International Journal of Cardiology 284 (2019) 105–109

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiovascular magnetic resonance imaging pattern in patients with autoimmune rheumatic diseases and ventricular tachycardia with preserved ejection fraction

Sophie I. Mavrogeni [a,*], Petros P. Sfikakis [b], George Markousis-Mavrogenis [a], Vasiliki-Kalliopi Bournia [b], George Poulos [a], Loukia Koutsogeorgopoulou [b], Georgia Karabela [c], Efthymios Stavropoulos [c], Gikas Katsifis [c], Kyriaki Boki [d], Vasiliki Vartela [a], Genovefa Kolovou [a], George Theodorakis [a], George D. Kitas [e]

[a] Onassis Cardiac Surgery Center, Athens, Greece
[b] Joint Rheumatology Programme, National and Kapodistrian University of Athens Medical School, Athens, Greece
[c] Naval Hospital, Athens, Greece
[d] Sismanoglion Hospital, Athens, Greece
[e] Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, UK

ARTICLE INFO

Article history:
Received 10 August 2018
Received in revised form 22 September 2018
Accepted 22 October 2018
Available online 25 October 2018

Keywords:
Cardiovascular magnetic resonance
Autoimmune rheumatic diseases
Ventricular tachycardia
Myocardial oedema
Myocardial fibrosis
Implantable defibrillators

ABSTRACT

Background: Ventricular tachycardia/fibrillation (VT/VF) may occur in autoimmune rheumatic diseases (ARDs). We hypothesized that cardiovascular magnetic resonance (CMR) can identify arrhythmogenic substrates in ARD patients.
Patients - methods: Using a 1.5 T system, we evaluated 61 consecutive patients with various types of ARDs and normal left ventricular ejection fraction (LVEF) on echocardiography. A comparison of patients with recent VT/VF and those that never experienced VT/VF was performed. CMR parameters included left and right ventricular (LV and RV) end-systolic and end-diastolic volumes (ESV and EDV), T2 signal ratio of myocardium over skeletal muscle, early/late gadolinium enhancement (EGE and LGE), T1/T2-mapping and extracellular volume fraction (ECV).
Results: 21 (34%) patients had a history of recent, electrocardiographically identified, VT/VF. No demographic or functional CMR variables differed significantly between groups. The same was the case for T2 signal ratio and EGE/LGE. Median native T1 mapping values were significantly higher in patients with VT/VF compared to those without [1135.0 (1076.0, 1201.0) vs. 1050.0 (1025.0, 1078.0), $p < 0.001$], as was the case for mean T2 mapping [60.4 (6.6) vs. 55.0 (7.9), $p = 0.009$] and median ECV values [32.0 (30.0, 32.0) vs. 29.0 (28.0, 31.5), $p = 0.001$]. After multivariate corrections for age, LVEDV, LVEF, RVEDV, RVEF, T2 signal ratio, EGE and LGE, these remained significant predictors of having experienced VT/VF in the past.
Conclusions: T1/T2-mapping and ECV offer incremental value as identifiers of arrhythmogenic substrates in ARD patients, beyond traditionally used indices. They can thus guide implantable cardiac defibrillator (ICD) implantation in ARD patients presenting with VT/VF and normal LVEF.

1. Introduction

Ventricular tachycardia/fibrillation (VT/VF) remains the most frequent cause of sudden cardiac death (SCD) in developed countries, occurring in 1–2 per 1.000 inhabitants each year [1]. The majority of patients with VT have few evident clinical signs and symptoms and SCD is usually the first presentation of an underlying cardiac disease [2]. Autoimmune rheumatic diseases (ARDs) constitute no exception in this regard. Non-sustained ventricular tachycardia (NSVT) or sustained ventricular tachycardia (VT) may either occur as the first presenting sign at diagnosis or later during the course of the disease [3]. More specifically, the prevalence of NSVT/VT in patients with systemic sclerosis (SSc) has been reported as 7–13%, while the incidence of SCD is 5–21% in unselected SSc patients [3]. Employed treatment modalities in such cases include ablation of arrhythmogenic loci [4] and/or implantation of implantable cardiac defibrillators (ICD) [5]. NSVT and VT may constitute the first disease manifestation in patients with systemic lupus erythematosus (SLE) [6] and chloroquine, a medication frequently used in the treatment of SLE, may protect from cardiac rhythm disturbances in these patients [7]. NSVT/VT episodes have also been reported in patients with rheumatoid arthritis (RA) during

* Corresponding author at: 50 Esperou Street, 175-61 P. Faliro, Athens, Greece.
E-mail addresses: soma13@otenet.gr (S.I. Mavrogeni), psfikakis@med.uoa.gr (P.P. Sfikakis), gkarabel@otenet.gr (G. Karabela), kboki@otenet.gr (K. Boki), genovefa@kolovou.com (G. Kolovou), kitas@dgh.nhs.uk (G.D. Kitas).

https://doi.org/10.1016/j.ijcard.2018.10.067
0167-5273/

infusion of infliximab [8] or after treatment with other anti-TNF monoclonal antibodies [9] and in patients with various types of vasculitides [10]. It is now clear that Kawasaki disease (KD) can be complicated by both myocarditis and cardiac vasculitis. Even if these entities are asymptomatic, episodes of NSVT/VT may be identified during the course of KD [11]. Patients with dermatomyositis and polymyositis may also exhibit recurrent episodes of NSVT or VT [12–14]. Ventricular arrhythmias may also occur in patients with other ARDs including polymyalgia rheumatica and giant cell myocarditis [13–17]. Although risk stratification in ARD patients at risk of SCD and primary prevention of SCD are of tremendous importance, no screening methods that can facilitate these desirable processes with acceptable reliability currently exist.

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging modality that does not utilize ionising radiation and has successfully been used for the evaluation of a multitude of cardiac diseases. The ability of CMR to characterize myocardial tissues with regard to the presence of myocardial oedema and replacement fibrosis, the latter using late gadolinium enhanced images (LGE), is of great value for guiding decision making in ARD patients with VT [18]. However, VT may occur without any evidence of fibrotic substrate to the extent this is identified in LGE images. Recently, the introduction of T1-mapping and the derivation of the extracellular volume fraction (ECV) in the myocardium has allowed for the detection of diffuse myocardial fibrosis, which would otherwise not be detected with conventional LGE images [19]. Furthermore, myocardial oedema has also been implicated as a causative factor for VT/VF in ARDs [20]. Oedema represents the acute myocardial reaction to any acute injury, be that ischemic or non-ischemic [20]. The presence of excess myocardial interstitial fluid increases the stiffness and decreases the compliance of the left ventricle (LV) [20]. Presence of myocardial oedema has been documented in a number of ARDs either at diagnosis or during the course of the underlying disease, even during seemingly quiescent phases [18,20].

Both myocardial oedema and fibrosis are the result of various pathologic processes, such as macrovascular and microvascular coronary artery disease, vasculitis or myocarditis and represent important pathophysiologic phenomena that can potentially lead to cardiac lesions in ARDs. Importantly, this can still be the case even if the left ventricular ejection fraction (LVEF) is preserved [18,20,21].

We hypothesized that CMR could provide important insights about potential arrhythmogenic substrates in patients with ARDs, due to its ability to characterize myocardial tissues with regard to oedema and fibrosis. The aim of our study was to evaluate, using CMR, adult patients with various ARDs and normal LVEF, who presented with recent episodes of VT/VF and to compare their CMR findings with those of ARD patients without VT/VF.

2. Patients - methods

2.1. Patients

A cohort of 61 consecutive patients with various ARDs and preserved LVEF (as assessed by echocardiography) were recruited and evaluated with CMR. The study population was selected based only on a previous ARD diagnosis blinded to other patient characteristics. After selection of the study population, 21 (34%) patients were discovered to have a history of recent VT/VF (last 1 month), as assessed either by 24 h Holter recording or by electrocardiography at the emergency outpatient clinic and 40 (66%) patients not having a history of VT/VF. The study was approved by the hospital ethics committee and all participants signed written inform consent.

2.2. Methods

CMR examinations were performed using a 1.5-T scanner (Ingenia, Philips Medical Systems, Best, The Netherlands). The CMR protocol included standard steady-state free-precession cine CMR, black-blood T2-weighted short tau inversion recovery images, T1-weighted spin-echo early gadolinium enhancement (EGE) images, and phase-sensitive inversion recovery late gadolinium enhancement (LGE) images as described previously. A dose of 0.1 mmol/kg gadobenate dimeglumine contrast-medium was injected for early gadolinium enhanced (EGE) images and another 0.1 mmol/kg for late gadolinium enhanced (LGE) images, according to the protocol suggested by the Lake Louise criteria [21].

T1-mapping was performed using a modified Look-Locker inversion recovery (MOLLI) sequence with a 3(3)5 scheme on 3 representative short-axis positions immediately before and 15 min after contrast-medium administration. T2-mapping was performed on 3 corresponding LV short axes using a black-blood prepared, navigator-gated, free-breathing hybrid gradient (echo planar imaging) and spin-echo multiecho sequences [18].

2.3. CMR data analysis

The short axis steady-state free-precession cine CMR was used to evaluate biventricular function (volumes and ejection fractions) according to the standard protocol [21]. Global myocardial inflammation was assessed on T2-weighted images by calculating the T2 signal intensity ratio as signal intensity of myocardium divided by signal intensity of skeletal muscle [21]. Global relative enhancement was calculated by measuring myocardial signal intensity on pre- and post-contrast T1-weighted spin-echo images relative to skeletal muscle [21]. The presence and pattern of non-ischemic LGE lesions were qualitatively assessed by consensus agreement of 2 experienced observers and expressed as a percentage of left ventricular mass (%LGE). Native and post-contrast T1, ECV, and T2 maps were generated using dedicated plug-ins written for the OsiriX software as described previously [22,23]. Global native/post-contrast myocardial T1, ECV, and T2 values were calculated as the mean value of 3 short-axis slices.

2.4. Validation of T1 and T2 measurements

The accuracy of the T1 and T2 mapping methods was evaluated by a relaxometry study in a Eurospin Gel-Phantom (TO5, Diagnostic Sonar LTD, Livingston, Scotland): the comparison of T1 values obtained by the MOLLI 3(3)5 and a reference scan has been previously reported [24]. T2 values obtained by the black-blood–prepared multiecho hybrid gradient and spin-echo sequence were compared with a spin-echo reference sequence with 16 echoes, 8-ms echo spacing, and 10-second time to repetition. Furthermore, myocardial T2 values were measured in 16 myocardial segments in an additional control group to assess reproducibility and regional variations of estimated myocardial T2 signals [24]. This control group consisted of 11 healthy subjects (median age, 25 years [IQR 24–28 years]) without symptoms or a history of any cardiovascular disease. In addition, interscan reproducibility was assessed for myocardial T1 and for T2 measurements by performing 10 repeated scans with identical imaging parameters. The interobserver reproducibility of 0.85 was assessed between 2 blinded observers in all subjects.

2.5. Statistical analysis

Statistical analyses were carried out with Stata SE v.15. Normality of variables was determined using Q-Q plots and histograms when necessary. Normally distributed variables are presented as mean (standard deviation), not – normally distributed continuous variables are presented as median (interquartile range) and binary/categorical variables are presented as n (%). Differences in variables between patients with and without VT were investigated with independent sample *t*-tests for normally distributed variables, Mann-Whitney *U* tests for continuous not-normally distributed variables and chi-square tests for categorical or binary variables. Logistic regression analysis was used to implement multivariate corrections for CMR indices that differed significantly between groups in univariate testing. Statistical significance for all tests was considered for $p \leq 0.05$.

3. Results

Baseline characteristics for the complete cohort of patients are presented in Table 1. Mean age was 46.9 (12.0) years, 21 (34%) patients experienced VT before the CMR examination and the most prevalent ARDs in this cohort were SLE [17 (28%)], SSc [15 (25%)] and sarcoidosis [6 (10%)]. Within the subgroups of SLE and SSc patients, 3/17 (18%) and 8/15 (53%) patients experienced VT in the past, respectively. The resulting p-values of univariate statistical testing of the same characteristics between patients with and without VT are also presented separately in Table 1.

No demographic variables or functional CMR indices differed significantly between groups. The same was the case for T2 signal ratio and EGE/LGE. Median native T1 mapping values were significantly higher in patients that experienced VT compared to those that did not [1135.0 (1076.0, 1201.0) vs. 1050.0 (1025.0, 1078.0), $p < 0.001$], as was the case for mean T2 mapping values [60.4 (6.6) vs. 55.0 (7.9), $p = 0.009$] and median ECV values [32.0 (30.0, 32.0) vs. 29.0 (28.0, 31.5), $p = 0.001$]. Median post-contrast T1 mapping values were in turn significantly lower in patients with VT compared to those without [340.0 (304.0, 377.0) vs. 387.0 (352.5, 410.5), $p = 0.013$]. Subgroup analyses for the two most prevalent ARDs in our cohort (SLE and SSc)

Table 1
Baseline characteristics for the entire cohort of 61 patients and separately for patients with and without ventricular tachycardia. Displayed p-vales refer to differences in variables between patients with and without ventricular tachycardia.

Variable	Total cohort	Patients without VT	Patients with VT	p-Value
Number of patients	61	40	21	N/A
ARD type:				
Granulomatosis with polyangiitis	2 (3%)	1 (3%)	1 (5%)	0.40
Eosinophilic granulomatosis with polyangiitis	5 (8%)	2 (5%)	3 (14%)	
Systemic sclerosis	15 (25%)	7 (18%)	8 (38%)	
Systemic lupus erythematosus	17 (28%)	14 (35%)	3 (14%)	
Sarcoidosis	6 (10%)	3 (8%)	3 (14%)	
Ankylosing spondylitis	4 (7%)	3 (8%)	1 (5%)	
Rheumatoid arthritis	4 (7%)	2 (5%)	2 (10%)	
Adamantiades-Behcet syndrome	3 (5%)	3 (8%)	0 (0%)	
Juvenile rheumatoid arthritis	1 (2%)	1 (3%)	0 (0%)	
Mixed connective tissue disease	1 (2%)	1 (3%)	0 (0%)	
Antiphospholipid syndrome	1 (2%)	1 (3%)	0 (0%)	
Takayasu arteritis	2 (3%)	2 (5%)	0 (0%)	
Age	46.9 (12.0)	46.3 (13.9)	48.0 (7.4)	0.60
Occurrence of VT	21 (34%)	N/A		
LVEDV	127.2 (36.5)	128.5 (39.6)	124.7 (30.2)	0.70
LVESV	45.0 (35.0, 54.0)	47.5 (35.0, 59.5)	43.0 (37.0, 51.0)	0.61
LVEF	63.0 (60.0, 68.0)	63.0 (60.0, 68.0)	63.0 (60.0, 68.0)	1.00
RVEDV	112.5 (32.1)	114.3 (34.8)	109.1 (26.7)	0.56
RVESV	42.1 (15.2)	42.2 (16.0)	41.8 (14.1)	0.91
RVEF	64.0 (60.0, 67.0)	64.0 (60.0, 66.0)	63.0 (56.0, 68.0)	0.65
T2 Ratio	2.2 (1.8, 2.6)	2.0 (1.7, 2.6)	2.3 (2.0, 2.8)	0.078
EGE	2.2 (1.2, 4.0)	2.6 (1.2, 3.1)	1.9 (1.4, 4.6)	0.88
LGE (%)	4.0 (0.0, 5.0)	2.5 (0.0, 5.0)	4.0 (0.0, 5.0)	0.50
Native T1 mapping	1065.0 (1032.0, 1132.0)	1050.0 (1025.0, 1078.0)	1135.0 (1076.0, 1201.0)	<**0.001**[*]
Post-contrast T1 mapping	377.0 (315.0, 405.0)	387.0 (352.5, 410.5)	340.0 (304.0, 377.0)	**0.013**[*]
ECV	30.0 (28.0, 32.0)	29.0 (28.0, 31.5)	32.0 (30.0, 32.0)	**0.001**[*]
T2 mapping	56.9 (7.8)	55.0 (7.9)	60.4 (6.6)	**0.009**[*]

VT ventricular tachycardia; ARD autoimmune rheumatic disease; LVEDV left ventricular end diastolic volume; LVESV left ventricular end systolic volume; LVEF left ventricular ejection fraction; RVEDV right ventricular end diastolic volume; RVESV right ventricular end systolic volume; RVEF right ventricular ejection fraction; EGE early gadolinium enhancement; LGE (%) late gadolinium enhancement as % of left ventricular mass; ECV extracellular volume fraction.
[*] $p < 0.005$.

also demonstrated a similar trend, with some comparisons also reaching statistical significance (Table 2).

The results of univariate and multivariate logistic regression for the variables that differed significantly between groups (T1/T2 mapping and ECV) are presented in Table 3. After multivariate corrections for age, left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), right ventricular end-diastolic volume (RVEDV), right ventricular ejection fraction (RVE), T2 signal ratio, EGE and %LGE, all of the examined variables remained significant predictors of having experienced VT in the past. A 10 unit increase in native T1 mapping values yielded an odds ratio (95% confidence interval) of 1.174 (1.055–1.305) for belonging to the VT group ($p = 0.003$). A 10 unit decrease in post-contrast T1 mapping yielded an OR (95%CI) of 0.876 (0.779–0.987) for the same outcome ($p = 0.030$). Similarly, a one unit increase in ECV and T2 mapping yielded an odds ratio of 1.464 (1.101–1.947) and 1.127 (1.023–1.242) respectively for the same outcome ($p = 0.09$ and 0.016 respectively). No significant statistical interactions were identified between the four aforementioned variables.

Table 2
Subgroup analysis of baseline characteristics separately for patients with SLE and SSc with and without ventricular tachycardia.

Variable	SLE patients			SSc patients		
	Patients without VT	Patients with VT	p-Value	Patients without VT	Patients with VT	p-Value
Number of patients	14	3	N/A	7	8	N/A
Age	42.6 (13.9)	44.0 (6.9)	0.87	49.0 (6.2)	47.5 (7.4)	0.68
LVEDV	127.4 (49.0)	112.0 (21.9)	0.61	128.7 (35.0)	114.5 (22.7)	0.36
LVESV	42.0 (31.0, 53.0)	36.0 (29.0, 53.0)	0.90	54.0 (42.0, 63.0)	44.5 (42.5, 48.5)	0.60
LVEF	64.5 (60.0, 71.0)	63.0 (62.0, 72.0)	0.61	60.0 (59.0, 60.0)	61.0 (55.5, 63.0)	0.41
RVEDV	100.6 (26.1)	97.7 (23.5)	0.86	125.0 (19.6)	110.8 (22.1)	0.21
RVESV	36.6 (13.9)	34.7 (4.5)	0.81	50.1 (8.7)	48.8 (14.0)	0.82
RVEF	64.0 (62.0, 69.0)	67.0 (56.0, 69.0)	0.95	60.0 (60.0, 64.0)	57.5 (47.5, 63.0)	0.48
T2 Ratio	1.9 (1.5, 2.6)	2.8 (2.2, 3.3)	0.067	2.2 (1.6, 2.9)	2.3 (1.6, 2.7)	0.68
EGE	3.0 (1.7, 5.0)	1.7 (1.1, 1.7)	0.14	1.1 (1.0, 2.8)	3.3 (1.1, 6.5)	0.16
LGE (%)	2.5 (0.0, 5.0)	0.0 (0.0, 5.0)	0.55	5.0 (0.0, 5.0)	5.0 (2.0, 12.0)	0.47
Native T1 mapping	1042.0 (1032.0, 1069.0)	1132.0 (1076.0, 1209.0)	**0.020**[*]	1050.0 (1010.0, 1110.0)	1142.0 (1083.0, 1236.5)	0.064
Post-contrast T1 mapping	367.0 (304.0, 395.0)	365.0 (340.0, 467.0)	0.57	395.0 (307.0, 409.0)	310.0 (289.0, 355.0)	0.38
ECV	28.0 (28.0, 31.0)	32.0 (30.0, 32.0)	**0.047**[*]	32.0 (29.0, 34.0)	32.0 (32.0, 33.5)	0.34
T2 mapping	55.6 (3.9)	58.0 (1.0)	0.31	58.6 (12.2)	60.9 (7.8)	0.67

VT ventricular tachycardia; ARD autoimmune rheumatic disease; LVEDV left ventricular end diastolic volume; LVESV left ventricular end systolic volume; LVEF left ventricular ejection fraction; RVEDV right ventricular end diastolic volume; RVESV right ventricular end systolic volume; RVEF right ventricular ejection fraction; EGE early gadolinium enhancement; LGE (%) late gadolinium enhancement as % of left ventricular mass; ECV extracellular volume fraction.
[*] $p < 0.005$.

Table 3
Univariate and multivariate logistic regression analysis with the occurrence of VT as outcome, for CMR indices that differed significantly between patients that did and did not experience VT in univariate analyses. Multivariate corrections were for age, LVEDV, LVEF, RVEDV, RVEF, T2 signal ratio, EGE and LGE (%).

Variable	Univariate		Multivariate	
	OR (95%CI)	p-Value	OR (95%CI)	p-Value
Native T1 mapping (per 10 unit change)	1.138 (1.051–1.243)	**0.002***	1.174 (1.055–1.305)	**0.003***
Post-contrast T1 mapping (per 10 unit change)	0.895 (0.817–0.990)	**0.031***	0.876 (0.779–0.987)	**0.030***
ECV	1.424 (1.120–1.810)	**0.004***	1.464 (1.101–1.947)	**0.009***
T2 mapping	1.104 (1.017–1.120)	**0.019***	1.127 (1.023–1.242)	**0.016***

VT ventricular tachycardia; LVEDV left ventricular end diastolic volume; LVEF left ventricular ejection fraction; RVEDV right ventricular end diastolic volume; RVEF right ventricular ejection fraction; EGE early gadolinium enhancement; LGE (%) late gadolinium enhancement as % of left ventricular mass; OR (95%CI) odds ratio (95% confidence interval); ECV extracellular volume fraction.
* $p \leq 0.05$.

Specifically for native and post-contrast T1 mapping, we also performed logistic regression analyses with these variables divided in quartiles. However, we felt that this added little to our existing results.

4. Discussion

In this study, we evaluated by CMR a mixed cohort of consecutive patients with various ARDs, all with preserved LVEF who had or did not have a history of recent VT/VF. VT/VF was more frequent in SSc than other ARDs, as expected due to significant primary cardiac involvement associated with this disease [25]. Native T1 mapping, T2 mapping and ECV values were significantly higher, while post contrast T1 mapping significantly lower in patients who had experienced VT compared to those who had not. Furthermore, after multivariate corrections for age, LVEDV, LVEF, RVEDV, RVEF, T2 signal ratio, EGE and %LGE, these CMR indices still remained significant predictors of having experienced VT in the recent past.

Traditionally, myocardial inflammation is diagnosed using the Lake Louise (JACC white paper) criteria, which require a combination of two or more of the following: a T2 signal ratio value > 2, EGE > 4 and/or %LGE > 0 [21]. These reflect the domains of myocardial oedema, hypaeremia and replacement fibrosis, respectively. It is already known that in patients with ARDs, the combination of myocardial oedema and fibrosis can be present even in treatment naïve ARD patients that present with cardiovascular symptoms at diagnosis [26]. However, conventional T2-weighted short tau imaging, which is currently used for the evaluation of myocardial oedema [21], has only modest sensitivity for detecting diffuse myocardial oedema [18] and %LGE does not represent diffuse myocardial fibrosis, both pathologic phenomena commonly observed in myocardial tissue samples of patients with ARDs [18]. Therefore, T1-, T2-mapping and ECV have emerged as novel methods that can overcome the aforementioned limitations of T2-weighted short tau and LGE imaging. These indices are better suited for identifying diffuse myocardial oedema and fibrosis. An increase in native T1- and T2-mapping and a decrease in post contrast T1-mapping are highly sensitive to myocardial water content and superior to T2-weighted short-tau imaging in detecting myocardial oedema [18]. Finally, ECV measurements can also be used as a surrogate measurement of diffuse fibrosis [27–30] as they have been shown to correlate well with histological indices of myocardial fibrosis in various clinical contexts [29].

These new CMR indices are of great importance in various types of ARDs, as cardiac fibrosis in these patients might not always present the replacement pattern (positive LGE), instead having a more diffuse pattern [31–34]. Additionally, due to the long subclinical period before overt manifestations of primary cardiac involvement, the detection of even mild oedema might prompt initiation of disease modifying treatment and might lead to resolution of myocardial inflammation at a very early stage [35].

Our results are in agreement with the aforementioned studies supporting the clinical significance of these new CMR indices for the detection of silent cardiac involvement in patients with ARDs and preserved LVEF. However, to our knowledge this is the first study demonstrating that these indices are independently associated with a higher likelihood of having experienced VT/VF in the recent past, specifically in patients with ARDs and preserved LVEF. These findings are in agreement with and expand upon a previous study demonstrating that quantitative myocardial tissue assessment using T1 mapping is an independent predictor of ventricular arrhythmia in both ischemic cardiomyopathies and dilated/hypertrophic cardiomyopathies [36]. Global ECV was the best parameter for identifying patients with hypertrophic cardiomyopathy at an increased risk for SCD and performed equally well compared to a validated SCD risk score for hypertrophic cardiomyopathy [37].

Currently, ICDs are the most effective preventive therapy for SCD. According to current guidelines, the indication for prophylactic ICD implantation is essentially an LVEF < 35% [38]. However, patients with ARDs and a normal to moderately reduced LVEF, something often seen in this patients group, may also experience SCD, even if they are traditionally considered as being at lower risk. It is now clear that SCD risk depends mainly on abnormal myocardial histopathologic and electrophysiologic characteristics, which may not necessarily be reflected by a worsening of left ventricular systolic function. Myocardial fibrosis is a known arrhythmogenic substrate that can lead to SCD and CMR is the only currently available imaging modality that is capable of quantifying both replacement and diffuse myocardial fibrosis; this can in turn allow for better stratification of patients with ARDs based on SCD risk compared with conventional functional cardiac systolic function assessment with LVEF [39]. However, cardiac involvement in ARDs is usually silent and may not lead to replacement fibrosis as in other diseases that cause more localised cardiac damage. In such cases, the novel CMR indices presented in our study (T1/T2 mapping and ECV) offer useful information to the clinician wishing to perform an SCD risk assessment in patients with ARDs [26].

5. Limitations of the study

This study had the following limitations:

1. This was a retrospective study based on VT/VF occurrences in the past. Longitudinal studies of similar structure that examine de novo occurrence of VT/VF with more long-term clinical follow-up after CMR examination are required to provide stronger evidence of the associations observed in this cross-sectional study.
2. Differences in more traditional indices including LGE and T2 ratio between groups might have been missed in this study due to insufficient statistical power afforded by the study population.
3. Our study population includes various types of ARDs. Further studies evaluating each ARD separately are needed to better clarify the role of CMR indices in predicting arrhythmic risk for each individual disease.

6. Conclusions

Both diffuse myocardial oedema and fibrosis, as assessed by T1/T2 mapping and ECV, may offer additional utility for the clinician beyond LVEF values in the evaluation of ARD patients at risk for SCD. Therefore, inclusion of CMR indices in the guidelines for ICD implantation, specifically for ARD patients presenting with a history of VT/VF and preserved LVEF may be warranted in the future, should the findings of this study be confirmed in future research.

Conflict of interest

The authors have no conflicts of interest to disclose.

References

[1] D.P. Zipes, A.J. Camm, M. Borggrefe, et al., ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, J. Am. Coll. Cardiol. 48 (2006) e247–e346.

[2] R.J. Myerburg, K.M. Kessler, A. Castellanos, Sudden cardiac death. Structure, function, and time-dependence of risk, Circulation 85 (1992) I2–10.

[3] P.M. Seferović, A.D. Ristić, R. Maksimović, D.S. Simeunović, G.G. Ristić, G. Radovanović, D. Seferović, B. Maisch, M. Matucci-Cerinic, Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases, Rheumatology (Oxford) 45 (Suppl. 4) (2006) iv39–42.

[4] D. Lacroix, F. Brigadeau, C. Marquié, D. Klug, Electroanatomic mapping and ablation of ventricular tachycardia associated with systemic sclerosis, Europace 6 (4) (2004) 336–342.

[5] S.I. Mavrogeni, G. Poulos, P.P. Sfikakis, G.D. Kitas, G. Kolovou, G. Theodorakis, Is there a place for cardiovascular magnetic resonance conditional devices in systemic inflammatory diseases? Expert. Rev. Cardiovasc. Ther. 14 (6) (2016) 677–682.

[6] C.N. Huang, H.H. Yu, S.N. Chiu, J.H. Lee, L.C. Wang, Y.H. Yang, B.L. Chiang, Acute myocarditis and ventricular fibrillation as initial presentation of paediatric systemic lupus erythematosus, Rheumatol. Int. 33 (4) (2013) 1093–1096.

[7] R.A. Teixeira, E.F. Borba, A. Pedrosa, S. Nishioka, V.S. Viana, J.A. Ramires, R. Kalil-Filho, E. Bonfá, M. Martinelli Filho, Evidence for cardiac safety and anti-arrhythmic potential of chloroquine in systemic lupus erythematosus, Europace 16 (6) (2014) 887–892.

[8] P.E. Lazzerini, M. Acampa, M. Hammoud, S. Maffei, P.L. Capecchi, E. Selvi, S. Bisogno, F. Guideri, M. Galeazzi, F.L. Pasini, Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis, J. Rheumatol. 35 (10) (2008) 1958–1965.

[9] J.F. Boyer, B. Jamard, S. El Mahou, M. Laroche, B. Mazières, A. Cantagrel, A. Constantin, New-onset acute heart failure and ventricular tachycardia after therapy with a tumor necrosis factor antagonist, Clin. Exp. Rheumatol. 23 (2) (2005) 274–275.

[10] R. Tung, A.R. Rahimi, E.V. Gelfand, K.F. Kwaku, Vasculitis presenting with ventricular tachycardia, J. Rheumatol. 36 (9) (2009) 2127–2129.

[11] M. Fujino, T. Hata, M. Kuriki, K. Horio, H. Uchida, Y. Eryu, H. Boda, M. Miyata, T. Yoshikawa, Inflammation aggravates heterogeneity of ventricular repolarization in children with Kawasaki disease, Pediatr. Cardiol. 35 (7) (2014) 1268–1272.

[12] G. Jindal, S. Singh, D. Suri, A. Rawat, M. Rohit, Recurrent ventricular tachycardia in a child with juvenile dermatomyositis - an unusual association, Int. J. Rheum. Dis. 15 (2) (2012) e26–e27.

[13] P. Dilaveris, P. Pietri, D. Tsiachris, K. Gatzoulis, C. Stefanadis, Inducible ventricular tachycardia due to dermatomyositis-related cardiomyopathy in the era of implantable cardioverter-defibrillator therapy, Circulation 125 (7) (2012) 967–969.

[14] M. Adler, S. Banerjeee, R. Stratton, Ventricular tachycardia as a presenting feature of dermatomyositis, Heart 88 (5) (2002) 443.

[15] E.D. Rosenstein, M.J. Zucker, N. Kramer, Giant cell myocarditis: most fatal of autoimmune diseases, Semin. Arthritis Rheum. 30 (1) (2000) 1–16.

[16] P.E. Lazzerini, I. Bertolozzi, M. Acampa, R. Fulceri, F. Laghi-Pasini, P.L. Capecchi, Torsades de pointes in patients with polymyalgia rheumatica, Curr. Pharm. Des. 24 (3) (2018) 323–340.

[17] P.E. Lazzerini, P.L. Capecchi, M. Acampa, M. Galeazzi, F. Laghi-Pasini, Arrhythmic risk in rheumatoid arthritis: the driving role of systemic inflammation, Autoimmun. Rev. 13 (9) (2014) 936–944.

[18] S.I. Mavrogeni, G.D. Kitas, T. Dimitroulas, P.P. Sfikakis, P. Seo, S. Gabriel, A.R. Patel, L. Gargani, S. Bombardieri, M. Matucci-Cerinic, M. Lombardi, A. Pepe, A.H. Aletras, G. Kolovou, T. Miszalski, P. van Riel, A. Semb, M.A. Gonzalez-Gay, P. Dessein, G. Karpouzas, V. Puntmann, E. Nagel, K. Bratis, G. Karabela, E. Stavropoulos, G. Katsifis, L. Koutsogeorgopoulou, A. van Rossum, F. Rademakers, G. Pohost, J.A. Lima, Cardiovascular magnetic resonance in rheumatology: current status and recommendations for use, Int. J. Cardiol. 217 (2016) 135–148.

[19] S. Mavrogeni, D. Apostolou, P. Argyriou, S. Velitsista, L. Papa, S. Efentakis, E. Vernardos, M. Kanoupaki, G. Kanoupakis, A. Manginas, T1 and T2 mapping in cardiology: "mapping the obscure object of desire", Cardiology 138 (4) (2017) 207–217.

[20] S. Mavrogeni, P. Sfikakis, T. Dimitroulas, G. Kolovou, G.D. Kitas, Edema and fibrosis imaging by cardiovascular magnetic resonance: how can the experience of cardiology be best utilized in rheumatological practice? Semin. Arthritis Rheum. 44 (1) (2014) 76–85.

[21] M.G. Friedrich, U. Sechtem, J. Schulz-Menger, G. Holmvang, P. Alakija, L.T. Cooper, J.A. White, H. Abdel-Aty, M. Gutberlet, S. Prasad, A. Aletras, J.P. Laissy, I. Paterson, N.G. Filipchuk, A. Kumar, M. Pauschinger, P. Liu, International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper, J. Am. Coll. Cardiol. 53 (2009) 1475–1487.

[22] S. Won, C. Davies-Venn, S. Liu, D.A. Bleumke, Noninvasive imaging of myocardial extracellular matrix for assessment of fibrosis, Curr. Opin. Cardiol. 28 (2013) 282–289.

[23] V.M. Ferreira, S.K. Piechnik, E. Dall'Armellina, T.D. Karamitsos, J.M. Francis, R.P. Choudhury, M.G. Friedrich, M.D. Robson, S. Neubauer, Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 14 (2012).

[24] D.R. Messroghli, A. Radjenovic, S. Kozerke, D.M. Higgins, M.U. Sivananthan, J.P. Ridgway, Modified Look-Locker Inversion recovery (MOLLI) for high-resolution T1 mapping of the heart, Magn. Reson. Med. 52 (2004) 141–146.

[25] V.-K. Bournia, C. Tountas, A.D. Protogerou, S. Panopoulos, S. Mavrogeni, P.P. Sfikakis, Update on assessment and management of primary cardiac involvement in systemic sclerosis, J. Scleroderma Relat. Disord. 3 (1) (2018) 53–65.

[26] S. Mavrogeni, G. Markousis-Mavrogenis, L. Koutsogeorgopoulou, T. Dimitroulas, K. Bratis, G.D. Kitas, P. Sfikakis, M. Tektonidou, G. Karabela, E. Stavropoulos, G. Katsifis, K.A. Boki, A. Kitsiou, V. Filaditaki, E. Gialafos, S. Plastiras, V. Vartela, G. Kolovou, Cardiovascular magnetic resonance imaging pattern at the time of diagnosis of treatment naïve patients with connective tissue diseases, Int. J. Cardiol. 236 (2017) 151–156.

[27] S. Piechnik, V.M. Ferreira, E. Dall'Armellina, L.E. Cochlin, A. Greiser, S. Neubauer, M.D. Robson, Shortened modified look-locker inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold, J. Cardiovasc. Magn. Reson. 12 (2010) 69.

[28] L. Iles, H. Pfluger, A. Phrommintikul, J. Cherayath, P. Aksit, S.N. Gupta, D.M. Kaye, A.J. Taylor, Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping, J. Am. Coll. Cardiol. 52 (2008) 1574–1580.

[29] S. Bull, S.K. White, S.K. Piechnik, A.S. Flett, V.M. Ferreira, M. Loudon, J.M. Francis, T.D. Karamitsos, B.D. Prendegrast, M.D. Robson, S. Neubauer, J.C. Moon, S.G. Myerson, Human non-contrast T1 values and correlation with histology in diffuse fibrosis, Heart 99 (2013) 932–937.

[30] U.K. Radunski, G.K. Lund, C. Stehning, B. Schnackenburg, S. Bohnen, G. Adam, S. Blankenberg, K. Muellerleile, CMR in patients with severe myocarditis: diagnostic value of quantitative tissue markers including extracellular volume imaging, JACC Cardiovasc. Imaging 7 (2014) 667–675.

[31] S. Greulich, A. Mayr, D. Kitterer, J. Latus, J. Henes, F. Vecchio, P. Kaesemann, A. Patrascu, A. Greiser, S. Groeninger, F. Romeo, N. Braun, M.D. Alscher, U. Sechtem, H. Mahrholdt, Advanced myocardial tissue characterisation by a multi-component CMR protocol in patients with rheumatoid arthritis, Eur. Radiol. 27 (11) (2017) 4639–4649.

[32] S. Greulich, A. Mayr, D. Kitterer, J. Latus, J. Henes, H. Steubing, P. Kaesemann, A. Patrascu, A. Greiser, S. Groeninger, N. Braun, M.D. Alscher, U. Sechtem, H. Mahrholdt, T1 and T2 mapping for evaluation of myocardial involvement in patients with ANCA-associated vasculitides, J. Cardiovasc. Magn. Reson. 19 (1) (2017) 6.

[33] S. Greulich, D. Kitterer, J. Latus, E. Aguor, H. Steubing, P. Kaesemann, A. Patrascu, A. Greiser, S. Groeninger, A. Mayr, N. Braun, M.D. Alscher, U. Sechtem, H. Mahrholdt, Comprehensive cardiovascular magnetic resonance assessment in patients with sarcoidosis and preserved left ventricular ejection fraction, Circ. Cardiovasc. Imaging 9 (11) (2016).

[34] A. Mayr, D. Kitterer, J. Latus, H. Steubing, J. Henes, F. Vecchio, P. Kaesemann, A. Patrascu, A. Greiser, S. Groeninger, N. Braun, M.D. Alscher, U. Sechtem, H. Mahrholdt, S. Greulich, Evaluation of myocardial involvement in patients with connective tissue disorders: a multi-parametric cardiovascular magnetic resonance study, J. Cardiovasc. Magn. Reson. 18 (1) (2016) 67.

[35] S.I. Mavrogeni, P.P. Sfikakis, T. Dimitroulas, L. Koutsogeorgopoulou, G. Katsifis, G. Markousis-Mavrogenis, G. Kolovou, G.D. Kitas, Can cardiovascular magnetic resonance prompt early cardiovascular/rheumatic treatment in autoimmune rheumatic diseases? Current practice and future perspectives, Rheumatol. Int. 38 (6) (2018) 949–958.

[36] Z. Chen, M. Sohal, T. Voigt, E. Sammut, C. Tobon-Gomez, N. Child, T. Jackson, A. Shetty, J. Bostock, M. Cooklin, M. O'Neill, M. Wright, F. Murgatroyd, J. Gill, G. Carr-White, A. Chiribiri, T. Schaeffter, R. Razavi, C.A. Rinaldi, Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators, Heart Rhythm. 12 (4) (2015) 792–801.

[37] M. Avanesov, J. Münch, J. Weinrich, L. Well, D. Säring, C. Stehning, E. Tahir, S. Bohnen, U.K. Radunski, K. Muellerleile, G. Adam, M. Patten, G. Lund, Prediction of the estimated 5-year risk of sudden cardiac death and syncope or non-sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy using late gadolinium enhancement and extracellular volume CMR, Eur. Radiol. 27 (12) (2017) 5136–5145.

[38] A.I. Guaricci, D. De Santis, M.G. Rabbat, G. Pontone, Cardiac magnetic resonance imaging and primary prevention implantable cardioverter defibrillator therapy: current recommendations and future directions, J. Cardiovasc. Med. (Hagerstown) 19 (5) (2018) 223–228.

[39] G. Pontone, A.I. Guaricci, D. Andreini, A. Solbiati, M. Guglielmo, S. Mushtaq, A. Baggiano, V. Beltrama, L. Fusini, C. Rota, C. Segurini, E. Conte, P. Gripari, A. Dello Russo, M. Moltrasio, F. Tundo, F. Lombardi, G. Muscogiuri, V. Lorenzoni, C. Tondo, P. Agostoni, A.L. Bartorelli, M. Pepi, Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and nonischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy, Circ. Cardiovasc. Imaging 9 (10) (2016).