Left Ventricular Involvement in Arrhythmogenic Right Ventricular Cardiomyopathy – A Cardiac Magnetic Resonance Imaging Study

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ABSTRACT

BACKGROUND: Few studies evaluated left ventricular (LV) involvement in arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C). The aim of this study is to determine the frequency, clinical presentation, and pattern of LV involvement in ARVD/C (LV-ARVD/C).

METHODS: We retrospectively evaluated the cardiac magnetic resonance (CMR) in 210 patients referred between 2008 and 2012 to our institution, and we determined the presence or the absence of CMR criteria in the revised task force criteria 2010 for the diagnosis of ARVD/C. A total of 21 patients were diagnosed with ARVD/C according to the revised task force criteria 2010. All included patients had no previous history of myocarditis, acute coronary syndrome, or any other cardiac disease that could interfere with the interpretations of structural abnormalities. The LV involvement in ARVD/C was defined by the presence of one or more of the following criteria: LV end-diastolic volume (LVEDV; >95 mL/m²), LV ejection fraction (LVEF; <55%), LV late enhancement of gadolinium (LVLE) in a non-ischemic pattern, and LV wall motion abnormalities (WMAs). In the follow-up for the occurrence of cardiac death, ventricular tachycardia (VT) was obtained at a mean of 31 ± 20.6 months.

RESULTS: A total of 21 patients had ARVD/C. The median age was 48 (33–63) years. In all, 11 patients (52.4%) had LV-ARVD/C. The demographic characteristics of patients with or without LV were similar. There was a higher frequency of left bundle–branch block (LBBB) VT morphology in ARVD/C (P = 0.04). In CMR, regional WMAs of right ventricle (RV) and RV ejection fraction (RVEF; <45%) were strongly correlated with LV-WMAs (r = 0.72, P = 0.02, r = 0.75, P = 0.02, respectively), LV late enhancement of gadolinium (RVLE) was associated with LV-WMAs and LVLE (r = 0.7, P = 0.03; r = 0.8, P = 0.006), LVLE was associated with LV-WMAs, LVEF, and LVEDV (r = 0.9, P = 0.001; r = 0.8, P = 0.001; r = 0.8, P = 0.01).

CONCLUSION: LV involvement in ARVD/C is common and frequently associated with moderate to severe right ventricular (RV) abnormalities. The impact of LV involvement in ARVD/C on the prognosis needs further investigations.

KEYWORDS: arrhythmogenic right ventricular dysplasia, left ventricle, cardiac magnetic resonance imaging, prognosis

Introduction

Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C) is a rare disease. The estimated prevalence of the disease in the general population ranges from 1 in 1000 to 1 in 5000.1 ARVD/C has been originally described as an inherited cardiomyopathy characterized by structural and functional abnormalities because of a progressive replacement of right ventricular (RV) myocardium by fibro-fatty tissues.2 ARVD/C predisposes patients to sudden death and ventricular arrhythmia, typically among young subjects and athletes,3 and leads to progressive heart failure.1,2,4

References

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Molecular genetic studies provide evidence that fibro-fatty replacement is caused by mutation-related desmosomal changes. The diagnosis of ARVD/C is still challenging and is currently based on a multi-disciplinary evaluation of the patient, as defined by the task force of 1994 and, more recently, the modified proposal of task force of 2010 to improve the diagnosis and management of ARVD/C with increased sensitivity and without loss of specificity.

A few studies reported left ventricular (LV) involvement in ARVD/C (LV-ARVD/C). In those studies, the diagnosis of LV-ARVD/C was based on echocardiography, myocardial scintigraphy, magnetic resonance imaging (MRI), and autopsy studies. The place of the LV involvement in the natural history of the disease remains to be established.

There are very few cardiac magnetic resonance (CMR) studies evaluating the LV involvement in ARVD/C. The aim of the present study was to report the frequency, the severity, and the prognosis of LV involvement using CMR in patients diagnosed with ARVD/C.

### Materials and Methods

**Patients and study design.** We retrospectively evaluated the CMR in 202 patients referred between 2008 and 2012 to our institution, and we determined the presence or the absence of CMR criteria in the revised task force criteria 2010 for the diagnosis of ARVD/C. The criteria used in order to sort the request of all CMR referred to our institution were LV-ARVD/C, RV dysplasia, RV akinesia, RV dyskinesia, RV hypokinesia, RV dilatation, sudden death, cardiac arrest, ventricular tachycardia (VT), and premature ventricular contractions (PVCs). Twenty one patients were diagnosed with ARVD/C according to the revised task force criteria in the revised task force criteria 2010. The clinical history and previous personal and family history were recorded for the 21 ARVD/C patients. All included patients had no previous history of myocarditis, acute coronary syndrome, or any other cardiac disease that could interfere with the interpretations of structural abnormalities. This research was exempt from the requirement of obtaining ethics committee approval, because of the retrospective nature of the research. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Electrocardiogram (ECG) analysis.** ECGs were analyzed according to the revised task force criteria 2010, looking for epsilon waves and inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age in the absence of complete right bundle-branch block (RBBB) QRS $\geq$ 120 milliseconds, in leads V1 and V2 in individuals >14 years of age in the absence of complete RBBB, in leads V4, V5, or V6, or in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB. Ventricular arrhythmia was recorded. Non-sustained ventricular tachycardia (NSVT) ($\geq$ 3 consecutive beats at $\geq$ 120 bpm with a duration <30 seconds) sustained VT (>30 seconds duration). PVCs of RBBB and left bundle-branch block (LBBB) morphologies were presumed of LV and RV origins, respectively. Biventricular arrhythmia was defined by the presence of PVCs of both RBBB and LBBB morphologies.

**CMR acquisitions.** Images were performed on a 1.5 Tesla MR system (Aera XQ, Siemens) using a cardiac phased-array coil and ECG gating. Steady-state free precession (SSFP) sequences were used for the evaluation of left and right ventricles (RVs).

**RV parameters.** Cine images were acquired in stacked axial datasets. The workstation calculated end-systolic and end-diastolic RV volumes using the method of summation of discs. The RV ejection fraction (RVEF) was calculated. The LV was divided into three levels in the short-axis plane: basal, mid, and apical. The infundibulum, anterior, inferior, and lateral walls were assessed.

**Left ventricle (LV) parameters.** Cine images were acquired in the short axis. The workstation calculated end-systolic and end-diastolic LV volumes using the method of summation of discs. The LV ejection fraction (LVEF) was calculated.

**RV involvement.** The study of the RV involvement is based on the revised task force criteria 2010 in CMR and echocardiography. CMR criteria of RV involvements were regional RV akinesia or dyskinesia or dys synchronous RV contraction and one of the following: ratio of RV end-diastolic volume to body size area (BSA) $\geq$ 100 mL/m$^2$ (male) or $\geq$ 90 mL/m$^2$ (female) or RVEF $\leq$ 45%.

**LV involvement.** In this study, LV involvement was considered present if one or more of the following CMR criteria were present, as determined by the first CMR study evaluating LV involvement in ARVD/C: LVEF $<55\%$, LVLE in a non-ischemic pattern, LV dilatation with LV end-diastolic volume (LVEDV) $>95$ mL/m$^2$ for male and 90 mL/m$^2$ for women, and/or LV wall motion abnormalities (WMAs).

**Clinical endpoints.** Cardiac death was defined as any death with demonstrable cardiac cause or any death that was not clearly attributable to a non-cardiac cause: the occurrence of syncope, VT, ventricular fibrillation (VF), implantable cardioverter defibrillator (ICD), hospitalization for heart failure, or cardiac transplantation. The follow-up was obtained at a mean of 31 $\pm$ 20.6 months.

**Statistical analysis.** Continuous variables were analyzed for normal distribution with the Shapiro-Wilk test. Continuous variables were expressed as median (25 and 75 interquartile ranges), and categorical variables were expressed as frequencies and percentages. Patients were classified into two groups: patients without LV involvement (ARVD/C) and patients with LV involvement (LV-ARVD/C). Continuous variables were compared between the two subgroups by non-parametric Mann–Whitney U test as the distribution was not normal. Fisher’s exact tests have been used for comparison of categorical variables. Relationship between two continuous variables was assessed with Pearson’s correlation coefficient;
Spearman’s rank correlation was used when either or both variables were ordinal. A $P$ value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 19.0 software.

**Results**

**Demographics, ECG, and arrhythmic findings.** A total of 21 patients had ARVD/C. Major and minor criteria, modified task force criteria 2010, met by each patient are summarized in Table 1. The median age of patients was 48 (33–63) years. In all, 11 patients (52%) had LV involvement (LV-ARVD/C) (Table 2). In ARVD/C, it was more common, but there was no difference in male/female ratio between ARVD/C and LV-ARVD/C. In all, 12 of the 21 patients (57%) were symptomatic; the most frequent symptom was palpitation. A total of 11 patients (52%) had ECG abnormalities with inverted T waves and 10 (48%) fulfilled the major revised task force criteria for repolarization abnormalities. In all, 12 (57%) patients presented NSVT or VT. The most frequent VT morphology was LBBB morphology (58.3%) originating from the RV. There was signi-

| TOTAL (n=21) | MODIFIED TASK FORCE MAJOR CRITERIA | MODIFIED TASK FORCE MINOR CRITERIA |
|--------------|-----------------------------------|-----------------------------------|
| N°1 (F)      | Sustained ventricular tachycardia of LBBB morphology with superior axis | Inverted T waves in leads V1, V2, V3, and V4 in the presence of complete RBBB |
|              | Epsilon wave in the right precordial leads (V1 to V3) | | |
|              | By CMR: RV anterior wall akinesia and inferior wall dyskinesia and RVEDV 130 ml/m², RVEF 27% | | |
| N°2 (M)      | Sustained ventricular tachycardia of LBBB morphology with superior axis | NSVT of RV outflow configuration, LBBB morphology with inferior axis |
|              | Inverted T waves in leads V1, V2, V3, and V4 in the absence of complete RBBB | | |
|              | By CMR: RV anterior, lateral and Infundibulum walls akinesia and RVEDV 159 ml/m², RVEF 30% | | |
| N°3 (M)      | By CMR: RV anterior and inferior walls akinesia and FEVD 30% | | |
| N°4 (M)      | Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB | NSVT of LBBB morphology with inferior axis |
|              | By CMR: RV lateral wall dyskinesia, RVEDV 140 ml/m² | Late potentials by SAECG, Filtered QRS duration (fQRS) 117 ms, duration of terminal QRS 40 <µV 50 ms |
| N°5 (M)      | Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB | >500 ventricular extrasystoles per 24 hours (Holler) |
|              | By CMR: RV inferior wall dyskinesia, RVEDV 115 ml/m² RVEF 30% | NSVT of RV outflow configuration, LBBB morphology with inferior axis |
| N°6 (M)      | By CMR: RV Infundibulum and inferior wall dyskinesia, RVEDV 120 ml/m² | >500 ventricular extrasystoles per 24 hours (Holler) |
|              | | RV Infundibulum dyskinesia, RVEDV 120 ml/m² |
|              | | NSVT of LBBB morphology with inferior axis |
| N°7 (M)      | Sustained ventricular tachycardia of LBBB morphology with superior axis | | |
|              | By CMR: RV Infundibulum and inferior dyskinesia, RVEDV 120 ml/m² | | |
| N°8 (M)      | Inverted T waves in right precordial leads (V1, V2, and V3) in the absence of complete RBBB | Late potentials by SAECG, Filtered QRS duration (fQRS) 118 ms, duration of terminal QRS 40 <µV 40 ms |
| N°9 (M)      | Sustained ventricular tachycardia of LBBB morphology with superior axis | | |
|              | Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB | | |
|              | By CMR: under RV tricuspid inflow dyskinesia, RVEF 30% | | |
| N°10 (M)     | Sustained ventricular tachycardia of LBBB morphology with superior axis | Late potentials by SAECG, Filtered QRS duration (fQRS) 116 ms, duration of terminal QRS 40 <µV 45 ms |
|              | By CMR: RV Infundibulum dyskinesia, RVEDV 120 ml/m² | | |
| N°11 (F)     | Sustained ventricular tachycardia of LBBB morphology with superior axis | >500 ventricular extrasystoles per 24 hours (Holler) |
|              | Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB | Late potentials by SAECG, Filtered QRS duration (fQRS) 116 ms, duration of terminal QRS 40 <µV 45 ms |
|              | By CMR: RV anterior and inferior walls akinesia, RVEDV 120 ml/m² | | |
| N°12 (M)     | Epsilon in the right precordial leads (V1 to V3) | | |
|              | Inverted T waves in leads V1, V2, V3, and V4 in the absence of complete RBBB | | |
|              | By CMR: RV anterior wall and Infundibulum dyskinesia, RVEDV 119 ml/m² RVEF 34% | | |

(Continued)
Table 1. ARVD/C modified task force criteria 2010 met by LV-ARVD/C population.

| TOTAL (n = 21) | MODIFIED TASK FORCE MAJOR CRITERIA | MODIFIED TASK FORCE MINOR CRITERIA |
|---------------|-----------------------------------|-----------------------------------|
| N°13 (F)      | – Sustained ventricular tachycardia of LBB morphology with superior axis  
               – Inverted T waves in right precordial leads V1, V2, V3, and V4 in absence of complete RBBB | |
| N°14 (F)      | – By CMR: RV anterior and inferior walls akinesia, FEVD 27%, RVEDV 110 ml/m²  
               – Sustained ventricular tachycardia of LBBB morphology with superior axis | |
| N°15 (M)      | – ARVD/C confirmed pathologically at autopsy in a first-degree relative  
               – By CMR: RV Infundibulum and anterior dyskinesia RVEDV 118 ml/m² | |
| N°16 (M)      | – ARVD/C confirmed pathologically at autopsy in a first-degree relative  
               – ARVD/C confirmed in a first-degree relative who meets modified Task Force criteria | |
| N°17 (F)      | – Inverted T waves in leads V1, V2, V3, and V4 in the absence of complete RBBB  
               – By CMR: RV inferior and anterior wall akinesia, RVEVD 104 ml/m² | – >500 ventricular extrasystoles per 24 hours (Holter) |
| N°18 (F)      | – Inverted T waves in V1, V2, and V3 in the absence of complete RBBB  
               – 2D echocardiography: PLAX RVOT 35 mm, RV anterior free wall dyskinesia | – >500 ventricular extrasystoles per 24 hours (Holter) |
| N°19 (F)      | – By CMR: RV anterior wall akinesia, RVEVD 115 ml/m² | – >500 ventricular extrasystoles per 24 hours (Holter)  
               – Late potentials by SAECG, Filtered QRS duration (fQRS) 116 ms, duration of terminal QRS 40 <μV 45 ms |
| N°20 (M)      | – By CMR: RV anterior wall akinesia, RVEVD 130 ml/m² | – >500 ventricular extrasystoles per 24 hours (Holter)  
               – Late potentials by SAECG, Filtered QRS duration (fQRS) 117 ms, duration of terminal QRS 40 <μV 50 ms |
| N°21 (M)      | – By 2D echocardiography: RV anterior free wall dyskinesia, PLAX RVOT 45 mm | – >500 ventricular extrasystoles per 24 hours (Holter) |

Abbreviations: ARVD/C: Arrhythmogenic right ventricular dysplasia/cardiomyopathy; LV-ARVD/C: Left ventricular involvement in arrhythmogenic right ventricular dysplasia/cardiomyopathy; Modified TF guidelines: Modified Task Force Guidelines 2010 for ARVD/C; ECG: Electrocardiogram; VT: Ventricular Tachycardia; NSVT: Non Sustained Ventricular Tachycardia; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; PVC: Premature Ventricular Contraction.

Table 2. ARVD/C modified task force criteria 2010 met by LV-ARVD/C population.

| TOTAL (F/22y) | MODIFIED TASK FORCE MAJOR CRITERIA | MODIFIED TASK FORCE MINOR CRITERIA |
|---------------|-----------------------------------|-----------------------------------|
| – Sustained ventricular tachycardia of LBBB morphology with superior axis  
   – Epsilon wave in the right precordial leads (V1 to V3)  
   – By CMR: RV anterior wall akinesia and inferior wall dyskinesia and RVEDV 130 ml/m², RVEF 27% | – Inverted T waves in leads V1, V2, V3, and V4 in the presence of complete RBBB |
| (M)/66y       | – Sustained ventricular tachycardia of LBBB morphology with superior axis  
   – Inverted T waves in leads V1, V2, V3, and V4 in the absence of complete RBBB  
   – By CMR: RV anterior, lateral and Infundibulum walls akinesia and RVEDV 159 ml/m², RVEF 30% | – NSVT of RV outflow configuration, LBBB morphology with inferior axis |
| (M)/24y       | – By CMR: RV anterior and inferior walls akinesia and FEVD 30% | – Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative  
               – NSVT of RV outflow configuration, LBBB morphology with inferior axis |
| (M)/62y       | – Inverted T waves in leads V1, V2, V3, and V4 in the absence of complete RBBB  
   – Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB  
   – By CMR: RV lateral wall dyskinesia, RVEDV 140 ml/m² | – NSVT of LBBB morphology with inferior axis  
               – Late potentials by SAECG, Filtered QRS duration (fQRS) 117 ms, duration of terminal QRS 40 <μV 50 ms |
| (M)/65y       | – By CMR: RV inferior wall dyskinesia, RVEDV 115 ml/m² RVEF 30%  
   – Inverted T waves in right precordial leads V1, V2, V3, and V4 in the absence of complete RBBB | – >500 ventricular extrasystoles per 24 hours (Holter)  
               – NSVT of RV outflow configuration, LBBB morphology with inferior axis |

(Continued)
Table 2. (Continued)

| TOTAL | MODIFIED TASK FORCE MAJOR CRITERIA | MODIFIED TASK FORCE MINOR CRITERIA |
|-------|------------------------------------|------------------------------------|
| (M)/65y | By CMR: RV Infundibulum and inferior wall dyskinesia, RVEDV 120 ml/m² | >500 ventricular extrasystoles per 24 hours (Holter) |
|        | – By CMR: RV Infundibulum and anterior dyskinesia RVEDV 118 ml/m² | – NSVT of LBBB morphology with inferior axis |
| (M)/29y | ARVD/C confirmed pathologically at autopsy in a first-degree relative | – By CMR: RV Infundibulum and inferior wall dyskinesia, RVEDV 120 ml/m² |
|        | – By CMR: RV Infundibulum and anterior dyskinesia RVEDV 118 ml/m² | – NSVT of LBBB morphology with inferior axis |
| (F)/42y | Inverted T waves in V1, V2, and V3 in the absence of complete RBBB | >500 ventricular extrasystoles per 24 hours (Holter) |
|        | – 2D echocardiography: PLAX RVOT 35 mm, RV anterior free wall dyskinesia | – Late potentials by SAECG, Filtered QRS duration (fQRS) 116 ms, duration of terminal QRS 40 <µV 45 ms |
| (F)/48y | By CMR: RV anterior wall akinesia, RVEVD 115 ml/m² | >500 ventricular extrasystoles per 24 hours (Holter) |
|        | – By CMR: RV anterior wall akinesia, RVEVD 130 ml/m² | – Late potentials by SAECG, Filtered QRS duration (fQRS) 117 ms, duration of terminal QRS 40 <µV 50 ms |

Table 3. Baseline clinical characteristics.

| | TOTAL (n = 21) | ARVD/C (n = 10) | LV-ARVD/C (n = 11) | P VALUE |
|---|----------------|-----------------|---------------------|---------|
| Fulfilled modified TF guidelines, n (%) | 15 (71) | 7 (33) | 8 (38) | 0.99 |
| Relatives satisfying modified criteria, n (%) | 6 (29) | 3 (14) | 3 (14) | 1 |
| Age, Median [25–75P] | 48 [43–63] | 48 [38–63] | 48 [30–64] | 0.75 |
| Sex male, n (%) | 14 (67) | 6 (29) | 8 (38) | 0.65 |
| Personal history of cardiac disease | 0 | 0 | 0 | – |
| Family history of ARVD/C or sudden death, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |
| ARVD/C, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| Sudden death, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |
| Ventricular arrhythmia, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |
| Personal History of ventricular arrhythmia (VT or NSVT), n (%) | 5 (24) | 1 (5) | 4 (19) | 0.62 |
| Symptomatic, n (%) | 12 (57) | 6 (29) | 6 (29) | 1 |
| Palpitations, n (%) | 9 (43) | 4 (19) | 5 (24) | 0.99 |
| Faintness, n (%) | 2 (10) | 2 (10) | 0 | 0.21 |
| Syncope, n (%) | 1 (5) | 0 | 1 (5) | 0.99 |
| Sport ≥4h/week, n (%) | 13 (62) | 6 (29) | 7 (33) | 0.99 |
| 12-lead ECG abnormalities, n (%) | 11 (52) | 6 (29) | 5 (24) | 0.99 |
| Inverted T waves according the major revised criteria, n (%) | 10 (48) | 5 (24) | 5 (24) | 1 |
| Inverted T waves according the minor revised criteria, n (%) | 1 (5) | 1 (5) | 0 | 0.99 |
| Epsilon waves, n (%) | 2 (10) | 1 (5) | 1 (5) | 1 |
| Late potentials, n (%) | 3 (14) | 2 (10) | 1 (5) | 0.99 |
| Notable ventricular arrhythmias (Non sustained or sustained VT), n (%) | 12 (57) | 6 (29) | 6 (29) | 1 |
| LBBB morphology VT or NSVT, n (%) | 7 (33) | 6 (29) | 1 (5) | 0.04 |
| – LBBB morphology according the major revised criteria, n (%) | 3 (14) | 2 (10) | 1 (5) | 0.99 |
| – LBBB morphology according the minor revised criteria, n (%) | 4 (19) | 4 (19) | 0 | 0.035 |
| RBBB morphology, n (%) | 4 (19) | 2 (10) | 2 (10) | 1 |
| Biventricular, n (%) | 2 (10) | 2 (10) | 0 | 0.21 |
| Isolated PVC (%) | 8 (38) | 4 (19) | 4 (19) | 1 |
| RBBB, n (%) | 5 (24) | 3 (14) | 2 (10) | 0.63 |
| LBBB, n (%) | 0 | 0 | 0 | – |
Ficient difference in demographic characteristics (age < 40 years, sex, personal previous history, clinical presentation, sport and family history) between ARVD/C and LV-ARVD/C. Baseline characteristics are summarized in Table 3. Three ARVD/C patients had lateral repolarization abnormalities. Only two LV-ARVD/C patients had such repolarization troubles, one in inferior leads and the other in apicolateral leads. LBBB-VT morphology was more frequent in ARVD/C compared to LV-ARVD/C (6 vs 1, \( P = 0.04 \)). LV-ARVD/C was negatively correlated with the LBBB-VT morphology (\( r = -0.539, P = 0.012 \)).

**Disease patterns.** **RV abnormalities.** A total of 15 patients (71%) had severe RV dilatation and 2 (10%) had mild RV dilatation. In all, 13 patients (62%) had RVEF alteration \( \leq 45\% \), 11 patients (52%) had severe RVEF alteration \( \leq 40\% \), and 2 patients (10%) had mild RVEF alteration between 40 and 45%. One patient (5%) had an infundibulum aneurysm. A total of 10 patients (48%) had RV late gadolinium enhancement. The distribution of RV-WMAs was quite homogeneous in ARVD/C and LV-ARVD/C, except for the RV infundibulum. There was higher RV infundibulum motion abnormalities in ARVD/C group compared to LV-ARCD/C group (\( P = 0.007 \)).

Using echocardiography, RV dilatation was detected in nine patients (43%) and segmental dilatation in two patients

**Table 4. Structural abnormalities and comparisons between isolated RV disease and LV involvement in ARVD/C.**

| Table 4. Structural abnormalities and comparisons between isolated RV disease and LV involvement in ARVD/C. |
| CMR | TOTAL | ARVD/C | LV-ARVD/C | P VALUE |
| --- | --- | --- | --- | --- |
| **CMR** | **TOTAL** | **ARVD/C** | **LV-ARVD/C** | **P VALUE** |
| RV dilatation according the major revised criteria, n (%) | 15 (71) | 6 (29) | 9 (43) | 0.36 |
| the minor revised criteria, n(%) | 2 (10) | 2 (10) | 0 | 0.47 |
| RV regional dilatation, n (%) | 3 (14) | 2 (10) | 1 (5) | 0.58 |
| Regional RV akinesia/dyskinesia or dyssynchronous, n (%) | 15 (71) | 9 (43) | 6 (29) | 0.36 |
| – RV Anterior free wall, n (%) | 10 (48) | 5 (24) | 5 (24) | 1 |
| – RV Inferior wall, n (%) | 7 (33) | 3 (14) | 4 (19) | 0.99 |
| – Under RV tricuspid inflow, n (%) | 1 (5) | 1 (5) | 0 | 0.99 |
| – RV infundibulum, n (%) | 8 (38) | 7 (33) | 1 (5) | 0.007 |
| – RV lateral wall, n (%) | 2 (10) | 2 (10) | 0 | 0.21 |
| RVEF >45%, n (%) | 13(62) | 6 (29) | 7 (33) | 0.99 |
| – RVEF ≤40% (severe), n (%) | 11 (52) | 6 (29) | 5 (24) | 0.99 |
| – RVEF >40 to ≤45% (mild), n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| RV Aneurysm, n (%) | 1 (5) | 1 (5) | 0 | 0.47 |
| RVLE, n (%) | 10 (48) | 6 (29) | 4 (19) | 0.39 |
| – RV Anterior free wall, n (%) | 8 (38) | 4 (19) | 4 (19) | 1 |
| – RV Inferior wall, n (%) | 6 (29) | 2 (10) | 4 (19) | 0.63 |
| – Under RV tricuspid inflow, n (%) | 2 (10) | 1 (5) | 1 (5) | 1 |
| – RV infundibulum, n (%) | 5 (24) | 3 (14) | 2 (10) | 0.99 |
| – RV lateral wall, n (%) | 2 (10) | 1 (5) | 1 (5) | 1 |
| LVEF alteration <55%, n (%) | 5 (24) | 0 | 5 (24) | 0.03 |
| LV dilatation with LV volume >95 ml/m², n (%) | 7 (33) | 0 | 7 (33) | 0.004 |
| LV wall motion abnormalities, n (%) | 4 (19) | 0 | 4 (19) | 0.09 |
| – Diffuse, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| – LV Septum, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| – LV Anterior wall, n (%) | 1 (5) | 0 | 1 (5) | 0.99 |
| LVLE, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |
| – Sub-epicardial, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| – Sub-endocardial, n (%) | 1 (5) | 0 | 1 (5) | 0.99 |
| – LV Septum, n (%) | 1 (5) | 0 | 1 (5) | 0.99 |
| – LV Lateral wall, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |
| – LV Inferior wall, n (%) | 1 (5) | 0 | 1 (5) | 0.99 |
| – LV Apex, n (%) | 3 (14) | 0 | 3 (14) | 0.21 |

**Echocardiography, n (%)**

| RV dilatation, n (%) | 9 (43) | 4 (19) | 5 (24) | 0.99 |
| RV regional dilatation, n (%) | 2 (10) | 2 (10) | 0 | 0.32 |
| Regional RV akinesia/dyskinesia or dyssynchronous,n (%) | 4 (19) | 3 (14) | 1 (5) | 0.58 |
| Regional RV hypokinesia (original TF), n (%) | 4 (19) | 3 (14) | 1 (5) | 0.58 |
| RV Aneurysm, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| LVEF alteration <55%, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| LV dilatation, n (%) | 2 (10) | 0 | 2 (10) | 0.47 |
| LV wall motion abnormalities, n (%) | 4 (19) | 0 | 4 (19) | 0.09 |
| LV Aneurysm, n (%) | 0 (0) | 0 | 1 (5) | 0.99 |
(10%). Only two patients (10%) with localized RV aneurysms were found, while regional RV hypokinesia was found in four patients (19%) and regional RV akinesia, dyskinesia, or dys-synchronous RV contraction was recorded in four patients (19%). Structural abnormalities are summarized in Table 4.

LV involvement. Seven patients (33%) presented LV dilatation with LV volume >95 mL/m². Five patients (24%) had LVEF alteration, 55% (the LVEF of those five patients were 37%, 40%, 50%, 53%, and 53%). Four patients (19%) had LV WMAs. Three (14%) patients had LV LE (Table 4). Subepicardial LVLE of the lateral and inferior walls of the LV of two LV-ARVD/C patients is shown in Figures 1 and 2. All LV-ARVD/C patients had no previous history of myocarditis or coronary artery disease.

Comparison of disease patterns. CMR data. RVEF was similar in ARVD/C and LV-ARVD/C (45% [32–51], 47% [30–54], \(P = 0.84\)). Although there was a trend for a larger RV in LV-ARVD/C as compared to ARVD/C, this difference did not reach statistical significance (107 mL/m² [89–114], 120 mL/m² [115–130], \(P = 0.09\)) (Table 5). The RV-WMAs, RVLE, and RVEF (≤45%) were strongly associated with LV-WMAs (\(r = 0.73, P = 0.02; r = 0.7, P = 0.03; r = 0.75, P = 0.02\), respectively) and with LVLE (\(r = 0.8, P = 0.01; r = 0.8, P = 0.006; r = -0.82, P = 0.006\), respectively). LV dilatation was associated with RV dilatation (\(r = 0.46, P = 0.036\)). LVLE was strongly associated with LV-WMAs, LVEF alteration,

Figure 1. (A) Turbo-spin echo image, 4-chamber view showing RV dilatation and prominent RV trabeculations. (B) Steady-state free-precession image, short-axis view showing dilatation of the right Ventricle. Irregular appearance of the myocardium with pathological thinned areas. (C) 4-chambers view demonstrating LVLE in a subepicardial distribution at the median and distal lateral wall (bottom red arrow) and RVLE of the anterior free wall (top red arrow). (D) Short axis LVLE in a subepicardial distribution at the lateral and inferolateral walls (top red arrow), RVLE of the inferior wall (top red arrow).

Figure 2. (A) Steady-state free-precession image, 4 chamber view showing dilatation of the right Ventricle. Irregular appearance of the myocardium with pathological thinned area (red arrow). (B) 4-chambers view demonstrating LVLE in a subepicardial distribution at the lateral wall and basal and median interventricular wall and RVLE of the anterior free wall (green arrows). (C) Steady-state free-precession image, short-axis view showing dilatation of the right Ventricle. Irregular appearance of the myocardium with pathological thinned areas (red arrows). (D) Short axis LVLE in a subepicardial distribution at the lateral, inferolateral and anterior walls (green arrows), RVLE of the inferior and lateral walls (green arrows).

Table 5. Left and right ventricular functions in ARVD/C.

|                      | TOTAL POPULATION (n = 21) | ARVD/C (n = 10) | LV-ARVD/C (n = 11) | P VALUE |
|----------------------|---------------------------|-----------------|-------------------|---------|
| **CMR**             |                           |                 |                   |         |
| RVEF (%)            | 47 [30–52]                | 45 [32–51]      | 47 [30–54]        | 0.84    |
| RVEDV (ml/m²)       | 115 [93–128]             | 107 [89–114]    | 120 [115–130]     | 0.09    |
| LVEF (%)            | 57 [54–65]                | 60 [55–68]      | 56 [50–59]        | 0.06    |
| LVEDV (ml/m²)       | 88 [71–97]                | 80 [68–90]      | 97 [76–116]       | 0.12    |
| **Echocardiography**|                           |                 |                   |         |
| LVEF (%)            | 60 [58–65]                | 62 [60–65]      | 60 [55–60]        | 0.02    |
| LVEDD (mm)          | 50 [48–56]                | 49 [48–50]      | 56 [51–57]        | 0.01    |
and LVEDV ($r = 0.9, P = 0.001$; $r = 0.8, P = 0.001$; $r = 0.8, P = 0.01$) (Table 6).

**Echocardiography data.** Regional RV hypokinesia and aneurysm were strongly associated with LVEF $\leq 50\%$ ($r = 0.89, P = 0.0001$; $r = 0.9, P = 0.0001$, respectively) and with LV dilatation ($r = 0.5, P = 0.04$; $r = 0.7, P = 0.001$, respectively). RV aneurysm was strongly correlated with LV-WMAs ($r = 0.9, P = 0.0001$) and LV aneurysm ($r = 0.7, P = 0.001$). Regional RV dyskinesia was correlated with LV aneurysm ($r = 0.46, P = 0.04$). The LV and RV dilatation, RV aneurysm, and RV regional dilatation were strongly associated with LBBB-VT morphology or NSVT ($r = 1, P = 0.0001$) (Table 6).

**Disease prognosis.** The follow-up was obtained at a mean of 31 ± 20.6 months. Four patients (19%) had ICD: one (5%) in secondary prevention after a sudden death, two (10%) in secondary prevention for symptomatic VT, and 1 (5%) in primary prevention for the purpose of resynchronization. Out of the 12 patients who had ventricular arrhythmia (VT/NSVT), 10 patients (83.3%) were treated with beta-blockers.

Table 6. Associations between right and left ventricular abnormalities in ARVD/C.

| CORRELATED WITH                  | R       | P     |
|----------------------------------|---------|-------|
| **CMR**                          |         |       |
| RV dilatation                    | LV dilatation | 0.46  | 0.03 |
| Akinesia or dyskinesis or dyssynchronous RV | LV wall motion abnormalities | 0.73  | 0.02 |
| LVLE                             |         |       |
| RVEF alteration <45%             | LV wall motion abnormalities | 0.75  | 0.02 |
| RVLE                             | LV wall motion abnormalities | 0.70  | 0.03 |
| RV aneurysm                      | LV aneurysm | 0.69  | 0.001|
| LV aneurysm                      | LV aneurysm | 0.69  | 0.001|
| Regional RV a/dyskinesia         | LV aneurysm | 0.46  | 0.04 |
| **Echocardiography**             |         |       |
| Regional RV hypokinesia          | LVEF alteration | 0.88  | 0.001|
| LV dilatation                    |         |       |
| LV aneurysm                      | LV dilatation | 0.46  | 0.04 |
| RV aneurysm                      | LVEF alteration | 0.89  | 0.0001|
| LV wall motion abnormalities     |         |       |
| RV aneurysm                      | LV aneurysm | 0.69  | 0.001|
| Regional RV a/dyskinesia         | LV aneurysm | 0.46  | 0.04 |
| LVEF alteration                  | Ventricular arrhythmia personal history | 0.53  | 0.02 |
| LBBB morphology VT or NSVT      |         |       |
| LV dilatation                    | Right Atrium/Left Atrium dilatation | 0.68  | 0.03 |
| LV aneurysm                      | LBBB morphology VT or NSVT | 1     | 0.0001|
| LV aneurysm                      | Personal history of isolated PVC | 0.45  | 0.04 |

Table 7. Cardiac events at follow-up.

| FOLLOW UP                      | ARVD/C (n = 10) | LV-ARVD/C (n = 11) |
|--------------------------------|----------------|--------------------|
| Sudden Death, n (%)             | –              | –                  |
| Death, n (%)                    | –              | –                  |
| ICD implantation, n (%)         | 2 (10)         | 2 (10)             |
| NSVT, n (%)                     | –              | –                  |
| VT, n (%)                       | 2 (10)         | 0 (0)              |
| VT ablation, n (%)              | 2 (10)         | 0 (0)              |
| Heart Transplant discussion, n (%) | –              | –                  |
| CMR re-evaluation, n (%)        | 2 (10)         | 2 (10)             |
| RVEF alteration, n (%)          | 1 (5)          | 2 (10)             |
| RV dilatation, n (%)            | 1 (5)          | 1 (5)              |
| RV wall motion abnormalities,n(%) | 2 (10)         | 2 (10)             |
| RVLE, n (%)                     | 0              | 1 (5)              |
| LVEF alteration, n (%)          | –              | –                  |
| LV dilatation, n (%)            | –              | –                  |
| LV wall motion abnormalities,n(%) | –              | –                  |
| LVLE, n (%)                     | 0              | 1 (5)              |
One patient (5%) had severe VT one month after the diagnosis, and one patient (5%) had VT 10 months after the diagnosis and an electrical storm four years after. No sudden death was recorded. There was no statistical difference between ARVD/C and LV-ARVD/C regarding cardiac events (Table 7).

Discussion
The present study showed that LV involvement as assessed by CMR is frequent in ARVD/C. Although the LV involvement in ARVD/C was reported, almost all studies focused on the RV and the LV were often misevaluated. Only few studies have been founded in the literature that assessed the LV involvement by CMR. The prevalence of LV involvement in ARVD/C was variable from 16% to 76% according to the technique used for the evaluation of left ventricle. In line with the literature, our study showed that 52% of ARVD/C patients had LV involvement evaluated by CMR. In contrast to a previous study reporting 30% of LVLE, our study showed 14% of LVLE. Peters and Reil reported a normal LVEF, but 40% of their 60 ARVD/C patients had LV WMAs. In contrast, our study showed that 24% of ARVD/C patients had LVEF <55% but had a lower frequency of LV WMAs. In an autopsy study, the most common location of LV involvement was the posterolateral wall in a subepicardial distribution. In accordance, the present study showed that lateral and apical walls were the most common locations of LV involvement in a subepicardial distribution. These data were in line with previous CMR studies.

In the present study, there was no difference in clinical presentation in patients with and without LV involvement in ARVD/C, which is in line with a previous study. There was no increase in the frequency of VT with RBBB morphology in LV-ARVD/C. Furthermore, the frequency of VT with LBBB morphology was higher in LV-ARVD/C. These data could suggest that the main origin of ventricular arrhythmia remains the RV, which could be related with the thinnest RV wall. The most frequent ECG repolarization abnormalities in ARVD/C with LV involvement were inverted T waves in the inferior and lateral leads. In our study, although there were few ECG lateral and inferior repolarization troubles, 18% of LV-ARVD/C had inferior and lateral repolarization vs 30% in ARVD/C.

In the first reports, LV involvement in ARVD/C was frequently considered as a late manifestation of an advanced disease. Later, after the first CMR study evaluating the pattern of ARVD/C and LV involvement, LV abnormalities were found to be associated with preserved RV function in 40% of ARVD/C. In the present study, the degree of RV impairment was similar in patients with isolated RV and those with LV involvement in ARVD/C. These data suggest that it is not necessary to have a severe RV impairment to imply a LV involvement. The present and previous studies showed various clinical pathological forms with only RV involvement or both RV and LV involvements, and even isolated LV involvement.

The natural course of ARVD/C is still not fully elucidated. There are few data evaluating long-term prognosis of ARVD/C. Aneq et al., followed up ARVD/C patients up to 10 years. They reported that LV involvement might occur early in the disease. Another study with 8.5 years follow-up reported a high rate of recurrent malignant ventricular arrhythmia in initially symptomatic patients. The occurrences of life-threatening ventricular arrhythmia and heart failure are the main components of the prognosis.

However, early and clustered recurrence of rapid VT/VF in patients who had ICD was common, whereas late recurrence of rapid VT/VF is very rare. Six years of follow-up studies showed a good survival rate with a cardiac death rate of 8% at long-term follow-up. In the present study, the population study was small to evaluate the impact of LV in ARVD/C on the long-term prognosis. In the present study, no death and no terminal heart failure were recorded. Two initially symptomatic and high-risk patients (10%) had recurrences of VT. The only one, who had ICD, received appropriate ICD therapy. In those patients, a short delay between the diagnosis and the recurrence of ventricular arrhythmia (1 and 10 months) was reported. Furthermore, we noted CMR structural RV and LV evolutions with worsening RV dilatation, WMAs, and LVLE apparition, in a delay of 2–3 years signing a progressive disease as described in the literature. Larger studies with longer follow-up are needed to evaluate the impact of LV involvement in ARVD/C on prognosis.

Clinical implication. The main aim of clinicians is to access the disease at an early stage, in order to propose an appropriate care and a closer follow-up. Indeed, the first diagnostic criteria were proposed by McKenna et al. The revision in the diagnostic criteria of ARVD/C has recently been proposed in 2010 by Marcus et al.; these revised criteria improved the diagnostic specificity and sensitivity. These revised criteria included RV CMR criteria, but no LV involvement criteria were proposed, as LV involvement in ARVD/C is frequent without specific clinical presentation predicting them. Our findings support the emerging evidence in favor of the need for a contemporaneous revision of task force criteria to include LV descriptions.

A previous study showed that LV late gadolinium enhancement was the most sensitive indicator of LV involvement. A localized LVLE occurred even without concomitant WMA or volume expansion. More and larger studies are needed to evaluate the predictive value, sensibility, and specificity of CMR in the diagnosis of LV involvement in ARVD/C.

Study Limitations
Although the data were recorded prospectively, the study was a retrospective monocentric study. Another limitation was the
relatively small number of patients explained by the rarity of the disease and many underrecognized patients. No genetic analyses were made. There were no enough data about all family members. The impact of LV involvement in ARVD/C on the prognosis could not be fully evaluated because of the small population study.

Conclusion
LV involvement in ARVD/C is common and not always associated with severe RV abnormalities. It seems to occur earlier in the natural history, and appears rather as a biventricular cardiomyopathy. Larger studies are needed to determine the potential predictive value of LV in the prognosis of the disease.

The LV CMR assessment could be of great value for the diagnosis of LV involvement in ARVD/C. More studies focused on LV assessment by CMR are needed to define specific diagnostic criteria of LV-ARVD/C.

Author Contributions
Conceived and designed the experiments: SE, PG. Analyzed the data: SE. Wrote the first draft of the manuscript: AN, SE. Contributed to the writing of the manuscript: SE, PG. Agree with manuscript results and conclusions: PG, Mi-YJ. Jointly developed the structure and arguments for the paper: SE, AN. Made critical revisions and approved final version: PG, Mi-YJ, AG, CR. All authors reviewed and approved of the final manuscript.

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