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Left ventricular myocardial dysfunction in arrhythmogenic cardiomyopathy with left ventricular involvement: A door to improving diagnosis

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ABSTRACT

Background: Diagnostic Task Force Criteria (TFC) for arrhythmogenic cardiomyopathy (AC) exhibit poor performance for left dominant forms. TFC only include right ventricular (RV) dysfunction (akinesia, dyssynchrony, volumes and ejection fraction). Moreover, cardiac magnetic resonance imaging (CMRI) assessment of left ventricular (LV) dyssynchrony has hitherto not been described. Thus, we aimed to comprehensively characterize LV CMRI behavior in AC patients.

Methods: Thirty-five AC patients with LV involvement and twenty-three non-affected family members (controls) were enrolled. Feature-tracking analysis was applied to cine CMRI to assess LV ejection fraction (LVEF), LV end-systolic and end-diastolic volume indexes, strain values and dyssynchrony. Regions with more frequent strain and dyssynchrony impairment were also studied.

Results: Radial dyssynchrony and LVEF were selected (sensitivities 54.3% and 48.6%, respectively at 100% specificity), with a threshold of 70 ms for radial dyssynchrony and 48.5% for LVEF. 71.4% of patients exceeded these thresholds (31.4% both, 22.9% only dyssynchrony and 17.1% only LVEF). Considering these cut-off values as a novel combined criterion, 30% of patients with 'borderline' or 'possible' AC following 2010 TFC would move to a 'definite' AC diagnosis. Strain was globally impaired whereas dyssynchronous regions were more often apical and located at the inferolateral wall.

Conclusions: Mirroring the RV evaluation, we suggest including LVEF and LV dyssynchrony to improve the diagnosis of AC. Two independent mechanisms can be claimed in AC patients with LV involvement: 1) decreased myocardial deformation with global LV affectation and 2) delayed myocardial contraction at localized regions.

1. Introduction

Arrhythmogenic cardiomyopathy (AC) is an inherited rare disease characterized by a progressive myocardial fibrofatty replacement [1,2]. It is associated with heart failure and life-threatening arrhythmias being one of the leading causes of sudden death in young people [3]. In the classic description, structural changes involved only the right ventricular (RV) myocardium and may extend to the left ventricular (LV) muscle in advanced forms. Its incomplete penetrance and variable phenotypic expression [2,4] hampers its diagnosis even with the scoring system stablished in the Task Force Criteria (TFC) in 1994 [5]. Once left

Abbreviations: AC, arrhythmogenic cardiomyopathy; RV, right ventricular; LV, left ventricular; TFC, Task Force Criteria; CMR, cardiac magnetic resonance imaging; EF, ejection fraction; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index.

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dominant forms were recognized [6,7], slight modifications regarding LV involvement were implemented in the revised version in 2010 (negative T waves in V4-6 as a minor criterion for repolarization abnormalities) [8]. Individually, each criterion has a high specificity at the expense of a low sensitivity, yielding good performance in the global assessment proposed by the 2010 TFC [9].

Although cardiac magnetic resonance imaging (CMR) provides comprehensive information on cardiac morphology, function, and tissue characterization [10] [11], the 2010 TFC do not include a non-invasive tissue evaluation based on late gadolinium enhancement (LGE) analysis and it does limit the global and regional dysfunction evaluation just to the right ventricle, both in terms of RV motility (akinesia and/or dyssynchrony without specific thresholds) and volume-related performance (RV end-diastolic volume to body surface area and decreased RV ejection fraction-EF).

Multiple commercial software tools implement feature-tracking algorithms for CMR strain and dyssynchrony assessment, including Medis Qstrain (Medis Medical Imaging Systems, Leiden, the Netherlands), TomTec (Tom-Tec Imaging Systems, Unterschleissheim, Germany) or Circle Cardiovascular Imaging (CVI^{42}, Calgary, Canada), among others. Ventricular dyssynchrony has been studied in patients with electrical and structural heart diseases [12–15] using echocardiography, CMR and nuclear imaging [15,16] with reasonable agreement among them [17,18]. Particularly, RV dyssynchrony has been shown to be higher in classical forms of AC, either with echocardiography [19] or with CMR [20,21]. Beyond its diagnostic potential, impaired strain measurements also correlate with a poor prognosis [22].

The aim of the present study is three-fold. Firstly, we describe for the first time LV dysfunction in AC patients with LV involvement from CMR analysis by means of: peak strain, dyssynchrony, LV ejection fraction (LVEF), and LV end-diastolic and end-systolic volume indexes (LVEDVi and LVESVi, respectively). Secondly, we report our cut-off values at 100% specificity and the subsequent reallocation of patients in the TFC categories after applying them. Finally, we explore the LV regions most prone to suffering from wall motion abnormalities.

We hypothesize that: 1) AC patients with LV involvement might exhibit less strain, more profound LV dyssynchrony, impaired LVEF and greater LVEDVi and LVESVi than controls; 2) To detect LV involvement, novel CMR criteria with appropriate thresholds would reclassify borderline and/or possible AC patients to definite AC and 3) LV wall motion abnormalities may match against LGE regions, i.e. the inferolateral wall.

2. Material and methods

2.1. Datasets

Thirty-five individuals diagnosed with AC with LV involvement (patients) and twenty-three non-affected family members (controls) were enrolled at a dedicated clinic.

Patients were included when a pathogenic/probably pathogenic mutation in AC-related genes was identified and the typical intramyocardial/subepicardial pattern of LGE was observed. Additionally, patients belonged to 17 families in which AC had been unequivocally identified (either histologically at autopsy or at heart transplantation and/or with 'definite' 2010 TFC criteria) in at least one family member and a good phenotype-genotype cosegregation had been confirmed. Thus, provided a typical LGE pattern was considered a major criterion, all these patients would fulfill a definite diagnosis of AC (positive for at least two major criteria). To characterize ventricular predominance in AC involvement, we applied the scoring system previously reported by our group [23].

From 14 families, controls were obtained as non-affected family members who attended the screening program, with no CMR sign of AC and no carriers of the mutation identified in affected relatives.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the institution's research ethics committee, and all subjects gave their informed consent.

CMR studies were performed in 1.5-Tesla scanners (Siemens Avanto, Siemens Symphony or GE Signa HDxt). Cine long-axis slices (two-, three- and four-chamber view) and a stack of contiguous cine short-axis slices from the atrioventricular ring to the LV apex were acquired using a steady-state free precession pulse sequence (20–25 phases per cardiac cycle, 6–8 mm slice thickness, no interslice gap, 360 × 480 field of view, 196 × 172 matrix size).

2.2. Feature tracking

Endocardial (without papillary muscles) and epicardial contours of the LV at the end-diastole were traced semi-automatically in the four cardiac chamber view. The automated tissue tracking algorithm (Circle CVI^{42} version 5.5.1, Calgary, Canada) was applied to obtain radial, circumferential and longitudinal strain curves for each of the LV American Heart Association segments, except for the apex (segment 17). Strain measurements are defined as:

$$S(t_i) = \frac{L(t_i) - L_0}{L_0},$$

where $L(t_i)$ stands for radial/circumferential/longitudinal lengths measured at each LV segment at the time corresponding to the i^{th} frame, where L_0 is the length measured from the initial frame. Consequently, the strain curves measure the temporal degree of deformation at each of the radial, circumferential and longitudinal axes. Time-to-peak was assessed as the time at which the strain curve reached its maximum. Fig. 1A shows radial strain curves and time-to-peak measurements.

2.3. Global LV alterations

Global strain values were computed as the mean peak strain whereas dyssynchronies were computed as the standard deviation of the time-to-peak, always in the three axes and in each of the 16 LV segments. The LVEF was computed from the endocardial (endo) volume curves:

$$EF = \frac{V_{endo}(t_D) - V_{endo}(t_S)}{V_{endo}(t_D)}$$

where $V_{endo}(t_s)$ stands for end-systolic volume and $V_{endo}(t_D)$ for end-diastolic volume [24]. End-diastolic and end-systolic volume indexes were calculated dividing the volumes by the body surface area according to the Du Bois formula [25].

2.4. Regional LV alterations

Wall motion abnormalities and the presence of LGE were qualitatively identified by highly-trained CMR experts. Additionally, a quantitative regional LV wall motion abnormality assessment was performed with *t*-tests comparing the individual peak strain and time-to-peak values at each region between controls and a subset of patients with markedly hypokinetic or dyssynchronic behavior since their global strain or their global dyssynchrony were below or above cut-off values, respectively.

2.5. Statistical analysis

Dichotomous variables are presented as percentages and compared with the chi-square test between clinical groups. Continuous variables with a normal distribution are presented as mean ± SD and compared with the Student *t*-test between clinical groups. Pearson's test was used for correlation assessments.

To be consistent with TFC, we maximized specificity for each individual criterion. Firstly, we selected the parameters with significant differences between patients and controls. The statistical p-values were Bonferroni-corrected to avoid spurious associations, as multiple comparisons were carried out (p-values <0.05 were considered statistically significant). We then constructed the Receiver Operating Characteristic curves and extracted the cut-off points for 100% specificity. All statistics were obtained with the statistical software SPSS (version 23.0 for Windows, SPSS Inc., Chicago, Illinois).

3. Results

3.1. Clinical and demographic features

Among clinical and demographic characteristics sex, arterial hypertension, ischemic heart disease and dyslipemia were similar in both groups (Table 1). However, controls were older and more often diabetic than patients ($p < 0.05$).

Twenty-two out of the 35 AC patients presented isolated LV involvement, whereas 13 exhibited biventricular AC. 'Definite AC' according to the 2010 TFC was diagnosed in 69%, 'borderline in AC' in 11% and 'possible AC' in up to 20% of patients since they fulfilled only one major criteria (mutation carriers), even though all subjects exhibited LV myocardial involvement to some extent with a typical LV LGE pattern. As expected, mutations were regularly identified in the desmoplakin gene (82.8%), with an infrequent representation of other genes, such as filamin C, desmin, plakophillin-2 and phospholamban (Table 1, Online Table 1).

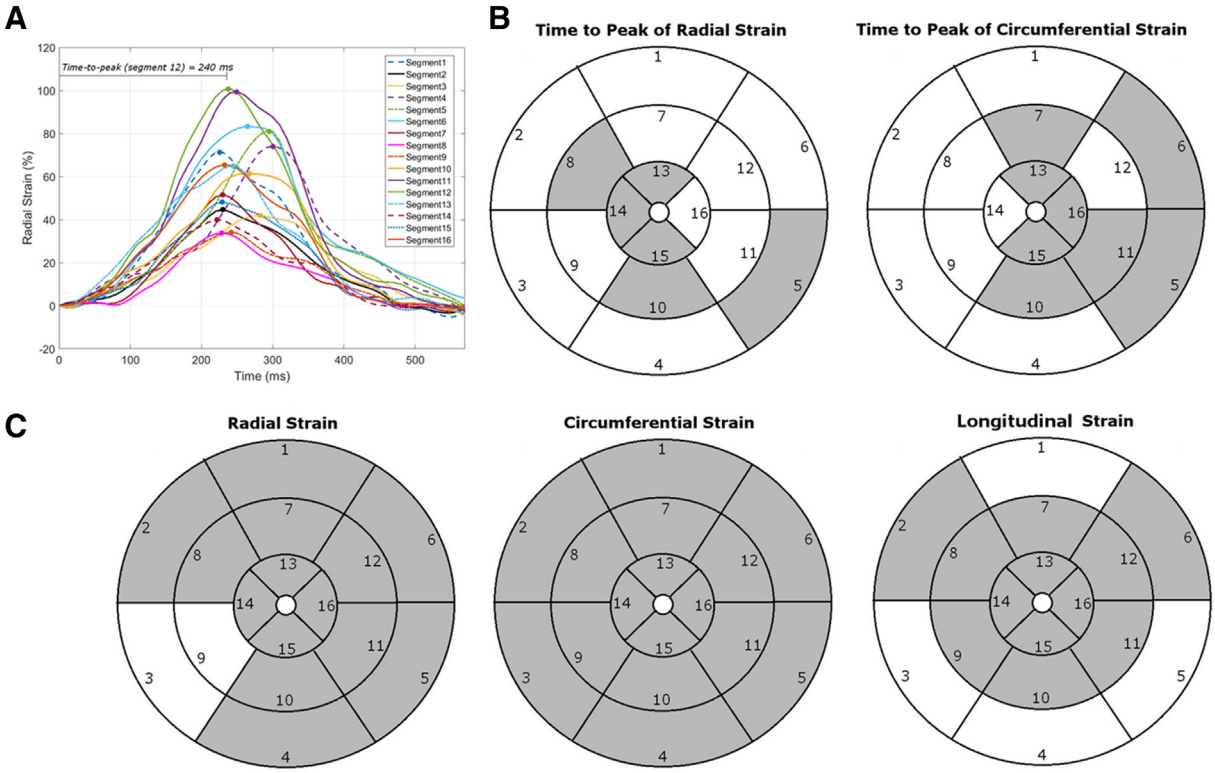


Fig. 1. Global and regional strain analyses. Example of the time-to-peak and peak radial strain of the 16 American Heart Association (AHA) segments (A). Quantitative regional analysis of myocardial dysfunction in patients when compared with controls. The AHA segments with significant wall motion abnormalities are represented in grey since they exhibited delayed time-to-peak (B) (B) and/or decreased strain values (not available for longitudinal analysis). Numbers refer to AHA classification.

3.2. Global LV alterations

Notably, CMR studies from patients exhibited lower LVEF, radial, circumferential and longitudinal strain, but greater LVEDVi, LVESVi, radial and circumferential dyssynchrony than controls, along with a non-significant trend towards increased longitudinal dyssynchrony (Table 1, Online Fig. 1). Our results showed that patients with AC with LV involvement more often presented impaired LVEF (LVEF ≤55%) than enlarged LVEDVi (LVEDVi >98 ml/m^2) (71.4% versus 25.7%, respectively).

For the sake of clarity, we display the Receiver Operating Characteristic curves in separate categories: volume-related variables (i.e. LVEF, LVEDVi and LVESVi) in Fig. 2A; strain variables in Fig. 2B and dyssynchrony parameters in Fig. 2C (only significant parameters were considered). The variables with the best performance in each category were LVEF (area under the curve-AUC = 0.85), longitudinal strain (AUC = 0.85) and radial dyssynchrony (AUC = 0.78). The selected cut-off values at maximal specificity were 48.5% for LVEF; 9.5% for longitudinal strain and 70.0 ms for radial dyssynchrony (Fig. 2D).

3.3. Correlations between volume-related parameters, strain and dyssynchrony variables

Volume and strain parameters were markedly correlated (LVEF and circumferential strain: r = −0.959, p-value <0.01). Conversely, dyssynchrony parameters were only moderately correlated with either volume or strain-related parameters (radial dyssynchrony and LVEF: r = −0.692; radial dyssynchrony and circumferential strain: r = 0.705, p-value <0.01) (complete results in Online Table 2).

3.4. Reallocation of patients according to TFC stratification

The parameters with the best performance in terms of sensitivity and AUC were selected from Fig. 2D. We excluded circumferential strain for this analysis due to its extremely high correlation with LVEF (Online Table 2). Accordingly, we focused on LVEF (from among the volume-related features) and radial dyssynchrony (from all three dyssynchronies). Their cut-off points at maximal specificity were used to build a contingency table with the percentage of patients in each category (Online Table 3). Controls were excluded since they were all allocated in the least affected categories, as these thresholds apply for 100% specificity. As shown, 71.4% of patients presented abnormal values in at least one parameter: 31.4% in both; 22.9% exclusively in radial dyssynchrony, and 17.1% only in LVEF. Conversely, 28.6% of the patients could not be detected after applying the proposed thresholds for LV dysfunction.

Considering a LVEF <48.5% and/or a radial dyssynchrony >70 ms as a novel major criteria, 30% of AC patients previously classified as 'borderline' or 'possible' categories according to 2010 TFC moved to a 'definite' AC diagnosis without affecting specificity. The bottom of Table 1 shows the distribution of patients and controls in the categories published in the 2010 TFC and with our suggested modification including LV dysfunction parameters.

3.5. Regional LV alterations

Remarkably, regional wall motion abnormalities were qualitatively seen in 30.3% of patients and usually involved the inferior and lateral LV walls, precisely the same preferred localization as that observed for the presence of LGE (Table 1). Furthermore, also in quantitative strain measurements regional differences were observed in patients. Briefly, the regional time-to-peak delays in radial and circumferential strain were increased in patients when compared with controls, especially at the inferolateral segments, whereas most of the basal segments were preserved (Fig. 1B). On the contrary, strain was globally decreased in the entire left ventricle, and only some basal segments maintained an unaltered longitudinal strain when compared to controls (Fig. 1C).

Table 1
Clinical, demographic and CMR variables.

	Total AC group with LV involvement (N = 35)	Controls (N = 23)	p-Value
Age	40.1 ± 17.9	49.6 ± 16.4	0.04
Sex (M/F)	16/19	10/13	0.87
Arterial hypertension	5	5	0.46
Diabetes mellitus	1	5	0.02*
Ischemic heart disease	0	1	0.21
Dyslipemia	9	7	0.69
Mutated gene††			
Desmoplakin	29 (82.8%)[1]	0	–
Filamin C	1 (2.9%)[2]	0	–
Desmin	1 (2.9%)[3]	0	–
Plakophillin-2	1 (2.9%)[4]	0	–
Transmembrane protein 43	2 (5.8%)[5]	0	–
Phospholamban	1 (2.9%)[6]	0	–
LGE (%)			
Location			
Subepicardial	21 (58%)	0	–
Intramyocardial	8 (22%)	0	
Both	7 (20%)	0	
LV walls			
Inferior	83	–	
Lateral	63	–	
Septal	49	–	
Anterior	26	–	
LVEDVi (ml/m^2)	80.9 ± 24.7	65.4 ± 14.9	0.01*
LVEDVi > 98 ml/m^2 (%)	25.7	4.3	0.072
LVESVi (ml/m^2)	45.3 ± 23.1	26.3 ± 9.2	<0.001*
LVEF (%)	46.6 ± 11.1	60.5 ± 6.7	<0.001*
LVEF ≤ 55% (%)	71.4	21.7	<0.001*
LV wall motion abnormalities† (%)			
Presence	30.3	0	–
Location			
Inferolateral	73.0	–	
Involving the anterior wall	23.0	–	
Strain (%)			
Radial	25.8 ± 9.9	40.5 ± 11.3	<0.001*
Circumferential	−13.1 ± 3.5	−17.7 ± 2.6	<0.001*
Longitudinal	−11.9 ± 2.9	−15.4 ± 2.0	<0.001*
Dyssynchrony (ms)			
Radial	70.7 ± 26.4	46.1 ± 14.0	<0.001*
Circumferential	52.1 ± 15.5	38.6 ± 10.0	0.001*
Longitudinal	56.5 ± 24.5	47.3 ± 10.6	0.054

	Total AC group with LV involvement (N = 35)	AC with isolated LV involvement (N = 22)	AC with biventricular involvement (N = 13)	Controls (N = 23)	p-Value
2010 TFC					
Definite AC	24 (69%)	12	12	0	–
Borderline AC	4 (11%)	4	0	1**	–
Possible AC	7 (20%)	6	1	18**	–
Proposed modification to 2010 TFC					
Definite AC	27 (77%)	15	12	0	–
Borderline AC	2 (6%)	2	0	1**	–
Possible AC	6 (17%)	5	1	18**	–

*Bonferroni-corrected p-value <0.05. †Qualitative and visually detected. Please note that controls often fulfilled family history criteria because they were first degree relatives of a patient with 'definite' AC assessed by the 2010 TFC (**). Please note that 6 AC patients (5 carriers of radical and 1 non-radical mutations) exhibited a second genetic hit (2 radical and 3 non-radical mutations in AC-related genes and 1 a radical mutation in DMD gene possibly influencing in the cardiac phenotype) (††). [1] 27 radical and 2 non-radical mutations, [2] 1 radical mutation, [3] 1 non-radical mutation, [4] 1 radical mutation, [5] 2 non-radical mutations, [6] 1 radical mutation.

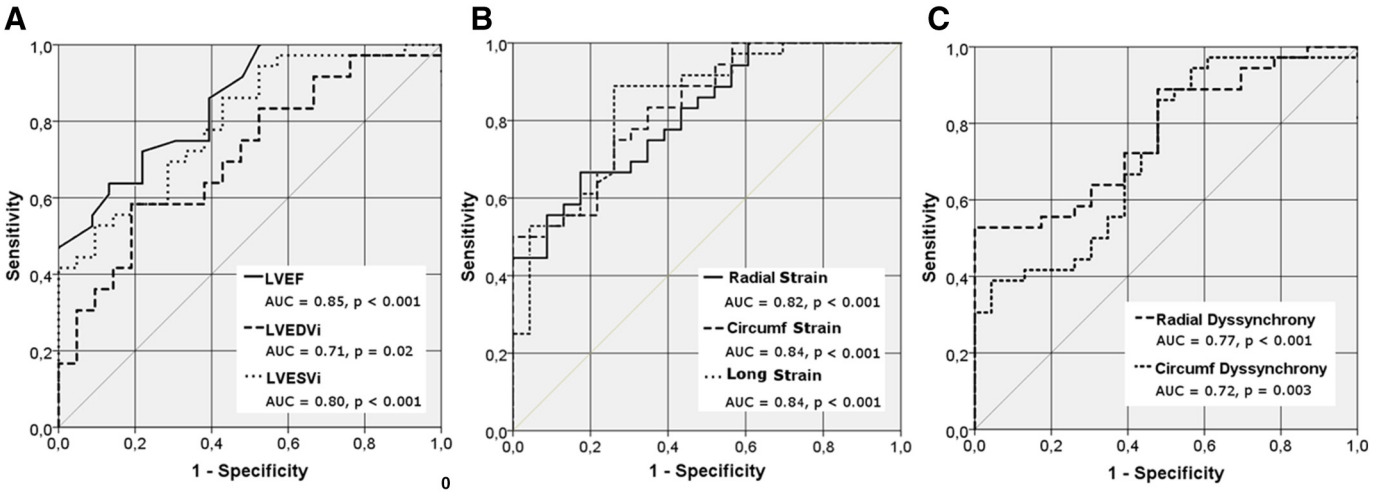
Fig. 3 depicts an example of delayed apical contraction in a patient with a radial dyssynchrony of 80.1 ms.

4. Discussion

The study presented herein describes, for the first time, a detailed pattern of LV dysfunction in AC patients with LV involvement. In sum, we found that: 1) Patients exhibit impaired LV mechanical dispersion and systolic function when compared with controls, 2) LVEF and radial dyssynchrony are the most discriminant parameters with a joint sensitivity of 71.4% (at least one parameter altered) for 100% specificity, 3) LVEF <48.5% and radial dyssynchrony >70 ms are the cut-off values for the sample under study, 4) their addition to the current TFC correctly reallocates 30% of the patients from 'borderline' and 'possible' AC to 'definite' AC and 5) strain alterations are widespread in the whole LV, whereas dyssynchronic patterns are regionally-restricted often to the apical and inferolateral segments.

4.1. Ventricular dysfunction assessment

Left ventricular ejection fraction has generally been considered abnormally depressed under 55% in AC patients as a sign of LV involvement [2,6,26]. Papers focusing on AC with significant LV involvement [6,26] reported a LVEF <55% in 24–56% of patients, whereas in our series it was slightly higher (71.4%, Table 1). With regard to LV volumes, LV enlargement was present in 26% of our AC patients with LV involvement (LVEDVi >98 ml/m^2), which is similar to the 24% previously reported



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	AUC	*Cut-off value*	*Sensitivity (%)*
LVEF (%)	0.85	48.5	48.6
LVEDVi (ml/m²)	0.70	102.1	17.1
LVESVi (ml/m²)	0.80	46.8	42.9
Radial strain (%)	0.82	23.7	45.7
Circumferential strain (%)	0.84	-14.0	51.4
Longitudinal strain (%)	0.85	-9.5	25.7
Radial dyssynchrony (ms)	0.78	70.0	54.3
Circumferential dyssynchrony (ms)	0.74	55.6	31.4

Fig. 2. Receiver-operating characteristic curves. Receiver-operating characteristic curves assessing the discriminative accuracy of volume (A) and strain (B, C) related parameters with statistically significant differences between patients and controls. Volume related parameters: LVEF, LVEDVi and LVESVi. Strain related parameters: radial, circumferential and longitudinal peak strain values and radial and circumferential dyssynchronies. Cut-off values and sensitivities for 100% specificity (D).

[6]. However, this parameter identified less patients than LVEF at 100% specificity.

As expected, global strain parameters were notably correlated with LVEF, thus the greater the deformation of the ventricle, the higher the LVEF obtained. Consequently, strain values barely identified more patients than LVEF. Surprisingly, dyssynchrony values were correlated with LVEF and strain to a lesser extent (Online Table 2) and allowed us to consider them as complementary parameters to improve the detection of LV involvement.

Some recent studies have assessed RV strain and dyssynchrony among AC patients [19,21,27] identifying it also as a useful tool to distinguish AC from idiopathic RV outflow tract arrhythmias [19] and sarcoidosis [28,29].

4.2. Improving AC diagnosis

Historically, the right ventricle has been the key location of AC involvement, and thus plays a pivotal role in the 2010 TFC. With these criteria, predominant LV involvement is difficult to diagnose. Following TFC rationale, we considered cut-off points so that a very high specificity is obtained for each LV parameter, despite poor isolated sensitivity. The RV cut-off points previously identified in the literature [27] were longitudinal dyssynchrony >113.1 ms and circumferential dyssynchrony >177.1 ms, with a sensitivity of 59% and 66% and a specificity of 95% and 83%, respectively. In this study, we found increased LV dyssynchrony in radial and circumferential axes with cut-off values of radial dyssynchrony >70 ms and circumferential dyssynchrony >55.6 ms, for 100% specificity and sensitivity levels of 54.3% and 31.4%, respectively (Fig. 2D). Our dyssynchrony cut-off values are notably lower than those reported for the right ventricle [27], probably due to differences in RV and LV mechanical dispersion, and also to lower specificities for a given RV cut-off (in accordance with the published Receiver Operating Characteristic curves, sensitivity for RV strain cut-offs decreases to under 22% when assessed for maximal specificity [27], which is much less than the values reported in this study).

With the reported thresholds for LVEF and radial dyssynchrony as a novel criterion to assess LV dysfunction, 30% of AC patients would move from 'borderline' or 'possible' AC to 'definite' AC (Table 1). However, further studies are needed to confirm our proposed criteria and to establish more accurate cut-offs, depending on the desired percentage of detection.

Beyond its current role in TFC, CMR data may provide additional valuable information regarding category I (ventricular global and regional dysfunction, from cine analysis) and category II (tissue characterization, from LGE analysis). Adding our proposed combined criteria would help to improve sensibility without losing specificity in the TFC by assessing the left ventricle in category I.

4.3. Left ventricular regional alterations

Left ventricular wall motion abnormalities were not rare in our AC patients (30.3%, Table 1), in accordance with the reported data in the literature (40–80%) [2,6], and their presence was associated with lower strain and/or higher dyssynchrony (Fig. 1B and C). The inferolateral LV

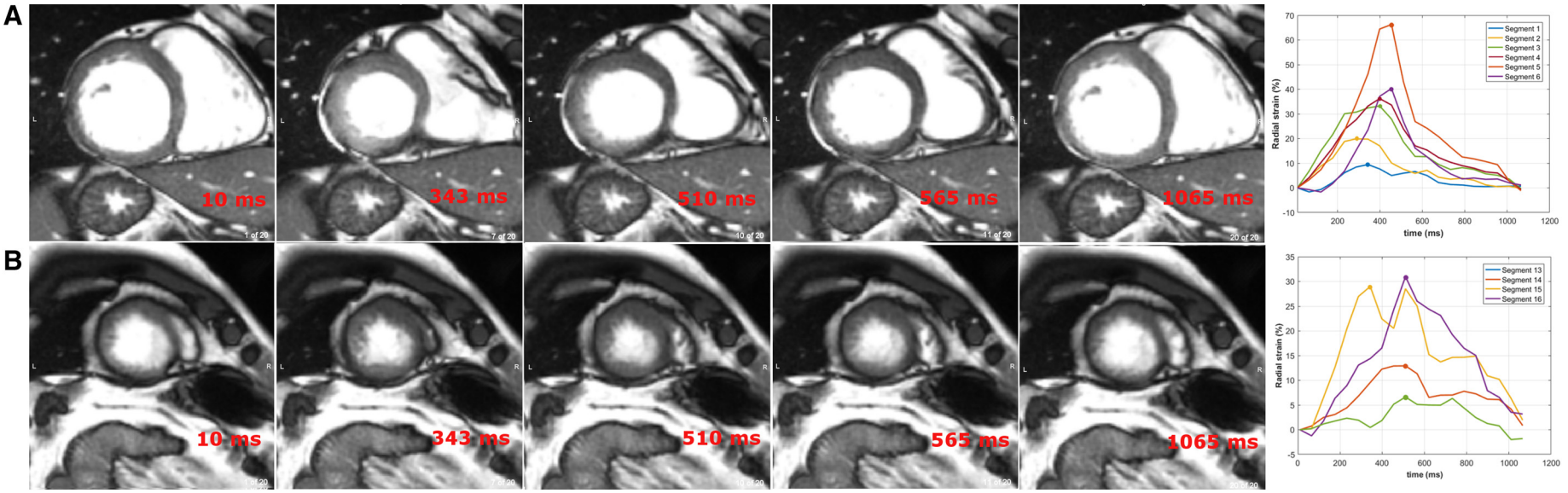

Fig. 3. Delayed apical contraction. CMR sequence in a patient with delayed apical contraction from telediastole (0 ms) and thereafter. Basal (A) and apical (B) segments are shown.

wall has been widely recognized as a part of the 'novel triangle of dysplasia' in AC patients, in conjunction with the subtricuspid region and the RV outflow tract [30]. It has also been described as the typical location of epicardial and/or intramyocardial LV LGE [6]. Consistent with the literature, our results indicate that the apical and inferolateral regions were associated with LGE (Table 1) and also to dyssynchronous behavior, which was extended to the anteroseptal wall in some cases (Table 1, Fig. 1B). Contrary to expectations, the widespread distribution of the hypokinetic regions (characterized by a globally decreased peak strain) involved the entire left ventricle (Fig. 1C), unlike the localized dyssynchronous abnormalities, and is thus poorly correlated. As a new insight into the physiological substrates involved in AC, we posit that the varying behavior of strain and dyssynchrony could depict different information. More specifically, our results suggest two independent mechanisms related to LV dysfunction. On the one hand, a *globally decreased* myocardial LV deformation, and on the other, a regional LV dysfunction with *locally delayed* myocardial contraction at the inferolateral apical wall associated with LGE areas. Patients with a definite AC diagnosis may exhibit these two mechanisms, only one of them, or neither. These results open up new questions regarding the causes and implications of these mechanisms, e.g. which one is the earliest biomarker or which one is associated with the highest ventricular arrhythmic burden.

The major contributions of this study are two-fold. Firstly, the novelty of assessing LV strain in AC with LV involvement. The possibility of introducing this approach in a modified TFC is, at least, tempting and challenging. The second strength lies in the fact that controls were not selected from the healthy general population, but instead were mutation negative non-affected family members of an AC proband. The control group could be affected to some extent by other heart diseases, which may go some way to explaining why nearly 22% of controls had a LVEF ≤55%.

4.4. Limitations

In this research, only one feature tracking package was available. A thorough validation of this approach should involve reproducibility with other tools. Moreover, commercial packages are limited by the fact that they have no FDA-approved feature tracking algorithms yet. Therefore, these results can only be used for research purposes and cannot be included in clinical practice.

Another limitation relates to the fact that we accepted the presence of a typical LGE pattern as AC LV involvement. However, they were young individuals without other causes to explain that LGE pattern, harbored a pathogenic/probably pathogenic mutation in an AC related gene (mostly a gene associated with LV involvement such as desmoplakin) and belonged to families with a definite diagnosis of AC in at least in one member. Thus, LV tissue involvement of AC was assumed from LGE images even though it is not included in the current 2010 TFC. Interestingly and out of the scope of the present study, it is possible that at an earlier stage also mutation carriers without LGE could exhibit LV dysfunction. Future research endeavors focused on AC patients without LGE and long follow up periods may validate this hypothesis.

We also acknowledge our reduced sample size. AC is regarded as a rare disease and limiting the patient group to AC with LV involvement and mutation positive individuals hampers the enrollment of patients to an even greater extent.

Overall, renewed interest based upon our results may prompt further studies to validate and fine-tune our approach by increasing the sample, repeating the procedure with different feature tracking algorithms and/or using other methodologies.

5. Conclusions

Strain analysis by feature tracking CMR helps to quantify global and regional LV dysfunction, dyssynchrony and LVEF in AC patients with LV involvement, a rare and lethal inherited cardiac disease. Radial dyssynchrony and LVEF were the variables with the most notable differences between patients and controls; while differences in circumferential dyssynchrony were also significant, though to a lesser extent. These parameters could be assessed to improve the detection of AC with LV involvement in conjunction with other TFC categories. Unexpectedly, we found regional discrepancies between strain and dyssynchrony analyses. Whereas delayed myocardial contraction was observed at the apical and inferolateral segments, a globally decreased myocardial deformation was widespread throughout the left ventricle. These results suggest new physiological pathways to improve the functional characterization and diagnosis of AC with LV involvement.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.024.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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