Myocardial fibrosis in all cases represents more than 5% of the myocardial mass.

contraindications for contrast administration. In addition, there were several patients with uncontrolled arrhythmias who generated significant acquisition artifacts, the MRI examination not being interpretable. The setting up of the study group is presented in Figure 1.

The patients underwent electrocardiogram (EKG) Holter monitoring, transthoracic echocardiography and CMR examinations during hospitalization, which in most cases did not

exceed 7 days. All subjects had complete image acquisition required to evaluate LGE. All of them were enrolled in research protocols after providing written informed consent. The study was carried out with the approval of the University of Medicine and Pharmacy Ethics Commission.

Variables and data sources. The main outcome measures were ventricular extrasystoles and/or ventricular tachycardia, as recorded

by 24h Holter monitoring. The exposure variables were the myocardial fibrosis characteristics (percentage, heterogeneity, localization, transmural extension), as well as of left ventricular ejection fraction, as found by CMR scans. As main predictors and potential confounders, the age, ischemic cardiomyopathy, and heart disease type were assessed.

CMR image acquisition. All subjects underwent CMR scans in a 1.5-T scanner (Avanto MRI system - Siemens Medical Systems, Erlangen, Germany) with an eight-element phased-array surface coil. Retrospective electrocardiographic gating was used during a breath-hold of 10 to 15 s for cardiac volumes and systolic function assessment.

After initial localizer sequences, a stack of steady-state free precession cine images were acquired in the short axis plane from the level of the mitral valve annulus to the left ventricle (LV) apex (Repetition time - TR 3.8 ms, echo time - TE 1.6 ms, 30 phases, slice thickness 8 mm no gap; flip angle 70°; average in-plane resolution 1.3×1.3 mm²). A stack of three long-axis planes (two, three, and four-chamber) was also obtained.

A phase-sensitive inversion recovery sequence for LGE was performed 10 min after the intravenous administration of 0.1 mmol/kg of Gadobutrol (Gadovist, Gadavist; Bayer Pharma AG, Leverkusen, Germany) on a stack of LV diastolic short-axis slices with the following parameters: TE 3.17 msec; TR 1× RR interval; flip angle 25°; voxel size 1.9×1.4×8 mm³; and field of view 360×290 mm².

A scout with increasing inversion time values was performed on a midventricular short-axis slice to determine the inversion time that allowed for optimal nulling of normal myocardium before the LGE images were obtained.

CMR image analysis. Volumetric analysis for quantification of LV volumes and LVEF was based on consecutive short-axis stacks of cine images using QMASS software (Medis Medical Imaging, Leiden, the Netherlands). Papillary muscles were regarded as part of the ventricular cavity. LV volumes and mass were normalized to body surface area.

LGE was assessed by two readers (by a senior and a junior reader) with consensus reading, and was defined as being present only if it was identified in both long-axis and short-axis views. Myocardial fibrosis analysis was performed using QMASS software (Medis Medical Imaging). Endocardial and epicardial LV myocardial borders were manually delineated on the short axis LGE-CMR images (Figure 2).

For LGE volume quantification, the full width at half maximum technique (FWHM) method was used, which takes half of the maximal signal intensity within the myocardial fibrosis as a cutoff for a scarred myocardium. Areas identified as a myocardial fibrosis by the software but not deemed to be myocardial fibrosis by the user were excluded manually.

The FWHM technique for LGE quantification is considered the most reproducible, regardless of underlying etiology, across the spectrum of cardiac disease in which LGE quantification is known to be important. It reduces the required sample sizes by up to one-half compared to other techniques used in the past (17).

Several complementary aspects of myocardial fibrosis were quantified: presence; heterogeneity; amount of myocardial fibrosis expressed as a percentage of the total LV myocardial mass; affected myocardial segments classified according to the standard American Heart Association 17-segment model; number of transmural affected segments.

Table I. Patient clinical characteristics.

Extrasystolic ventricular arrhythmia:	Yes (n=104)	No (n=65)	p-Value
Age (years), mean (SD)	46.04 (16.5)	47.23 (15.79)	0.643 [n1=104, n2=65]
Gender (F), no (%)	26 (24.53)	21 (31.34)	0.326
BMI (kg/m ²), mean (SD)	26.15 (5.04)	26.71 (4.2)	0.485 [n1=100, n2=56]
Smoker, no (%)	47 (46.08)	21 (37.5)	0.298
Diabetes mellitus, no (%)	21 (20.59)	11 (19.64)	0.888
SBP (mmHg), median (IQR)	120 (110-130)	120 (110-140)	0.223 [n1=97, n2=53]
DBP (mmHg), median (IQR)	75 (62-80)	80 (70-80)	0.148 [n1=97, n2=53]
Associated cardiovascular diseases, no (%)	82 (91.11)	41 (83.67)	0.189
Family history of SCD, no (%)	7 (12.96)	2 (7.14)	0.711
Syncope, n (%)	4 (4.04)	0 (0)	0.299

SD, Standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SCD, sudden cardiac death.

Statistical analysis. Categorical data were presented as counts and percentages. Normally distributed continuous data were presented as means and standard deviations, while data not following the normal distribution were presented as medians and interquartile ranges. Comparing two groups of categorical data was performed using the chi-squared test or the Fisher exact test (in case of low expected frequencies). Comparing two groups of normally distributed continuous data were performed with the *t*-test for independent samples, while for data not following the normal distribution, the Wilcoxon rank-sum test was used. In order to assess the relationship between the myocardial fibrosis characteristics (percentage, heterogeneity, localization), as well as of LVEF observed with the MRI with the extrasystolic ventricular arrhythmia, and then multivariate logistic regression models for this association were built. The models included known or physiopathological likely implicated characteristics in this relation: age, septal wall involvement, lateral wall involvement, ischemic cardiomyopathy, heart disease type. Next, since the dataset contained some missing values, an iterative imputation method based on random forests (18) was used for the variables included in the regression. Then the main multivariate model (model 1: age (years), myocardial fibrosis >15% (26), myocardial fibrosis heterogeneity, septal wall fibrosis, lateral wall fibrosis, ischemic cardiomyopathy, LVEF MRI) was fitted again on these data. The main multivariate model (model 1) was specified to have no more than 7 degrees of freedom – when predicting the extra systolic ventricular arrhythmia, to prevent overfitting. For all the models, the goodness-of-fit with the Hosmer and Lemeshow test was checked. For continuous predictors, the assumption of linearity to the logit using splines was checked, and it was found that the percentage of myocardial fibrosis assumption did not hold; thus, was

Table II. Heart-related characteristics comparison between extrasystolic ventricular arrhythmia.

Extrasystolic ventricular arrhythmia:	Yes (n=106)	No (n=67)	p-Value
NYHA class, n (%)	1: 26 (27.96) 2: 27 (29.03) 3: 39 (41.94) 4: 1 (1.08)	1: 18 (36) 2: 14 (28) 3: 18 (36) 4: 0 (0)	0.751
Ventricular tachycardia, n (%)	48 (45.28)	9 (13.43)	<0.001
Interventricular septal diameter, median (IQR)	10 (8-11)	11 (10-13)	<0.001
LV Lateral wall diameter, median (IQR)	7.75 (6-10)	9 (6.25-11)	0.347
Myocardial fibrosis mass (g), median (IQR)	16.56 (5.97-26.6)	7.32 (0-16.64)	<0.001
Myocardial fibrosis (%), median (IQR)	11.72 (5.26-17.18)	7.42 (0-12.46)	0.002
Myocardial fibrosis, n (%)	95 (89.62)	51 (76.12)	0.017
Myocardial fibrosis >5%, n (%)	75 (76.53)	28 (54.9)	0.007
Myocardial fibrosis >15%, n (%)	30 (30.61)	7 (13.73)	0.024
Myocardial fibrosis heterogeneity, n (%)	63 (64.95)	28 (56)	0.29
Basal, n (%)	76 (73.08)	40 (61.54)	0.116
Mid, n (%)	80 (76.92)	39 (60)	0.019
Apical, n (%)	50 (48.08)	33 (50.77)	0.733
Lateral wall or septum involvement, n (%)	92 (86.79)	46 (68.66)	0.004

NYHA, New York Heart Association; LV, left ventricle; IQR, interquartile range.

used the percentage of myocardial fibrosis >15% instead (26). For the multivariable logistic regression models, the multicollinearity and the functional form were checked. For all models, the odds ratio, along with the 95% confidence interval and the *p*-value were reported. For all statistical tests used, a significance level alpha of 0.05 was chosen, and the two-tailed *p*-value was computed. All statistical analyses were carried out with the R environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria), version 4.0.2 (19).

Results

The study sample consisted of 173 patients diagnosed with dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis. The mean age of patients was 46.5 years (SD=16.2 years), ranging from 9 to 81 years old. The majority of patients were males (n=126) (72.8%). There were no statistically significant differences between patients with and without extrasystolic arrhythmia regarding the main clinical characteristics (Table I).

Regarding heart pathology, the cardiomyopathy type, and the New York Heart Association (NYHA) class were similar between patients with and without extrasystolic arrhythmia (Table II). Similarly, the heart weight and the left ventricle wall-size were not statistically significantly different between the two groups. However, the septum size was statistically significant larger in the group without extrasystolic arrhythmia. The mass and percentage of fibrosis were statistically significant higher in the group with extrasystolic arrhythmia. Other findings were that fibrosis in either lateral or septal walls, and fibrosis in the midwall were statistically

significant more frequent in the group with extrasystolic ventricular arrhythmia.

In order to characterize the relationship between myocardial fibrosis characteristics (percentage, heterogeneity, localization), as well as of LVEF observed with the MRI with the extrasystolic ventricular arrhythmia, several logistic regression models were built (Table III). An increased percentage of myocardial fibrosis was statistically significantly associated with extrasystolic ventricular arrhythmia episodes in the univariate model. Furthermore, a model (model 1) was built including age (years), myocardial fibrosis >15%, myocardial fibrosis heterogeneity, septal wall fibrosis, lateral wall fibrosis, ischemic cardiomyopathy, LVEF MRI variables. In this model the relation between of myocardial fibrosis and extrasystolic ventricular arrhythmia episodes, was close to the statistical significance level, as well as in a model that included the heart disease types. Finally, model 1 was fitted on the same dataset, but with missing values imputed. Here too, an increased percentage of myocardial fibrosis was found, being statistically significant associated with extrasystolic ventricular arrhythmia episodes. However, in all models the myocardial fibrosis heterogeneity, the fibrosis localization (septal wall, or lateral wall), as well as LVEF MRI were not statistically significant associated with the extrasystolic ventricular arrhythmia episodes. There was no statistically significant relation between the heart disease type and the extrasystolic ventricular arrhythmia episodes in the univariate and multivariate models (where it was used to control for confounders). Model 1 was computed on 173 observations. The Hosmer Lemeshow goodness of fit test *p*-value was 0.341. For

Table III. Univariate and multivariate logistic regression models predicting extrasystolic ventricular arrhythmia in relation to myocardial fibrosis characteristics.

Characteristic	OR unadjusted*	(95% CI)	p-Value	OR adjusted Model 1*	(95% CI)	p-Value	OR adjusted Model 1 with imputation	(95% CI)	p-Value	OR adjusted Model 2 with imputation	(95% CI)	p-Value
Age (years)	1	(0.98-1.02)	0.921	1	(0.98-1.02)	0.965	1.01	(0.98-1.03)	0.63	1	(0.98-1.02)	0.884
Myocardial fibrosis %	1.05	(1.01-1.09)	0.015									
Myocardial fibrosis >15%	2.99	(1.27-7.92)	0.018	2.4	(0.89-7.15)	0.096	2.81	(1.02-8.64)	0.056	3.78	(1.52-10.62)	0.007
Myocardial fibrosis	1.49	(0.74-2.98)	0.258	0.92	(0.4-2.06)	0.836	0.99	(0.41-2.32)	0.979	0.76	(0.36-1.57)	0.472
heterogeneity												
Septal wall	1.68	(0.84-3.36)	0.141	2	(0.87-4.65)	0.104	1.99	(0.84-4.79)	0.119	1.8	(0.82-4)	0.145
Lateral wall	1.39	(0.75-2.58)	0.302	1.23	(0.55-2.73)	0.614	1.25	(0.55-2.83)	0.597	1.02	(0.49-2.08)	0.963
LVEF MRI	0.99	(0.97-1.01)	0.205	0.98	(0.96-1)	0.125	0.99	(0.97-1.02)	0.668	0.99	(0.97-1)	0.151
Heart disease												
Dilative cardiomyopathy	1	ref	ref	1	ref	ref	1	ref	ref	1	ref	ref
Hypertrophic cardiomyopathy	0.56	(0.22-1.38)	0.204				0.34	(0.09-1.29)	0.119	0.43	(0.12-1.44)	0.173
Myocarditis	0.91	(0.42-2.02)	0.811				0.81	(0.25-2.55)	0.718	0.88	(0.3-2.59)	0.817

OR, Odds ratio; CI, confidence interval; LVEF MRI, magnetic resonance imaging measured left ventricular ejection fraction; *the models built without imputation; ref, reference group. Model 1 includes: age, myocardial fibrosis >15%, myocardial fibrosis heterogeneity, septal and lateral wall fibrosis presence, LVEF MRI; Model 2 includes additionally to model 1 the heart disease type.

this model, the overall percent of correct classification was 66.5%, and the area under the receiver operating characteristic was 69.2 (61.1-77.2).

Discussion

The present study provides further support for the predictive utility of LGE quantification in patients with non-ischemic cardiomyopathy (NICM). The study succeeded to objectify that: i) myocardial fibrosis was a common feature in NICM; ii) regardless of cardiomyopathy etiology, there was an association between ventricular arrhythmias and the presence, percentage (threshold value of 15% of myocardial mass), and specific location of fibrosis; iii) a significant association between LVEF or and ventricular arrhythmias was not observed. Likewise, no significant association was observed with the NYHA class.

LGE assessment using CMR is considered the noninvasive method of choice for imaging the presence and pattern of myocardial fibrosis (10). We found that both the presence and extent of myocardial fibrosis were associated with an increased likelihood of ventricular arrhythmias. A significant association from a threshold value of 15% of myocardial mass was observed. This association was independent of LVEF, NYHA class and other established prognostic factors. Our findings suggest that detection and quantification of midwall fibrosis by LGE-CMR may represent useful markers for the risk stratification of ventricular arrhythmia, and possibly (further studies needed) HF and death for patients with non-ischemic cardiomyopathy. There are other studies that support this aspect, where a relation between LGE transmural and an increased risk for arrhythmic events was also found (20, 21). Regarding the subgroup of patients with hypertrophic cardiomyopathy (HCM), there are two independent studies that have consistently found that a large amount of LGE predicts major adverse cardiac events in patients with hypertrophic cardiomyopathy (22, 23), a threshold value of 15% being suggested by Chan *et al.* (24).

The present study observed that fibrosis in either lateral or septal walls, as well as fibrosis in the midwall are statistically significant more frequent in the group with extrasystolic ventricular arrhythmia. The midwall localization was also observed in the study carried out by Gulati *et al.*, where patients with chronic dilated NICM had an increased frequency of a secondary composite arrhythmic end point consisting of SCD or aborted SCD (21).

In this study a possible link between extrasystolic ventricular arrhythmia and LVEF was analyzed. No association was found, irrespective of NICM etiology, even though MRI examination is considered the gold standard in its calculation because of its high accuracy and reproducibility (25). The same was observed by analyzing the NYHA class. As in the present study, the studies performed

by Almeshmadi and Gulati observed that LVEF was not associated with arrhythmic events in dilated cardiomyopathy suggesting that the prognostic value of LGE by CMR might be superior and independent from LVEF (21, 26).

Myocardial fibrosis assessed by CMR can ameliorate clinical practice regarding therapeutic decisions in non-ischemic cardiomyopathy patients. The significant link between myocardial fibrosis and arrhythmias suggests an increased risk of sudden cardiac death through malign arrhythmias. This SCD can be prevented with ICD implantation. Therefore, assessing myocardial fibrosis by CMR, can be an important decision criterion in deciding ICD implantation. Current clinical guidelines recommend ICD implantation in patients with advanced HF using LVEF as the main criterion. But, it was shown that the majority of patients never receive appropriate therapy (5). Therefore, selecting patients for ICD therapy based on LVEF alone, is an imperfect and inexact method. The present study observed a significant link between myocardial fibrosis and arrhythmias, and no significant association between LVEF was measured by the reference method (CMR) or the NYHA class. Therefore, CMR could add incremental prognostic value, with its precise tissue characterization, leading to better classifying patients who benefit from ICD implantation, and in determining their treatment with ICD. One possibility could be the replacement of LVEF criterion altogether, with myocardial fibrosis assessed by CMR, in the choice of ICD implantation. Another possibility could be the use of CMR as a supplementary criterion along LVEF. On one hand, patients who fall outside current indications could benefit from ICD, and have their life expectancy improved. Thus, in asymptomatic patients with normal LVEF, a high myocardial fibrosis would help the decision to introduce ICD therapy. A reduced myocardial fibrosis would reassure that there is no need for ICD therapy. On the other hand, in patients with low LVEF, the absence of myocardial fibrosis might avoid ICD implantation due to low risk of arrhythmias, and low risk of SCD. This might bring major benefits due to the limitation of exposure to specific complications of the device implantation, and lower costs, in patients who have a low risk of SCD (where ICD therapy would have a reduced benefit, without a significant improvement in life expectancy). Another important fact is that, according to Chen *et al.*, the absence of focal myocardial fibrosis (as our study quantified too) is associated with better response to LV reverse modeling following cardiac resynchronization therapy (CRT) (27). Also, there is a lower rate of arrhythmic events observed in responders to CRT (28). Thus, if there are patients without myocardial fibrosis, with high prognosis for LV remodeling, it would be more appropriate to install a pacemaker and not a defibrillator. Taking all this into account myocardial fibrosis assessed by CMR might have an important role on ameliorating clinical practice regarding complex decisions in the use of ICD therapy or CRT, and also in its cost-effectiveness.

The strengths of our study are represented by its number of subjects, which is higher than that of many other studies carried out on this topic. Also, myocardial fibrosis was evaluated quantitatively. Moreover, besides assessing the fibrosis degree relation with arrhythmias, it also checked the location and heterogeneity of fibrosis, which were found to be important.

Regarding limitations, the diffuse myocardial fibrosis has not been analyzed, through techniques such as T1 mapping and extracellular volume fraction calculation. LGE only assesses fibrosis distributed in a regional pattern. Diffuse myocardial fibrosis is also likely to influence the development of ventricular arrhythmias. A limitation of the MRI technique is its specific absolute and relative contraindications or related to contrast injection. In addition, there were several patients with significant arrhythmias who generated significant acquisition artifacts, the MRI examination not being interpretable. Since this study is observational in nature, residual confounding cannot be ruled out. To minimize this bias, we adjusted the regression for known important confounders.

Conclusion

The present study showed that above 15% fibrosis of the total myocardial mass was significantly correlated with malignant arrhythmias. This observation suggests that a new criterion for ICD therapy could be the percentage of fibrosis from the total myocardial mass. Other findings were that fibrosis in either lateral or septal walls, as well as fibrosis in the midwall were statistically significant more frequent in the group with extrasystolic ventricular arrhythmia in univariate analyses.

The present study did not find any statistical relationship between LVEF and the frequency of arrhythmic events. This suggest that LVEF might not be an optimal predictor of arrhythmic events in NICM, even though it is an important criterion in the introduction of ICD therapy. Therefore, the prognostic value of fibrosis as LGE quantified by CMR was superior and independent from LVEF and could be a powerful tool to improve risk stratification in patients irrespective of NICM etiology.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, C.S., S.M.D. and S.M.; methodology, C.S., D.C.L., S.M.D. and S.M.; software, S.M.; validation, C.S. and S.M.; formal analysis, C.S., D.C.L., S.M.D. and S.M.; investigation, C.S.; resources, S.M.D. and S.M.; data curation, C.S., D.C.L. and S.M.; writing—original draft preparation, C.S.; writing—review and editing, C.S.,

D.C.L., S.M.D. and S.M.; visualization, C.S.; supervision, S.M.D. and S.M.; project administration, S.M.D. and S.M. The Authors had full access to the data and take responsibility for its integrity. All Authors have read and agreed to the manuscript as written.

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Received January 24, 2021

Revised February 10, 2021

Accepted February 18, 2021