ORIGINAL RESEARCH

Arrhythmogenic Right Ventricular Cardiomyopathy: Characterization of Left Ventricular Phenotype and Differential Diagnosis With Dilated Cardiomyopathy

Alberto Cipriani, MD; Barbara Bauce, MD, PhD; Manuel De Lazzari, MD, PhD; Ilaria Rigato, MD, PhD; Riccardo Bariani, MD; Samuele Meneghin, MD; Kalliopi Pilichou, MD, PhD; Raffaella Motta, MD, PhD Camillo Aliberti, MD; Gaetano Thiene, MD; William J. McKenna, MD, DSc; Alessandro Zorzi, MD, PhD; Sabino Iliceto, MD; Cristina Basso, MD, PhD; Martina Perazzolo Marra, MD, PhD;* Domenico Corrado, MD, PhD*

***Background*—**This study assessed the prevalence of left ventricular (LV) involvement and characterized the clinical, electrocardiographic, and imaging features of LV phenotype in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Differential diagnosis between ARVC-LV phenotype and dilated cardiomyopathy (DCM) was evaluated.

***Methods and Results*—**The study population included 87 ARVC patients (median age 34 years) and 153 DCM patients (median age 51 years). All underwent cardiac magnetic resonance with quantitative tissue characterization. Fifty-eight ARVC patients (67%) had LV involvement, with both LV systolic dysfunction and LV late gadolinium enhancement (LGE) in 41/58 (71%) and LV-LGE in isolation in 17 (29%). Compared with DCM, the ARVC-LV phenotype was statistically significantly more often characterized by low QRS voltages in limb leads, T-wave inversion in the inferolateral leads and major ventricular arrhythmias. LV-LGE was found in all ARVC patients with LV systolic dysfunction and in 69/153 (45%) of DCM patients. Patients with ARVC and LV systolic dysfunction had a greater amount of LV-LGE (25% versus 13% of LV mass; $P<0.01$), mostly localized in the subepicardial LV wall layers. An LV-LGE ≥20% had a 100% specificity for diagnosis of ARVC-LV phenotype. An inverse correlation between LV ejection fraction and LV-LGE extent was found in the ARVC-LV phenotype ($r=-0.63$; $P<0.01$), but not in DCM ($r=-0.01$; $P=0.94$).

***Conclusions*—**LV involvement in ARVC is common and characterized by clinical and cardiac magnetic resonance features which differ from those seen in DCM. The most distinctive feature of ARVC-LV phenotype is the large amount of LV-LGE/fibrosis, which impacts directly and negatively on the LV systolic function. **(*J Am Heart Assoc*. 2020;9:e014628. DOI: 10.1161/JAHA.119.014628.)**

Key Words: arrhythmogenic right ventricular cardiomyopathy • cardiac magnetic resonance • dilated cardiomyopathy • late gadolinium enhancement • left ventricular involvement • left ventricular phenotype

According to its original descriptions, the classical disease phenotype of arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by early and predominant right ventricular (RV) involvement, with no or mild left ventricular (LV) disease.[1,2] From the original view of natural history of ARVC, the LV involvement was considered the result of disease progression, occurring late and in association with advanced RV disease.[3,4] Subsequent studies based on autopsy investigation, genotype-phenotype correlations, and the increasing use of cardiac magnetic resonance (CMR) showed that the LV involvement is common, often occurs earlier than initially thought, and may have a distinctive genetic background.[5–9] The increasing recognition of biventricular and left dominant phenotypic variants led to the concept that ARVC is a disease involving the myocardium of both ventricles.

Although post-mortem studies showed that LV involvement can be detected in about two thirds of cases of pathologically proven ARVC,[10,11] the prevalence of LV involvement and morpho-functional features of the LV phenotype in living patients have not been elucidated.

From the Department of Cardio-Thoraco-Vascular Sciences and Public Health (A.C., B.B., M.D.L., I.R., R.B., S.M., K.P., G.T., A.Z., S.I., C.B., M.P.M., D.C.) and the Department of Medicine, Institute of Radiology (R.M., C.A.), University of Padua, Italy; Institute of Cardiovascular Science, University College London, London, United Kingdom (W.J.M.).

*Dr Perazzolo Marra and Dr Corrado are co-senior authors.

Correspondence to: Domenico Corrado, MD, PhD, Inherited Arrhythmogenic Cardiomyopathy Unit, Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua Medical School, Via N. Giustiniani, 2. 35128 Padua, Italy. E-mail: domenico.corrado@unipd.it

Received September 16, 2019; accepted January 27, 2020.

Clinical Perspective

What Is New?

- Left ventricular (LV) involvement on cardiac magnetic resonance is present in two thirds of patients with a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC), according to the 2010 International Task Force diagnostic criteria.
- The ARVC-LV phenotype is characterized in all cases by a subepicardial/midmyocardial fibrosis/late gadolinium enhancement, with or without LV systolic dysfunction.
- Clinical and cardiac magnetic resonance features allow differential diagnosis between ARVC- and dilated cardiomyopathy-LV phenotypes; the most distinctive features of ARVC-LV phenotype were the low QRS voltages on the ECG and the extensive amount of LV myocardial fibrosis/late gadolinium enhancement, which was directly related to the LV systolic dysfunction.

What Are the Clinical Implications?

- The remodeling pattern of "hypokinetic, non-dilated, and fibrotic" LV is more consistent with the ARVC-LV phenotype than with that of dilated cardiomyopathy.
- The large fibro-fatty myocardial replacement of LV myocardium accounts for the low QRS voltages on the ECG and may act as a substrate for life-threatening ventricular arrhythmias.
- Unlike dilated cardiomyopathy, in ARVC patients with a large amount of LV myocardial fibrosis, the implantation of a prophylactic cardiac defibrillator may be considered even if the LV systolic function is not severely depressed.

Furthermore, the LV phenotype of ARVC overlaps with that of dilated cardiomyopathy (DCM), making differential diagnosis challenging. The distinction between the 2 LV phenotypes is clinically relevant for patient management. In patients affected by left-sided ARVC therapy is focused on life-threatening ventricular arrhythmias and prevention of sudden cardiac death (SCD), which can occur as first manifestation of the disease, while treatment of patients with DCM is aimed at relieving heart failure symptoms and improving exercise capacity and outcomes. Criteria for differentiating LV phenotypes of these 2 conditions have not been established.

Because there are not defined criteria for diagnosing left-sided ARVC variant, in the present study we assessed the prevalence of LV involvement and the clinico-imaging features of LV phenotype in a cohort of ARVC patients fulfilling the 2010 International Task Force (ITF) diagnostic criteria,[12] which currently represent the only available "gold standard" for the disease diagnosis.

In addition, the study aimed to identify the clinical, electrocardiographic, and CMR features, which could help in differentiating LV phenotype of ARVC from that of DCM.

Methods

Study Population

The data, analytic methods, and study materials will be available to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request.

This observational, single-center study included 2 consecutive series of patients: the ARVC group (n=87) and the DCM group (n=153). Patients of both groups were evaluated at the Inherited Arrhythmogenic Cardiomyopathy Unit of University of Padua from September 2012 to January 2018, where they underwent the CMR study, which included tissue characterization with late gadolinium enhancement (LGE), according to a homogeneous protocol of images acquisition.

All patients from the ARVC group fulfilled the 2010 ITF diagnostic criteria.[12] In this group, LV involvement was defined on the basis of CMR demonstration of LV systolic dysfunction, LV LGE, or both.

Dilated cardiomyopathy was defined by the presence of both LV systolic dysfunction and LV dilatation, not explained by abnormal loading conditions or coronary artery disease.[13] Coronary angiography was performed in all DCM patients to exclude an underlying coronary artery disease. Moreover, none of these patients had active myocarditis, congenital heart disease, hypertrophic cardiomyopathy, infiltrative disease, moderate-to-severe valvular heart disease, substance abuse, untreated hypertension, or any contraindication to CMR.

All patients underwent a routine cardiovascular evaluation including medical history, 12-lead ECG, 2D color Doppler echocardiography. Technical equipment, protocols, reference values of each routine investigation have been reported in details elsewhere.[14] Molecular genetic testing was performed in all patients with ARVC and in the subset of DCM patients with clinical evidence of familial disease, according to a previously reported protocol.[15]

Major ventricular arrhythmias were defined as SCD, aborted cardiac arrest because of ventricular fibrillation, and sustained ventricular tachycardia.

The aim of the present investigation was to assess the clinical and imaging features of the LV phenotype of ARVC and their value for differential diagnosis with the LV phenotype of DCM. No analysis combining molecular genetic findings (cardiomyopathy causing-genes, mutation types, and genotype complexity) and electrical or structural ventricular abnormalities was analyzed because this was not a genotype–phenotype correlation study.

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki (2001). The study protocol was approved by the cardiovascular section in-house Ethics Committee on Human Research of the Padua Province. All patients provided written informed consent before inclusion in the study.

Electrocardiographic Analysis

All patients underwent a standard 12-lead ECG, which were analyzed by 2 observers (R.B., A.Z.), masked to clinical data and CMR findings. Standard measurements included P-wave abnormalities and PR interval; QRS axis, voltage and duration; ST-segment and T-wave abnormalities. Specifically, first degree atrioventricular block was defined as PR interval >200 ms; low QRS voltages if QRS amplitude was ≤0.5 mV in limb leads, including both negative and positive components; left axis deviation when mean electrical axis of QRS laid in the frontal plane direction was between −30° and −90°; left anterior hemiblock and left bundle branch block (LBBB) as previously recommended[14]; left ventricular hypertrophy was identified by standard Sokolow–Lyon voltage criteria (S_{V1}+$R_{V5\ or\ V6}$ ≥3.5 mV); strain pattern was characterized as downsloping convex ST segment with an inverted asymmetric T-wave opposite to the QRS axis, in the absence of LBBB; and left atrial enlargement when the length of the P wave in lead II was >120 ms; T-wave inversion (TWI) when ≥0.1 mV in depth in ≥2 contiguous leads, in the absence of LBBB.[16]

CMR Protocol and Images Analysis

CMR images were acquired using a 1.5 T scanner (Magnetom Avanto, Siemens Healthineers, Erlangen, Germany) with ECG-triggering and phased array coil system. Study protocol, techniques and post-processing analysis (software CMR,[42] Circle Cardiovascular Imaging Inc, Calgary, Canada) are described in details in previous works of our group.[17,18] LV dilatation and LV systolic dysfunction were defined with reference to age- and sex-related CMR nomograms.[19] In our age-group of patients, an impaired LV systolic function was defined as an LVEF ≤0.48 for men and 0.50 for women. Regional wall motion abnormalities (WMA) were evaluated by a subjective assessment: for RV regional WMA we considered akinesia, dyskinesia, or dyssynchronous contraction, for LV regional WMA hypokinesia was also included. Fat infiltration was evaluated in the ARVC group, by comparing localizer, cine, T1-weighted non-fat-suppressed Turbo Spin Echo and post-contrast images, to distinguish the normal epicardial fat from the pathological fibrofatty myocardial replacement.

LGE imaging was performed using 2-dimensional segmented breath-held fast low-angle shot inversion recovery sequences (TE/TR/flip-angle=3.2 ms/5.2 ms/25°) 10 to 15 minutes after contrast agent intravenous administration (gadobenate dimeglumine; 0.2 mmol/kg of body weight) in the short-axis views from cardiac base to apex (slice thickness=6 mm, gap=2 mm) and in the long-axis 2-, 3- and 4-chamber views; inversion times were adjusted to null normal myocardium using Look-Locker sequence. To exclude artefacts, images were repeated in 2 separate phase-encoding directions. Focal fibrosis, as demonstrated by LGE, was qualitatively evaluated in all LV segments according to the American College of Cardiology/American Heart Association 17-myocardial-segment model.[20] LGE was deemed present only if appreciable on 2 contiguous or orthogonal slices or another readout direction. Patterns of replacement fibrosis were classified based on previously published criteria[21]: (1) subepicardial; (2) midwall; (3) subendocardial.

Quantification of LGE was then performed by tracing endocardial and epicardial contours in the short axis view, using the full width at half maximum technique, which uses half the maximal signal within the scar as the threshold: the regions of interest were manually drawn around hyperintense myocardium and used to define maximal signal for the full width at half maximum threshold. Blood pool or pericardial partial voluming and artefacts were manually corrected and removed from the regions of interest. Extent of LGE was expressed as a percentage of total LV mass.

All measurements were performed by 2 experienced cardiologists (A.C., M.D.L.), who were masked to patient clinical data. Ambiguous cases were reviewed by a third expert (M.P.M.).

Statistical Analysis

Categorical variables are presented as absolute frequencies with percentages and were compared using Chi-squared test or the Fisher exact test; continuous variables are presented as median with 25th to 75th percentiles and were compared using the Student *t*-test or Mann–Whitney *U* test. Simple and multivariable (adjusted for age and sex) linear regression analyses were performed to study the correlation between left ventricular ejection fraction (LVEF) and LV LGE amount in the 2 groups. Receiver operating characteristic analysis and area under the curve were calculated to identify the LV LGE% amount cut-off value, which discriminates better between the 2 LV phenotypes. Interobserver variability in LV LGE quantification between 2 independent observers was examined in a random sample of 20 patients with LGE and the intraclass correlation coefficient was calculated. A 2-tailed probability value of 0.05 was considered statistically significant. All analyses were performed using SPSS 25 (SPSS Inc, Chicago, IL).

Results

Clinical Characteristics of ARVC Patients With LV Involvement

Baseline characteristics of 87 patients (56% men, median age 34 years) with ARVC are reported in Table 1. The study population included 59 ARVC-causing gene-mutation carriers (68%) with the following gene distribution: *DSP* n=19 (32%); *PKP2* n=24 (41%); *DSG* n=10 (17%); *DSC2* n=2 (3%); *JUP* n=1 (2%); others n=8 (14%). Fifty-eight (67%) patients (36% men, median age 34 years) showed LV involvement, characterized by LV LGE and LV systolic dysfunction in 41/58 subjects (71%) and LV LGE with preserved LV function in 17/58 (29%).

There were no statistically significant differences between patients with and without LV involvement with regard to family history, symptoms and previous major arrhythmic events. *DSP* gene mutations were more frequently found among patients with LV involvement (17/58, 29% versus 2/29, 7%; *P*=0.02).

The ECG in patients with LV involvement more frequently showed low QRS voltages in limb leads (24/58, 41% versus 5/29, 17%; *P*=0.02), TWI in either lateral (21/58, 36% versus 3/29, 10%; *P*=0.01) or inferolateral leads (15/58, 26% versus 2/29, 7%; *P*=0.03); no patients had LBBB. A major ventricular arrhythmia occurred in 22/58 patients (38%) and included 11/22 (50%) episodes of sustained ventricular tachycardia.

Cine-CMR analysis showed LV dilatation in 24/87 (28%), LV systolic dysfunction in 41/87 (47%) and LV WMA in 44/87 (51%). All patients with LV systolic dysfunction showed LV LGE (Figure 1).

No differences with regard to RV volumes, RVEF and the prevalence of RV WMA, RV LGE and fat infiltration were found on CMR among patients with and without LV involvement (Table 1).

Clinical Characteristics of DCM Patients

The study population of DCM included 153 patients (69% men, median age 51 years), whose baseline characteristics are reported in Table 2. A family history for SCD was ascertained in 14/153 (9%) and familial DCM in 22/153 (14%). Among the 22 probands with familial DCM, 7 (32%) showed DCM-causing gene-mutation, with the following gene distribution: *TTN* n=2 (29%); *MYH6* n=2 (29%); *ACTN2* n=1 (14%); *TNNT2* n=1 (14%); *LAMA4* n=1 (14%). A major ventricular arrhythmia occurred in 10/153 patients (7%) and included 2 (20%) episodes of sustained ventricular tachycardia. The ECG showed an LV hypertrophy pattern in 32/153 (21%) and an LBBB in 41/153 (27%). Low QRS voltages in limb leads were present in 4/153 (3%), T-wave inversion in lateral leads in 43 of 112 patients without LBBB (38%), or in inferolateral leads in 6/112 (5%). On CMR, LV LGE was detected in 69/153 patients (45%).

Comparison Between ARVC-LV Phenotype and DCM

An overlapping LV phenotype characterized by the combination of LV systolic dysfunction and LV LGE was observed in 41/87 (47%) patients with ARVC and in 69/153 (45%) patients with DCM (Figure 1). Comparison between the clinical and imaging features of the 2 subgroups is reported in Table 3. Patients with ARVC-LV phenotype were younger than patients with that of DCM (39 versus 54 years, *P*<0.01). Compared with DCM patients, those with ARVC-LV phenotype more often had familial SCD (9/41, 22% versus 6/69, 9%; *P*=0.05), syncope (11/41, 27% versus 5/69, 7%; *P*<0.01) and major ventricular arrhythmias (13/41, 32% versus 4/69, 6%; *P*<0.01). On 12-lead ECG, low QRS voltages in limb leads (24/41, 59% versus 3/69, 4%; *P*<0.01) and inferolateral TWI (13/41, 32% versus 3/50, 6%; *P*<0.01) were significantly more often found in patients with ARVC-LV phenotype, while an LV hypertrophy pattern (1/41, 2% versus 14/69, 20%; *P*=0.05) and an LBBB (19/69, 28% versus 0%, *P*<0.01) were more prevalent in DCM patients. Monomorphic sustained ventricular tachycardia with a right bundle branch block (RBBB) morphology of the QRS more frequently occurred in patients with ARVC-LV phenotype, than in those with DCM (4/41, 10% versus 1/69, 1%; *P*<0.01).

At CMR evaluation, patients with ARVC-LV phenotype had lower LV volumes (97 mL/m^2 versus 141 mL/m^2, *P*<0.01) and LV mass (66 g/m^2 versus 86 g/m^2, *P*<0.01) and less depressed LVEF (46% versus 29%, *P*<0.01) compared with DCM patients. The amount of LV LGE was greater in patients with ARVC-LV phenotype (24.6% versus 13.1%, *P*<0.01) (Figure 2A). The regional distribution of LV LGE differed between the 2 conditions, predominately affecting the inferolateral segments in ARVC versus septal segments in DCM (Figure 3).

There was a good interobserver agreement in quantification of the extent of LGE (intraclass correlation coefficient=0.85). Compared with DCM, in ARVC-LV phenotype the LV LGE significantly more often appeared as a stria pattern than a spot/patchy pattern (40/41, 98% versus 57/69, 82%; *P*=0.03). LV LGE more frequently affected the subepicardial layers (40/41, 98% versus 11/69, 16%; *P*<0.01) in ARVC and the midmural layers in DCM (66/69, 96% versus 9/41, 22%; *P*<0.01).

According to receiver operating characteristic analysis, the area under the curve of percentage of LV LGE for diagnosis of ARVC was 0.84 (SE=0.05, 95% CI 0.75–0.93, *P*<0.01) (Figure 2B). The best cut-off value of LGE% was 20%, which provided a sensitivity of 68% and a specificity of 100% for diagnosis of ARVC-LV phenotype.

Table 1. Baseline Characteristics of ARVC Population

	ARVC Patients (n=87)	LV Involvement No (n=29)	LV Involvement Yes (n=58)	*P* Value
Age at diagnosis, y	34 (22–47)	36 (25–43)	34 (19–50)	0.689
Male sex	56 (64)	20 (69)	36 (62)	0.527
Symptoms				
Chest pain	10 (11)	3 (10)	7 (12)	1.00
Syncope	29 (33)	13 (45)	16 (28)	0.108
Palpitations	13 (15)	1 (3)	12 (21)	0.06
Exertional dyspnea	20 (23)	4 (14)	16 (28)	0.149
Family history				
Clinical ARVC diagnosis in relatives	57 (66)	20 (69)	37 (64)	0.632
Family history of SCD	22 (25)	10 (35)	12 (21)	0.163
Gene mutation carriers	59 (68)	23 (79)	36 (62)	0.105
Arrhythmic history				
Atrial fibrillation	6 (7)	1 (3)	5 (9)	0.659
Major ventricular arrhythmias	33 (38)	11 (38)	22 (38)	1.00
Electrocardiographic features				
First degree atrioventricular block	6 (7)	0	6 (10)	0.07
Complete left bundle branch block	0	0	0	1.00
LV hypertrophy (Sokolow-Lyon Index)	1 (1)	0	1 (2)	0.333
Left axis deviation	8 (9)	1 (3)	7 (12)	0.260
Left anterior fascicular block	5 (6)	0	5 (9)	0.103
Left atrial enlargement	10 (12)	2 (7)	8 (14)	0.485
Strain pattern	1 (1)	0	1 (2)	1.00
Low QRS voltages in limb leads	29 (33)	5 (17)	24 (41)	0.024
TWI in anterolateral leads (V1–V6)	16 (18)	3 (10)	13 (22)	0.243
TWI in lateral leads (V5–V6±V4, I, aVL)	24 (28)	3 (10)	21 (36)	0.011
TWI in inferolateral leads (II, III, aVF+V5–V6±V4 or I, aVL)	17 (20)	2 (7)	15 (26)	0.032
CMR findings				
ARVC CMR major TFC	58 (67)	19 (66)	39 (67)	1.00
ARVC CMR minor TFC	4 (5)	1 (3)	3 (5)	1.00
RV analysis				
RV EDV, mL/m^2	106 (94–117)	104 (93–112)	108 (97–118)	0.240
RV regional WMA	74 (85)	26 (90)	48 (83)	0.530
RVEF, %	45 (38–52)	46 (41–52)	46 (38–51)	0.324
RV fat infiltration	38 (43)	12 (43)	26 (47)	0.703
RV LGE	48 (55)	13 (45)	35 (60)	0.180
LV analysis				
LV EDV, mL/m^2	88 (75–100)	79 (74–84)	93 (82–105)	<0.001
LV dilatation	24 (28)	2 (7)	22 (38)	0.002
LV regional WMA	44 (51)	0	44 (51)	<0.001
LVEF, %	53 (46–59)	60 (57–62)	49 (44–54)	<0.001
LV systolic dysfunction	41 (47)	0	41 (71)	<0.001

Continued

Table 1. Continued

	ARVC Patients (n=87)	LV Involvement No (n=29)	LV Involvement Yes (n=58)	*P* Value
LV fat infiltration	35 (40)	3 (11)	32 (57)	<0.001
LV LGE	58 (67)	0	58 (100)	<0.001
LV LGE amount, g	…	…	16.1 (9.3–26.8)	…
LV LGE amount, %	…	…	21.8 (12.6–30.9)	…
N° segments involved	…	…	7 (6–9)	…
>6 segments	…	…	34 (59)	…
LV LGE morphology				
Stria	…	…	54 (93)	…
Spot/patchy	…	…	6 (11)	…
LV LGE layer				
Subendocardial	…	…	2 (3)	…
Midmural	…	…	11 (19)	…
Subepicardial	…	…	55 (95)	…

Values are expressed as number of patients (%) or median (25th and 75th percentiles). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiovascular magnetic resonance; EDV, end-diastolic volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; SCD, sudden cardiac death; TFC, Task Force criteria; TWI, T-wave inversion; WMA, wall motion abnormalities.

In ARVC patients, there was a linear correlation between LVEF reduction and extent of LV LGE (expressed as percentage of LV mass) (r=−0.63, P<0.01) (Figure 4A), also after adjustment for age and sex (β=−0.60, 95% CI −0.64 to −0.26, P<0.01). In DCM patients, LV systolic dysfunction and LV LGE were unrelated (r=−0.01, P=0.94) (Figure 4B), even after adjustment for age and sex (β=−0.18, 95% CI −0.76 to −0.41, P=0.54).

The results of a subanalysis comparing the ARVC-LV phenotype (median value LVEF 46%, interquartile range 41–48) versus DCM with LVEF >40% (median value LVEF 43%, interquartile range 41–45) are reported in Table 4. On 12-lead ECG, low QRS voltages in limb leads (24/41, 59% versus 1/32, 3%; P<0.01) and TWI were significantly more often found in patients with ARVC-LV phenotype, while an LV hypertrophy pattern (1/41, 2% versus 7/32, 22%; P=0.018) and an LBBB (0% versus 11/32, 34%, P<0.01) were more prevalent in DCM patients. At CMR, ARVC-LV phenotype had lower LV volumes (97 mL/m^2 versus 120 mL/m^2, P<0.01) and LV mass (66 g/m^2 versus 79 g/m^2, P<0.01) compared with DCM. The amount of LV LGE was greater in patients with ARVC-LV phenotype (24.6% versus 10.4%, P<0.01). Compared with DCM, in ARVC-LV phenotype the LV LGE significantly more often appeared as a stria pattern than a spot/patchy pattern (40/41, 98% versus 27/32, 84%; P=0.03). LV LGE more frequently affected the subepicardial layers (40/41, 98% versus 5/32, 16%; P<0.01) in ARVC and the midmural layers in DCM (30/32, 94% versus 9/41, 22%; P<0.01). No linear correlation between LVEF reduction and extent of LV LGE was found in DCM patients with LVEF >40% (r=−0.13, P=0.49), even after adjusted for age and sex (β=−0.11, 95% CI −0.36 to −0.16, P=0.42).

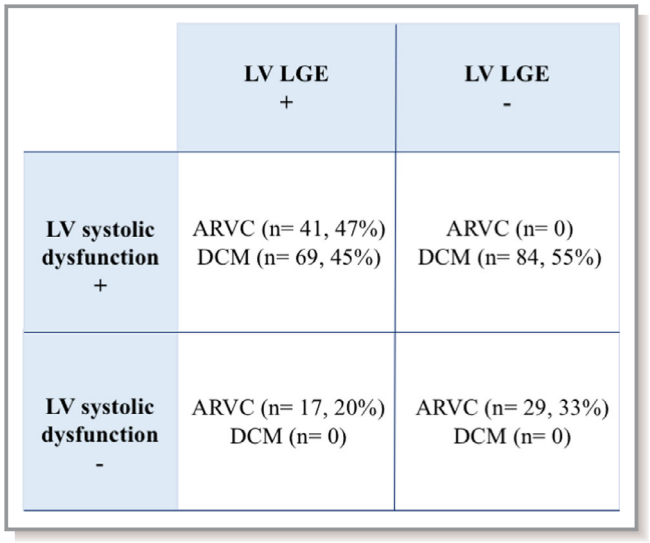

Figure 1. Classification of the study patients according to LV systolic dysfunction and LV LGE. An overlapping LV phenotype was found in 47% of ARVC patients and 45% of DCM patients who showed both LV systolic dysfunction and LV LGE. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular.

Table 2. Baseline Characteristics of DCM Group

	DCM Patients (n=153)
Age at diagnosis, y	51 (41–59)
Male sex	106 (69)
Symptoms	
Chest pain	2 (1)
Syncope	8 (5)
Palpitations	40 (26)
Exertional dyspnea	63 (41)
Family history	
Clinical DCM diagnosis in relatives	22 (14)
Family history of SCD	14 (9)
Mutation carriers	7/22 (32)
Arrhythmic history	
Atrial fibrillation	25 (16)
Major ventricular arrhythmias	10 (7)
Electrocardiographic features	
First degree atrioventricular block	15 (10)
Complete left bundle branch block	41 (27)
LV hypertrophy (Sokolow-Lyon Index)	32 (21)
Left axis deviation	49 (32)
Left anterior fascicular block	31 (20)
Left atrial enlargement	54 (35)
Strain pattern	26 (17)
Low QRS voltages in limb leads (<0.5 mV)	6 (4)
TWI in anterolateral leads (V1–V6)	14/112 (13)*
TWI in lateral leads (V5–V6±V4, I, aVL)	43/112 (38)*
TWI in inferolateral leads (II, III, aVF+[V5–V6±V4 or I, aVL])	6/112 (5)*
CMR findings	
RV EDV, mL/m^2	80 (67–91)
RVEF, %	54 (41–61)
LV analysis	
LV EDV, mL/m^2	137 (112–171)
LV dilatation	153 (100)
LV regional WMA	21 (14)
LV global WMA	132 (86)
LVEF, %	29 (22–37)
LV systolic dysfunction	153 (100)
LV LGE	69 (45)

Values are expressed as number of patients (%) or median (25th and 75th percentiles). CMR indicates cardiovascular magnetic resonance; DCM, dilated cardiomyopathy; EDV, end-diastolic volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; SCD, sudden cardiac death; TFC, Task Force criteria; TWI, T-wave inversion; WMA, wall motion abnormalities.
*LBBB excluded.

Discussion

The present study was designed to assess the prevalence of LV involvement and characterize the clinical and imaging features of LV phenotype in living patients with a diagnosis of ARVC according to the 2010 ITF criteria. Moreover, the study aimed to identify the characteristics of LV phenotype of ARVC which could be useful to obtain a differential diagnosis with the LV phenotype of DCM.

The major results were the following: (1) LV involvement, defined as the evidence of LV systolic dysfunction, non-ischemic LV LGE, or both, was found in two thirds of ARVC patients; (2) LV systolic dysfunction was always associated with the presence of LV LGE; (3) the ARVC-LV phenotype was characterized by peculiar electrocardiographic abnormalities and distinctive imaging and tissue characterization findings; (4) tissue characterization by CMR allowed an accurate differential diagnosis between LV phenotype of ARVC and DCM, which mostly relied on different amount of LV LGE and its relationship to the LV systolic dysfunction. Compared with DCM, the LV phenotype of ARVC was characterized by a larger amount of myocardial fibrosis/LGE, which impacted directly and negatively on the LV systolic function.

LV Involvement in ARVC

LV involvement in ARVC was initially reported by pathological studies, which demonstrated fibrofatty replacement in the LV myocardium in up to 76% of ARVC hearts.[3,4] A recent post-mortem pathological study on ARVC decedents reported histopathologic evidence of LV involvement in 87% of cases.[11] The lower prevalence (67%) of LV involvement in our cohort may be explained by the demographic and clinical characteristics of our study population, which consisted of living patients fulfilling the 2010 ITF criteria, which were designed for the diagnosis of RV phenotype and not for that of biventricular phenotype. Moreover, the criteria for LV involvement used in our study were mostly based on post-contrast CMR images analysis, which may fail to evidence patchy or interstitial myocardial fibrosis.

LV involvement was originally considered an end-stage complication of ARVC, occurring late during the disease course and leading ultimately to biventricular pump failure. Subsequent genotype-phenotype correlations studies showed early and greater LV involvement in relation to specific gene defects.[5,6] In our study, ARVC patients with LV involvement did not show more severe RV disease. This finding further supports the perspective that LV involvement can occur in early stages of ARVC, independently or concurrently with mild RV involvement. These findings are in keeping with the modern concept that ARVC is a cardiomyopathy affecting both ventricles.

Table 3. Clinical, Electrocardiographic, and Imaging Characteristics of LV-Phenotypes in ARVC vs DCM Patients

	ARVC-LV Phenotype n=41	DCM-LV Phenotype n=69	*P* Value
Age at diagnosis, y	39 (18–59)	54 (46–61)	0.001
Male sex	28 (68)	52 (75)	0.421
Symptoms			
Chest pain	5 (12)	1 (1)	0.026
Syncope	11 (27)	5 (7)	<0.001
Palpitations	12 (29)	16 (23)	0.479
Exertional dyspnea	13 (32)	22 (32)	0.985
Family history			
Familial cases of SCD	9 (22)	6 (9)	0.05
Arrhythmic history			
Atrial fibrillation	5 (12)	9 (13)	0.897
Major ventricular arrhythmias	13 (32)	4 (6)	<0.001
Electrocardiographic characteristics			
First degree atrioventricular block	5 (12)	11 (16)	0.590
Complete left bundle branch block	0	19 (28)	<0.001
Sokolow-Lyon Index	1 (2)	14 (20)	0.005
Left axis deviation	7 (17)	26 (38)	0.023
Left anterior fascicular block	5 (12)	14 (20)	0.277
Left atrial enlargement	6 (15)	30 (43)	0.002
Strain pattern	1 (2)	12 (17)	0.029
Low (<0.5 mV) QRS voltages in limb leads	24 (59)	3 (4)	<0.001
TWI in anterolateral leads (V1–V6)	11 (27)	10/50 (20)*	0.442
TWI in lateral leads (V5–V6±V4, I, aVL)	20 (49)	25/50 (50)*	0.908
TWI in inferolateral leads (II, III, aVF+[V5–V6±V4 or I, aVL])	13 (32)	3/50 (6)*	0.001
CMR findings			
LV EDV, mL/m^2	97 (90–108)	141 (120–175)	<0.001
LV dilatation	19 (46)	69 (100)	<0.001
CMR LV mass, g/m^2	66 (55–73)	86 (73–110)	<0.001
LV regional WMA	38 (93)	10 (15)	<0.001
LV global WMA	3 (7)	59 (86)	<0.001
LVEF, %	46 (41–48)	29 (21–39)	<0.001
CMR tissue characterization findings			
LV LGE amount, g	17.2 (12.3–22.5)	11.7 (8.9–15.1)	<0.001
LV LGE amount, %	24.6 (16.8–33.3)	13.1 (9.8–16.3)	<0.001
N° segments involved	9 (7–11)	5 (4–8)	<0.001
>6 segments	32 (78)	21 (30)	<0.001
LV LGE morphology			
Stria	40 (98)	57 (82)	0.029
Spot/patchy	6 (15)	15 (22)	0.359
LV LGE layer			
Subendocardial	1 (2)	4 (6)	0.649

Continued

Table 3. Continued

	ARVC-LV Phenotype n=41	DCM-LV Phenotype n=69	*P* Value
Midmural	9 (22)	66 (96)	<0.001
Subepicardial	40 (98)	11 (16)	<0.001

Values are expressed as number of patients (%) or median (25th and 75th percentiles). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiovascular magnetic resonance; DCM, dilated cardiomyopathy; EDV, end-diastolic volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; SCD, sudden cardiac death; TFC, Task Force criteria; TWI, T-wave inversion; WMA, wall motion abnormalities.
*LBBB excluded.

LV Phenotype in ARVC

Our ARVC patients with LV involvement showed typical electrocardiographic abnormalities, such as low QRS voltages in limb leads, and TWI in the leads exploring the inferolateral LV regions. These electrocardiographic abnormalities reflect the replacement of LV myocardial mass by electrically inert fibrofatty tissue, which mostly involves the inferolateral LV regions.[22] In keeping with previous reports, LV involvement in ARVC was more frequently associated with *DSP* gene mutations.[6,7] Moreover, one third of patients experienced major ventricular arrhythmias, with sustained ventricular tachycardia with an RBBB morphology accounting for half events.

The CMR imaging findings were consistent with the morpho-functional pattern of an "hypokinetic, non-dilated, and fibrotic" LV, ie, a ventricular remodeling characterized by mild systolic dysfunction, mild (or no) dilatation, and large amount of non-ischemic LGE, with or without fatty infiltration.

The mean LVEF ranged from 44% to 54%, with a median value of 49%; a reduced LVEF was found in 71% of patients. The LV end-diastolic volume (indexed for body surface area) ranged from 82 to 105 mL/m^2, with a median value of 93 mL/m^2. Regional WMA were detected in 76%, and most often involved the inferior and lateral LV segments.

The ARVC-LV phenotype was characterized by the large extent of myocardial fibrosis as evidenced by CMR, with an estimated amount of LV LGE ranging from 12.6% to 30.9%, median value of 21.8%. All patients with a reduced LVEF showed LV LGE, whose extent was significantly greater than that of patients with a preserved LV systolic function (24.6% versus 5.1%).

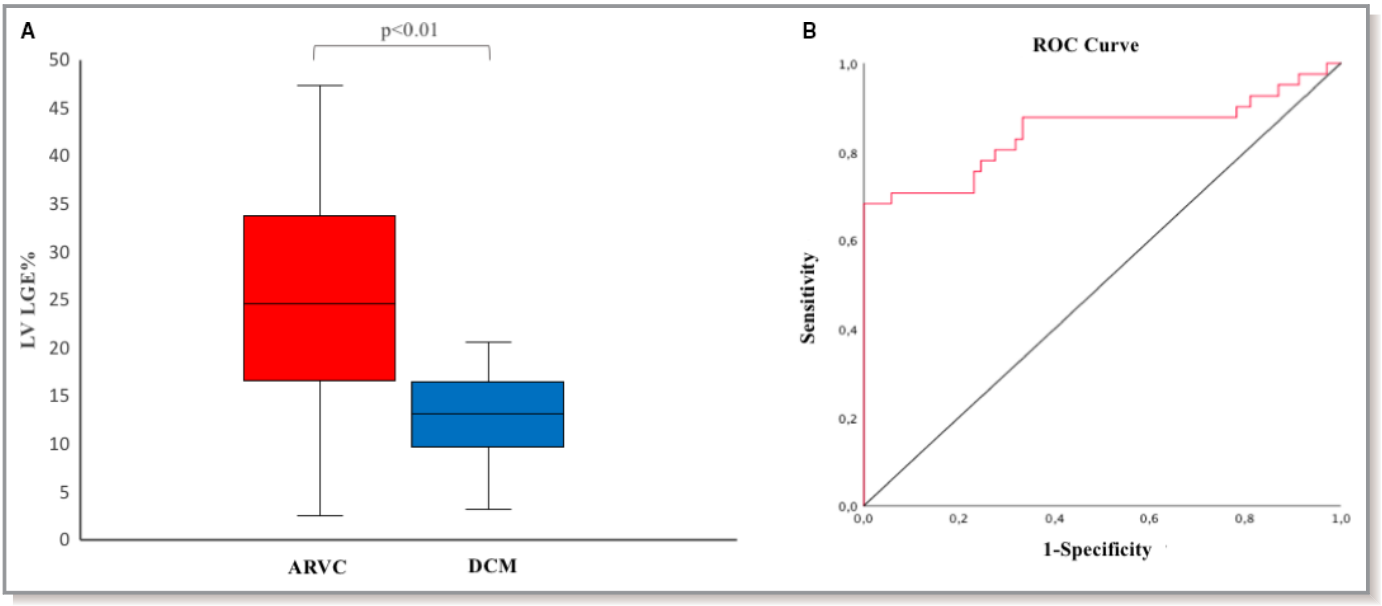

Figure 2. Amount of LGE in ARVC vs DCM. Box plot showing difference of the amount of LV LGE between ARVC- and DCM-LV phenotype (24.6% vs 13.1%, *P*<0.01) (**A**). ROC curve showing the ability of LGE percentage in distinguishing the ARVC- from DCM-LV phenotype: the AUC was 0.84 (SE=0.05, 95% CI 0.75–0.93, *P*<0.01). The best cut-off value of LGE percentage was 20%, which provided a sensitivity of 68% and a specificity of 100% for diagnosis of ARVC-LV phenotype (**B**). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; AUC, area under the curve; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; ROC, receiver operating characteristic.

In keeping with previous reports,[5–7] in our cohort of ARVC patients the LV myocardial fibrosis was predominantly located in the subepicardial layers (93% of cases), and most often involved specific regions such as the inferior and the inferolateral wall. This finding agrees with the notion that the wave-front of myocardial loss and fibrofatty replacement in the LV wall proceeds from the epicardium to the endocardium, with scar tissue mostly confined to the outer layers of the wall, similarly to the RV lesions.[23,24] The subendocardial layer which mostly accounts for the regional LV wall contractility[25] is usually saved, a finding which explains the preservation of global LV systolic function and the lack of WMA in a sizeable proportion of patients. As a corollary, an imaging approach limited to a mere evaluation of the LV function, either global or regional, by echocardiography or cine-CMR appears insufficient to detect LV involvement and characterize the LV phenotype in patients with ARVC.[26]

We found an inverse correlation between the LGE extent and LVEF ($r=-0.63$, $P<0.01$, Figure 4A), a finding which suggests a cause-effect relationship between the amount of myocardial loss with fibrofatty replacement and the severity of LV systolic impairment.

Concomitant LV intramyocardial fat was detected in 57% of patients and was mostly located in the same regions of the deposition of LGE. However, our study may have underestimated the prevalence of fatty tissue because of limitations of conventional non-fat-suppressed Turbo Spin Echo sequences because of poor contrast of microscopic fat and partial-volume effects.[27]

Although myocardial fibro-fatty replacement as evidenced by LGE is the key morphological feature of ARVC, the 2010 ITF diagnostic criteria did not include LGE findings because of concerns about their accuracy and reproducibility. Our study results support the need to revise the ITF diagnostic scoring system for inclusion of CMR myocardial tissue characterization findings among diagnostic criteria for ARVC, because the diagnosis of LV involvement depends on demonstration and quantitation of LGE.

Differential Diagnosis

The LV phenotype of ARVC may overlap with that of DCM because both conditions may show LV systolic dysfunction and myocardial fibrosis. The distinction between the 2 conditions is clinically relevant for risk stratification and treatment. In DCM, the focus with heart failure treatments is on improving quality of life, exercise capacity and outcomes, and the risk from life threatening arrhythmias in the early stages of disease is low. In ARVC, sudden death may be the initial manifestation in the absence of symptoms which limit exercise capacity. Criteria for differentiating these 2 conditions have not been established.

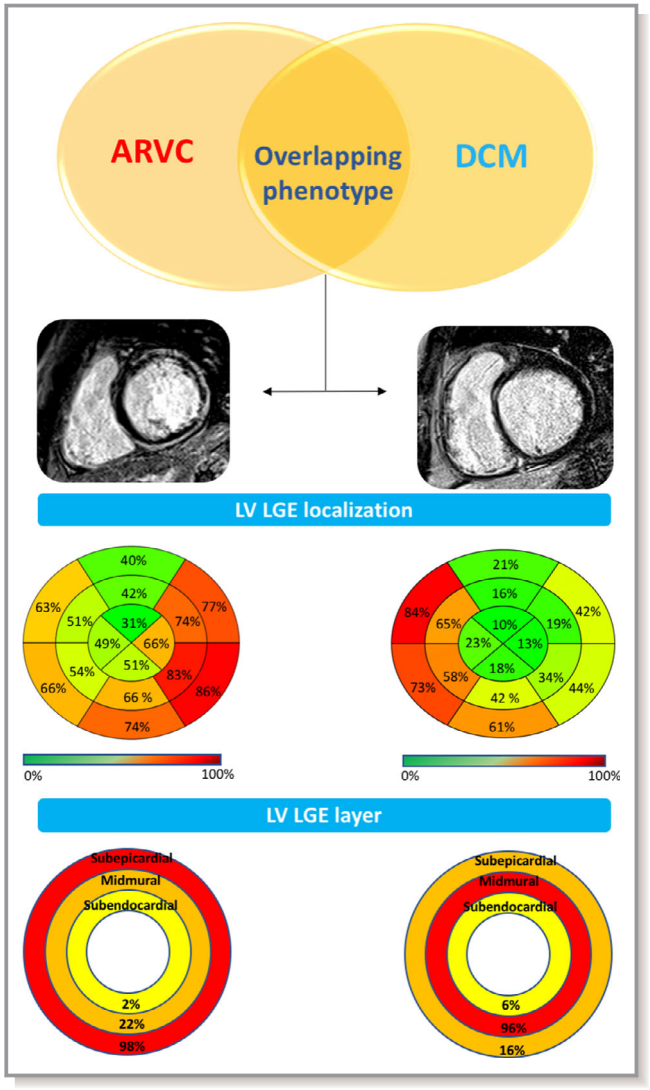

Figure 3. Left ventricular regional and wall layer distribution of LGE in ARVC- and DCM-LV phenotype. Comparison between CMR findings in the subgroup of ARVC (left) and DCM (right) patients with overlapping LV phenotypes (ie, combination of LV systolic dysfunction and LV LGE). Patients with ARVC-LV phenotype had lower LV volume and mass, less depressed LVEF (not shown) and greater amount of LV LGE (ie, "hypokinetic, non-dilated and fibrotic left ventricle") compared with DCM patients. LV LGE predominately affected the infero-lateral segments in ARVC-LV phenotype and septal segments in DCM. Compared with DCM, in ARVC the LV LGE significantly more often appeared as a stria pattern than a spot/patchy pattern and more frequently affected the subepicardial layers. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction.

In our study, familial history of SCD, syncopal episodes, electrocardiographic low QRS voltages in limb leads and T-wave inversion in the inferolateral leads, and major

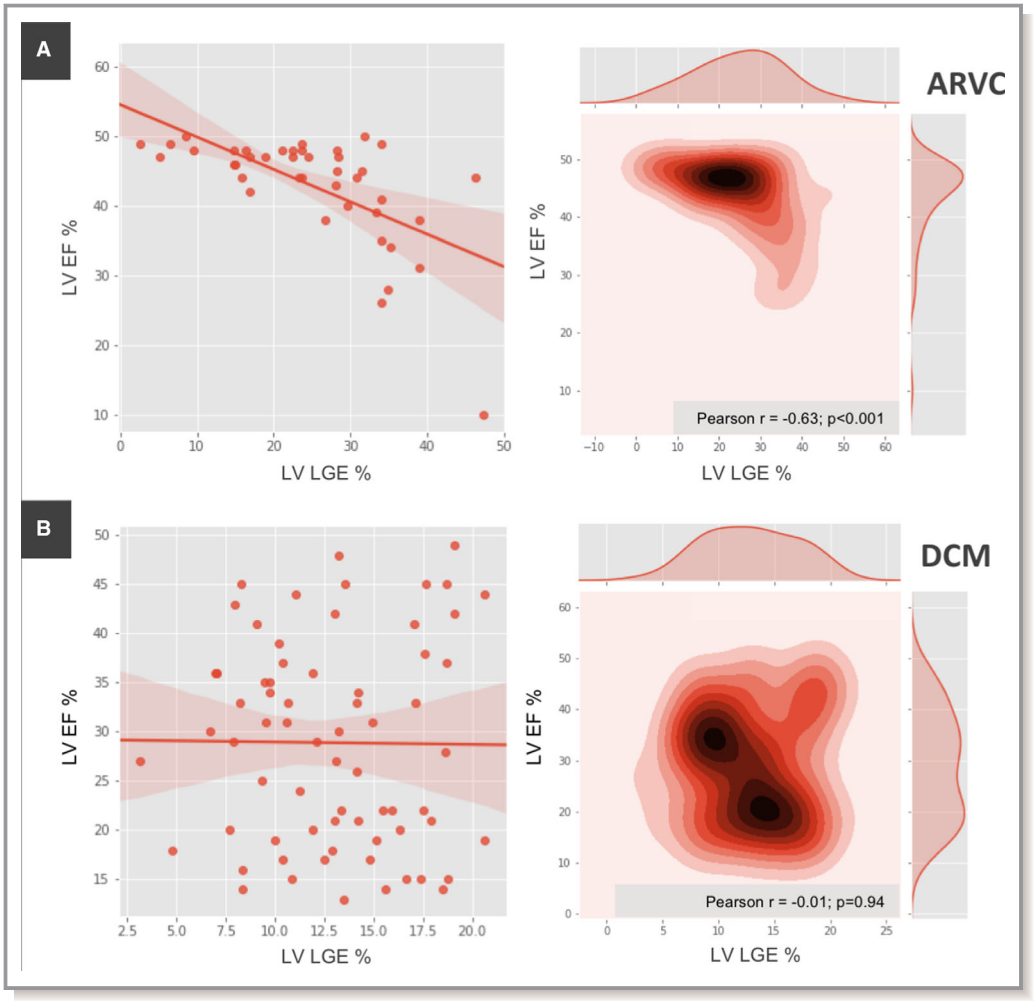

Figure 4. Relationship between the amount of LV LGE and LVEF. Graphs (regression plot—left, joint plot—right) showing the relationship between the amount of LV LGE and LVEF in ARVC- (**A**) and DCM-LV phenotype (**B**). LGE indicates late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction.

ventricular arrhythmias were more frequently associated with the ARVC-LV phenotype. Of note, monomorphic sustained ventricular tachycardia with an RBBB QRS morphology was more frequently observed in patients with ARVC-LV phenotype.

Most important, we identified some differential morpho-functional features which reflect the different pathobiology of the 2 conditions. The primary mechanism of DCM is the depression of ventricular systolic function attributable to impairment of myocyte contractility, which induces a compensatory LV remodeling characterized by ventricular dilatation (according to the Frank-Starling law) and eccentric hypertrophy. At variance with DCM, the ARVC-LV phenotype is characterized by mild hypokinesis and no (or mild) LV dilatation because fibrofatty myocardial replacement is confined to the outer layers of the wall and does not induce a significant reduction of the global LV systolic function. Accordingly, compared with patients with DCM, most of our patients with ARVC-LV phenotype had a milder depression of LVEF with LV volume and mass within normal values.

Our study results showed that the most important differences between the 2 LV phenotypes rely on LGE extent and regional distribution. In keeping with previous studies, LGE was detected in <50% of DCM cases[28–31]; by contrast, 100% of ARVC patients with LV systolic dysfunction showed the presence of LV LGE. The amount of LGE was significantly greater in ARVC-LV phenotype than in DCM (Figure 2A): the presence of LV LGE ≥20% of the LV mass, provided a 100% specificity for diagnosis of the ARVC-LV phenotype. The distribution of LGE also differed between the 2 conditions, predominately affecting mid-mural septal segments in DCM versus subepicardial inferolateral regions in ARVC-LV phenotype (Figures 5 and 6). Unlike ARVC-LV phenotype, the amount of LV LGE in DCM was unrelated to the severity of LV

Table 4. Electrocardiographic and Imaging Characteristics of LV-Phenotypes in ARVC Patients vs DCM Patients With LVEF >40%

	ARVC-LV Phenotype n=41	DCM-LV Phenotype (LVEF >40%) n=32	*P* Value
Electrocardiographic characteristics			
First degree atrioventricular block	5 (12)	4 (13)	0.969
Complete left bundle branch block	0	11 (34)	<0.001
Sokolow-Lyon Index	1 (2)	7 (22)	0.018
Left axis deviation	7 (17)	10 (31)	0.155
Left anterior fascicular block	5 (12)	6 (19)	0.518
Left atrial enlargement	6 (15)	6 (19)	0.638
Strain pattern	1 (2)	3 (9)	0.313
Low (<0.5 mV) QRS voltages in limb leads	24 (59)	1 (3)	<0.001
TWI in anterolateral leads (V1–V6)	11 (27)	2/23 (9)*	0.043
TWI in lateral leads (V5–V6±V4, I, aVL)	20 (49)	4/23 (17)*	0.001
TWI in inferolateral leads (II, III, aVF+[V5–V6± V4 or I, aVL])	13 (32)	2 (6)	<0.001
CMR findings			
LV EDV, mL/m^2	97 (90–108)	120 (108–136)	<0.001
LV dilatation	19 (46)	32 (100)	<0.001
CMR LV mass, g/m^2	66 (55–73)	79 (63–90)	0.012
LV regional WMA	38 (93)	6 (19)	<0.001
LV global WMA	3 (7)	26 (81)	<0.001
LVEF, %	46 (41–48)	43 (41–45)	0.091
CMR tissue characterization findings			
LV LGE amount, g	17.2 (12.3–22.5)	7.8 (6.4–13.1)	<0.001
LV LGE amount, %	24.6 (16.8–33.3)	10.4 (8.3–17.3)	<0.001
N° segments involved	9 (7–11)	5 (3–7)	<0.001
>6 segments	32 (78)	7 (22)	<0.001
LV LGE morphology			
Stria	40 (98)	27 (84)	0.034
Spot/patchy	6 (15)	6 (19)	0.574
LV LGE layer			
Subendocardial	1 (2)	0	0.956
Midmural	9 (22)	30 (94)	<0.001
Subepicardial	40 (98)	5 (16)	<0.001

Values are expressed as number of patients (%) or median (25th and 75th percentiles). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiovascular magnetic resonance; DCM, dilated cardiomyopathy; EDV, end-diastolic volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; SCD, sudden cardiac death; TFC, Task Force criteria; TWI, T-wave inversion; WMA, wall motion abnormalities.
*LBBB excluded.

systolic dysfunction (Figure 4B). All these findings support the concept that at variance with ARVC-LV phenotype, LV fibrosis in DCM should be considered an epiphenomenon, unrelated to the mechanism primarily responsible for the myocardial contractile impairment.

To overcome a potential bias towards patients with DCM and severe LVEF depression, we performed a subanalysis comparing electrocardiographic and CMR features of ARVC-LV phenotype (median value LVEF 46%, interquartile range 41–48) with those in the subgroup of DCM with LVEF >40% (median value LVEF 43%, interquartile range 41–45). The subanalysis confirmed the significant differences of electrocardiographic alterations and CMR abnormalities between the 2 groups of

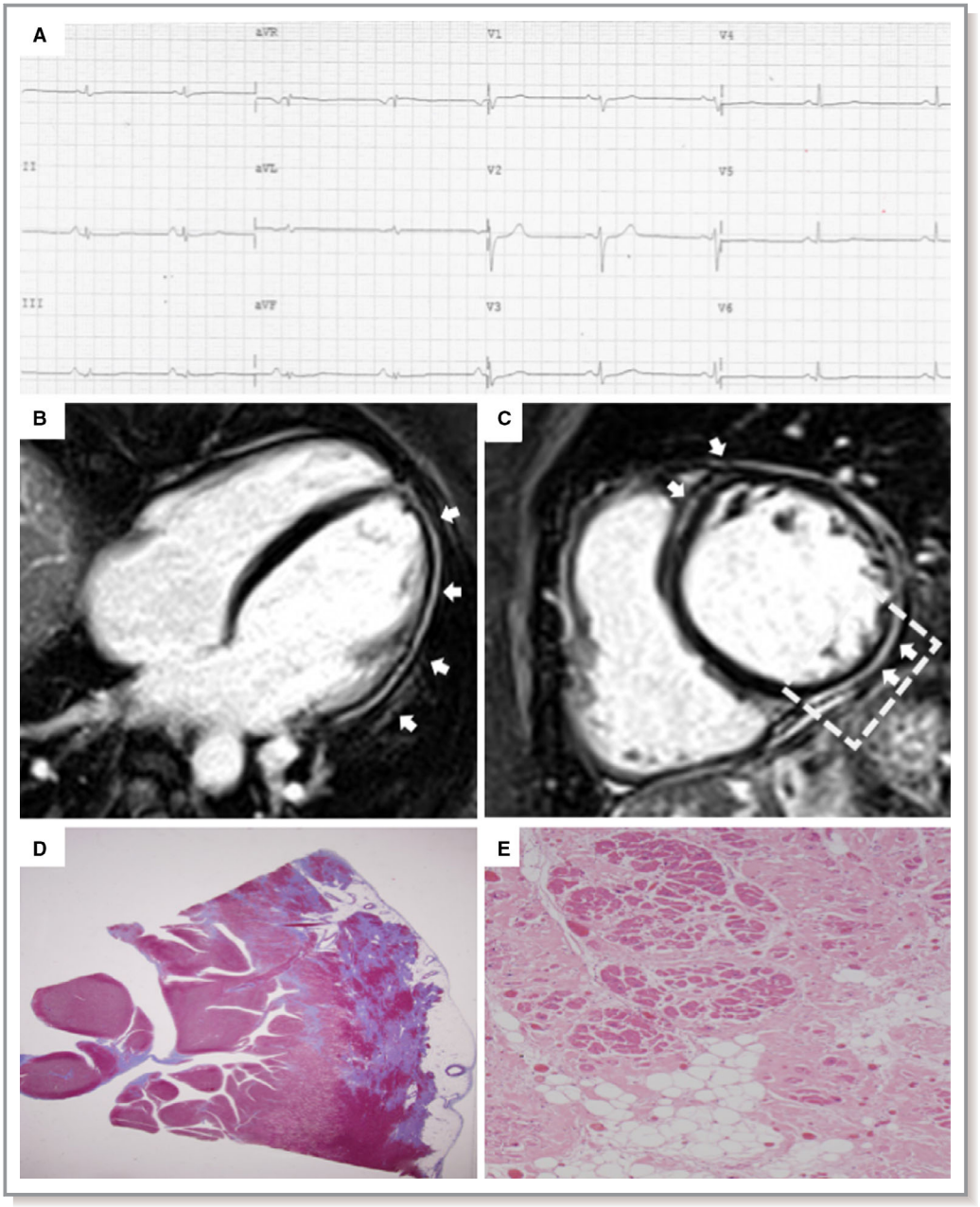

Figure 5. Electrocardiographic, CMR imaging, and histological features of a representative patient with ARVC undergoing cardiac transplantation. Basal ECG showing low voltages in limb leads and flattened T-waves in the inferolateral leads (**A**). Post-contrast CMR images in long-axis (**B**) and short-axis (**C**) views showing normal LV cavity size and subepicardial LGE (white arrows) involving the LV free wall (boxed area) and septum, from basal to apical regions (white arrows). Histologic examination of the boxed area showing fibro-fatty myocardial replacement affecting the subepicardial LV layer (Heidenhain trichrome stain) (**D**); close up detailing residual myocytes embedded within fibrous and fatty tissue (E.E stain) (**E**). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular.

cardiomyopathies, that were found in the principal analysis. These findings substantiate the concept that the differences in the LV phenotypes are unrelated to the severity of LV systolic dysfunction, representing an intrinsic characteristic of the 2 cardiomyopathies.

In the current guidelines of the European Society of Cardiology, the so-called "hypokinetic, non-dilated cardiomyopathy (HNDC)" has been classified as part of the clinical spectrum of DCM and considered as a less expressed disease phenotype.[13] However, the increasing use of CMR for better

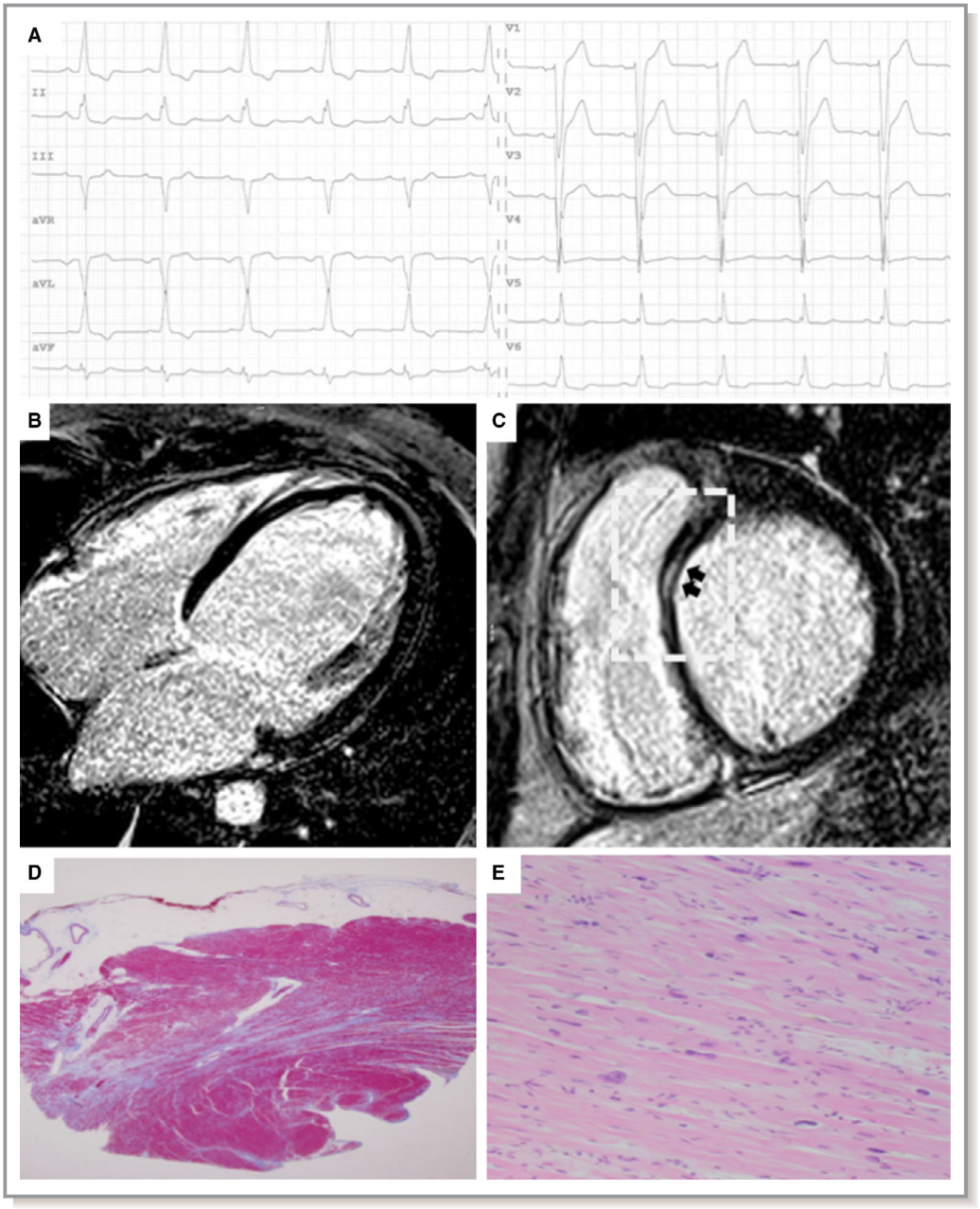

Figure 6. Electrocardiographic, CMR imaging, and histological features of a representative patient with DCM undergoing cardiac transplantation. Basal ECG showing complete left bundle branch block (**A**). Post-contrast CMR images in long-axis (**B**) and short-axis (**C**) view showing a severe dilatation LV cavity and myocardial LGE (black arrows), confined to the anteroseptal region (boxed area). Histologic examination of the boxed area confirming a patchy midmural fibrosis (Heidenhain trichrome stain) (**D**); close up showing dilated myocytes (normal cell count) with dysmetric and dysmorphic nuclei (E.E stain) (**E**). CMR indicates cardiac magnetic resonance; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular.

characterization of the myocardial changes in DCM provided new insights in our understanding of DCM phenotype, showing that HNDC is distinctively characterized by a large, non-transmural scarring of the LV which scarcely affects the global LV systolic function. According to the result of our study, the LV phenotype of ARVC fits well with that of HNDC, suggesting that a proportion of cardiomyopathies previously deemed as less phenotypically expressed DCM may be re-classified as biventricular or left-dominant ARVC.

The ARVC-LV phenotype is associated with a distinctively higher risk of SCD because myocardial fibrosis may act as a substrate for life-threatening ventricular arrhythmias. This has

significant implications for treatment of ARVC patients with LV involvement, including indication for implantable cardioverter-defibrillator that, unlike DCM, should be considered in the presence of large ventricular scarring, even if the LV systolic function is not severely impaired.[32]

Study Limitations

Major limitations include the retrospective nature of the study and a possible referral bias because of recruitment of study patients from a tertiary center. T1-weighted non-fat-suppressed Turbo Spin Echo sequences were not performed in DCM patients, because they were not included in the study protocol for DCM in our CMR laboratory. However, none of the DCM patients showed signs of fat infiltration through evaluation of localizer, cine, or post-contrast images. By study design, we did not address the genetic background and the genotype-phenotype correlation of ARVC and DCM because the aim of the present investigation was to assess the distinctive clinical and imaging features of ARVC-related LV phenotype and their value for differential diagnosis with DCM. In addition, a genotype-phenotype analysis of our study population was not feasible because of the limited number of probands with familial DCM who underwent molecular genotyping. Hence, the relationship of electrocardiographic and CMR features with the specific genetic defects remains unaddressed. Follow-up data were not provided because they were beyond the scope of our study.

Conclusions

LV involvement in ARVC is common and characterized phenotypically by clinical and CMR features which allow differential diagnosis with DCM. The most distinctive feature of ARVC-LV phenotype was the large amount of LV myocardial fibrosis/LGE, which was directly related to the LV systolic dysfunction. The remodeling pattern of "hypokinetic, non-dilated, and fibrotic" LV fits better with an ARVC-LV phenotype than with a phenotypically less expressed DCM. The fibro-fatty myocardial replacement of a significant proportion of LV musculature accounts for the low QRS voltages on the ECG and acts as a substrate for life-threatening ventricular arrhythmias. These findings have significant implications for diagnosis, prognosis, and treatment of ARVC.

Sources of Funding

This work was supported by the Registry for Cardio-Cerebro-Vascular Pathology, Veneto Region, Venice, Italy; Ministry of Health grant RF-2013-02356762 and RF-2014-00000394; University Research grants CPDA144300, BIRD162733 and BIRD160519, Padua, Italy; PRIN Ministry of Education, University and Research 2015ZLNETW, Rome, Italy, and the CARIPARO Foundation 2018-0110, Padua, Italy.

Disclosures

None.

References

1. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation*. 1982;65:384–398.
2. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med*. 1988;318:129–133.
3. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation*. 1996;94:983–991.
4. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom-Lundqvist C, Wlodarska EK, Fontaine G, Camerini F. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol*. 1997;30:1512–1520.
5. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, Pennell DJ, McKenna WJ. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol*. 2008;52:2175–2187.
6. Bauce B, Basso C, Rampazzo A, Beffagna G, Daliento L, Frigo G, Malacrida S, Settimo L, Danieli G, Thiene G, Nava A. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. *Eur Heart J*. 2005;26:1666–1675.
7. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation*. 2007;115:1710–1720.
8. Perazzolo Marra M, Rizzo S, Bauce B, De Lazzari M, Pilichou K, Corrado D, Thiene G, Iliceto S, Basso C. Arrhythmogenic right ventricular cardiomyopathy. Contribution of cardiac magnetic resonance imaging to the diagnosis. *Herz*. 2015;40:600–606.
9. Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P, Sen-Chowdhry S, Rowland E, Crosby A, McKenna WJ. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. *Circulation*. 2005;112:636–642.
10. D'Amati G, Leone O, di Gioia CR, Magelli C, Arpesella G, Grillo P, Marino B, Fiore F, Gallo P. Arrhythmogenic right ventricular cardiomyopathy: clinico-pathologic correlation based on a revised definition of pathologic patterns. *Hum Pathol*. 2001;32:1078–1086.
11. Miles C, Finocchiaro G, Papadakis M, Gray B, Westaby J, Ensam B, Basu J, Parry-Williams G, Papatheodorou E, Paterson C, Malhotra A, Robertus JL, Ware JS, Cook SA, Asimaki A, Witney A, Ster IC, Tome M, Sharma S, Behr ER, Sheppard MN. Sudden death and left ventricular involvement in arrhythmogenic cardiomyopathy. *Circulation*. 2019;139:1786–1797.
12. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. *Circulation*. 2010;121:1533–1541.
13. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J*. 2016;37:1850–1858.
14. Nava A, Bauce B, Basso C, Muriago M, Rampazzo A, Villanova C, Daliento L, Buja G, Corrado D, Danieli GA, Thiene G. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol*. 2000;36:2226–2233.
15. Rigato I, Bauce B, Rampazzo A, Zorzi A, Pilichou K, Mazzotti E, Migliore F, Marra MP, Lorenzon A, De Bortoli M, Calore M, Nava A, Daliento L, Gregori D, Iliceto S, Thiene G, Basso C, Corrado D. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6:533–542.

16. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2009;119:e235–e240.

17. Zorzi A, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, Pilichou K, Migliore F, Rizzo S, Giorgi B, De Conti G, Sarto P, Serratosa L, Patrizi G, De Maria E, Pelliccia A, Basso C, Schiavon M, Bauce B, Iliceto S, Thiene G, Corrado D. Nonischemic left ventricular scar as a substrate of life-threatening ventricular arrhythmias and sudden cardiac death in competitive athletes. *Circ Arrhythm Electrophysiol*. 2016;27:80–87.

18. Cipriani A, Zorzi A, Sarto P, Donini M, Rigato I, Bariani R, De Lazzari M, Pilichou K, Thiene G, Iliceto S, Basso C, Corrado D, Perazzolo Marra M, Bauce B. Predictive value of exercise testing in athletes with ventricular ectopy evaluated by cardiac magnetic resonance. *Heart Rhythm*. 2019;16:239–248.

19. Petersen SE, Aung N, Sanghvi MM, Zemrak F, Fung K, Paiva JM, Francis JM, Khanji MY, Lukaschuk E, Lee AM, Carapella V, Kim YJ, Leeson P, Piechnik SK, Neubauer S. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson*. 2017;19:18.

20. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. *Circulation*. 2002;105:539–542.

21. Almehmadi F, Joncas SX, Nevis I, Zahrani M, Bokhari M, Stirrat J, Fine NM, Yee R, White JA. Prevalence of myocardial fibrosis patterns in patients with systolic dysfunction: prognostic significance for the prediction of sudden cardiac arrest or appropriate implantable cardiac defibrillator therapy. *Circ Cardiovasc Imaging*. 2014;7:593–600.

22. De Lazzari M, Zorzi A, Cipriani A, Susana A, Mastella G, Rizzo A, Rigato I, Bauce B, Giorgi B, Lacognata C, Iliceto S, Corrado D, Perazzolo Marra M. Relationship between electrocardiographic findings and cardiac magnetic resonance phenotypes in arrhythmogenic cardiomyopathy. *J Am Heart Assoc*. 2018;7:e009855. DOI: 10.1161/JAHA.118.009855.

23. Corrado D, Basso C, Judge DP. Arrhytmhogenic cardiomyopathy. *Circ Res*. 2017;121:784–802.

24. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med*. 2017;376:61–62.

25. Rademakers FE, Rogers WJ, Guier WH, Hutchins GM, Siu CO, Weisfeldt ML, Weiss JL, Shapiro EP. Relation of regional cross-fiber shortening to wall thickening in the intact heart. Three-dimensional strain analysis by NMR tagging. *Circulation*. 1994;89:1174–1182.

26. Kellman P, Hernando D, Shah S, Zuehlsdorff S, Jerecic R, Mancini C, Liang ZP, Arai AE. Multi-echo dixon fat and water separation method for detecting fibrofatty infiltration in the myocardium. *Magn Reson Med*. 2009;61:215–221.

27. Zorzi A, Rigato I, Pilichou K, Perazzolo Marra M, Migliore F, Mazzotti E, Gregori D, Thiene G, Daliento L, Iliceto S, Rampazzo A, Basso C, Bauce B, Corrado D. Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. *Europace*. 2016;18:1086–1094.

28. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarj K, Brown TD, Ismail NA, Dweck MR. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA*. 2013;309:896–908.

29. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, Vettor G, Tona F, Tarantini G, Cacciavillani L, Corbetti F, Giorgi B, Miotto D, Thiene G, Basso C, Iliceto S, Corrado D. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm*. 2014;11:856–863.

30. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation*. 2003;108:54–59.

31. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, Arzanauskaite M, Lota A, Tayal U, Vassiliou VS, Gregson J, Alpendurada F, Frenneaux MP, Cook SA, Cleland JGF, Pennell DJ, Prasad SK. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *JACC Cardiovasc Imaging*. 2019;12(8 Pt 2):1645–1655.

32. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, Basso C, Bauce B, Brunckhorst C, Bucciarelli-Ducci C, Duru F, Elliott P, Hamilton RM, Haugaa KH, James CA, Judge D, Link MS, Marchlinski FE, Mazzanti A, Mestroni L, Pantazis A, Pelliccia A, Marra MP, Pilichou K, Platonov PGA, Protonotarios A, Rampazzo A, Saffitz JE, Saguner AM, Schmied C, Sharma S, Tandri H, Te Riele ASJM, Thiene G, Tsatsopoulou A, Zareba W, Zorzi A, Wichter T, Marcus FI, Calkins H; International Experts. Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J*. 2019; DOI: 10.1093/eurheartj/ehz669 [Online ahead of print].