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MINI-REVIEW

Left Ventricular Dysfunction in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Can We Separate ARVC From Other Arrhythmogenic Cardiomyopathies?

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ABSTRACT: Arrhythmogenic right ventricular cardiomyopathy was first described as a right ventricular disease that is an important cause of death in young adults. However, with the advent of advanced imaging, arrhythmogenic right ventricular cardiomyopathy has been found to commonly have biventricular involvement, and a small portion of patients have left ventricular–dominant forms. On the other hand, a number of primarily left ventricular disease such as sarcoid and myocarditis can be arrhythmogenic and have right ventricular involvement. A few recent publications on arrhythmogenic right ventricular cardiomyopathy cohorts have average left ventricular functions that are comparable to sarcoid or myocarditis cohorts. We review the current literature and compare these cohorts of patients, and call for left ventricular functional criteria for arrhythmogenic right ventricular cardiomyopathy as inherited arrhythmogenic cardiomyopathy.

Key Words: arryhthmogenic cardiomyopathy ■ arrhythmogenic right ventricular cardiomyopathy ■ arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an important cause of sudden cardiac death and progressive ventricular dysfunction in young adults.[1,2] ARVC is characterized by fibrofatty myocardial replacement, which predominantly involves the right ventricle, leading to regional wall abnormalities that progress to global right ventricular (RV) dilation and dysfunction.[2] Some degree of left ventricular (LV) involvement is often observed in imaging and postmortem studies of patients with ARVC; however, the definition of LV involvement is highly variable in the literature.[3–5] More recently, the recognition of the LV dominant (without clinically demonstrable RV involvement, arrhythmogenic LV cardiomyopathy) and biventricular subtypes has broadened the disease spectrum and has led the field to use the term *arrhythmogenic cardiomyopathy* (ACM).[6,7] Although the prevalence of LV dysfunction has been described in only 7% to 24% of cases in large cohorts,[3,8] some recent studies have reported LV dysfunction at 47% to 60% rates,[9–11] which is almost as high as the prevalence of LV dysfunction in LV cardiomyopathies. Thus, it is unclear whether more truly positive cases with LV dysfunction are being identified, or other diseases are being included as left-dominant or biventricular subtypes of inherited ACM.

The Heart Rhythm Society expert consensus (2019) defined the overarching term *ACM* as an arrhythmogenic myocardial disorder not explained by ischemic, hypertensive, or valvular disease.[7] Etiologies in this group may be genetic (eg, ARVC, arrhythmogenic LV cardiomyopathy, biventricular forms), infectious (eg, Chagas disease), or part of a systemic disorder (eg,

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Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
LGE	late gadolinium enhancement

sarcoidosis). With this definition, ACM can be seen as a comprehensive phenotype of diseases that have in common a clinical presentation with documented or symptomatic arrhythmia. However, most recent clinical studies still us the terms *left-dominant ARVC* and *biventricular ARVC* for inherited ACM with LV involvement.[8–11] This expanded phenotype of ACM may be an additional source of confusion in research studies, as some patients with biventricular disease caused by systemic disorders (eg, sarcoidosis) may have been wrongly classified as "biventricular ARVC" in those studies. Here, we describe 5 cohorts of patients with ARVC (and biventricular forms) that present strikingly high prevalence of LV disease. However, to prevent confusion when comparing these studies, we will maintain the original designation of ARVC when referring to inherited ACM (ARVC, arrhythmogenic LV cardiomyopathy, and biventricular disease).

In a recent issue of the *Journal of the American Heart Association*, Chen and colleagues[9] investigated the value of cardiac magnetic resonance (CMR) feature tracking analysis in early detection of LV abnormalities in ARVC with preserved LV ejection fraction (LVEF; ≥55%). This was a cross-sectional study from China including healthy controls and consecutive patients with ARVC who underwent clinical and CMR evaluation and were diagnosed according to the revised Task Force Criteria.[12] The final sample consisted of 68 participants diagnosed with ARVC, of whom 27 had preserved LVEF (39.7%), 41 had LVEF <55% (60.2%), and 46 had LV late gadolinium enhancement (LGE; 67.6%) (Table). Virtually all patients from the LV dysfunction group had LV LGE. The degree of LV dysfunction was significant (mean LVEF, 41±11%) and accompanied by severe RV dysfunction (mean RV ejection fraction, 21.2±8%). Another Chinese cohort from Shen et al[11] has shown a similar rate of LV dysfunction (48.3%), but the presence of LV LGE was less frequent (38.3%). Are the ARVC cohorts in China different from established cohorts around the world?

However, Chen and Shen are not alone. In another recent issue of *Journal of the American Heart Association*, Cipriani et al[10] also reported a high prevalence of LV dysfunction in their Italian ARVC population. In this observational, single-center study, the authors compared clinical and imaging characteristics of participants with ARVC and dilated cardiomyopathy. LV involvement was defined as the presence of LV dysfunction or LV LGE. A total of 41 of the 87 ARVC patients (47.1%) showed LVEF ≤50% (median LVEF, 46%, interquartile range, 41%–48%) and LV LGE, while 17 patients (19.5%) had LV LGE but LVEF >50%. This group of 58 patients with either LV dysfunction or LV LGE had a significantly higher prevalence of desmoplakin gene mutation (29.3% versus 6.9%; *P*=0.02) but no differences in RV volumes, RV ejection fraction, or prevalence of RV LGE compared with those with no LV involvement. Interestingly, the group with LV involvement had a median RV ejection fraction of 46% (interquartile range, 38%–51%), which was much higher than that reported by Chen et al in patients with LV dysfunction.

Bhonsale et al[3] published the largest cohort of patients with ARVC, which derived from the American and the Dutch ARVC registries. Only 53 of the 220 (24%) probands with a definitive diagnosis of ARVC were reported to have LV dysfunction on CMR, which was more commonly associated with desmocollin-2, phospholamban, and desmoplakin gene mutation carriers. In another recent multicenter cohort of 140 patients by Aquaro and colleagues, only 10 participants (7%) had an LVEF <50%.[8] However, a total of 68 patients (48.5%) had LV involvement, defined by the presence of any of the following: LV LGE (n=49, 35%), LV wall motion abnormalities (n=30, 21%), LV fat infiltration (n=43, 31%), or LV dilation (n=9, 6%) or dysfunction (n=10, 7%).

Therefore, there is an important difference in the prevalence of LV dysfunction between these 2 larger ARVC cohorts and the cohorts by Chen and Cipriani. This heterogeneity could be attributable to differences in the genetic background of the participants in each study (Table), but there are other possible explanations. First, more patients with LV dysfunction are being diagnosed with biventricular or LV-dominant ARVC because of the recognition that LV involvement is more common than previously thought (true positives).[4] Alternatively, more patients with sarcoidosis and myocarditis, which are LV-dominant diseases with frequent arrhythmias, heart failure, and often RV involvement, are being diagnosed as biventricular or LV-dominant ARVC.[6,14,16] CMR parameters of patients with sarcoidosis or myocarditis can be easily called biventricular or LV-dominant ARVC as shown in Table. In the study by Velangi et al,[13] 35 (12%) patients with sarcoidosis evaluated with CMR were found to have RV dysfunction. The prevalence of LV LGE (74.3%) and mean LVEF (41.9%) of this group was similar to that reported by Chen et al. Another study by Philips et al[14] described 15 patients who met Task Force Criteria for diagnosis of ARVC and were subsequently diagnosed with cardiac sarcoidosis at a specialized center. Gräni et

Table. Characteristics of the Studies

	Chen et al[9] (n=68)	Cipriani et al[10] (n=87)	Shen et al[11] (n=60)	Bhonsale et al[3] (n=220)	Aquaro et al[8] (n=140)	Velangi et al[13] (n=38)	Philips et al[14] (n=15)	Gräni et al[15] (n=670)
Diagnosis	ARVC	ARVC	ARVC	ARVC	ARVC	Sarcoidosis	Sarcoidosis	Myocarditis
Age, y	39±13.8	34 (22–47)	38.7±17.6	35±17	42±17	54.3±12.9	45 (40–47)	47±16.0
Male, n (%)	45 (66.1)	56 (64)	36 (60)	146 (66.3)	97 (69)	23 (60.5)	12 (80)	392 (58.5)
Family history, n (%)	6 (8.8)	57 (66)	4 (6.6)	NA	32 (23)	…	…	…
Mutations, n (%)								
PKP2	…	24 (27.5)	…	156 (70.9)	27 (19.2)	…	…	…
DSP	…	19 (21.8)	…	9 (4)	14 (10)	…	…	…
DSG2	…	10 (11.4)	…	2 (0.9)	8 (5.7)	…	…	…
DSC2	…	2 (2.2)	…	5 (2.2)	0	…	…	…
JUP	…	1 (1.1)	…	2 (0.9)	5 (3.5)	…	…	…
PLN	…	0	…	18 (8.1)	0	…	…	…
>1 mutation	…	0	…	14 (6.3)	0	…	…	…
Negative	…	28 (32.1)	…	0	41 (29.2)	…	…	…
Unknown	68 (100)	8 (9.1)	60 (100)	0	45 (32.1)	…	…	…
CMR findings								
RVEDVi, mL/m^2	125±49.5	106 (94–117)	NA	NA	84 (71–95)	85.1 (69–96)	NA	79.9±21.3
RVEF, %	21.9±9.2	45 (38–52)	35±13.3	NA	53±13	34.8 (30–38)	38 (28–45)	48.8±11.1
LVEDVi, mL/m^2	73.7±22.4	88 (75–100)	72.2±24.1	NA	85±17	63.9 (54–92)	NA	97.6±33.1
LVEF, %	48.2±12.5	53 (46–59)	53.8±10.4	NA	62±8	41.9 (29–54)	57 (35–60)	49.6±15.0
LV LGE, n (%)	46 (67.6)	58 (67)	23 (38.3)	NA	49 (35)	26 (74)	6 (50)	294 (43.8)
LWMA, n (%)	NA		13 (21.6)	NA	30 (21)	NA	NA	280 (42)
LV fat infiltration, (%)	NA		3 (0.5)	NA	43 (31)	NA	1 (8)	NA
LVEF <55%, n (%)	41 (60.2)	…	29 (48.3)	53 (24)	…	NA	…	NA
LVEF <50%, n (%)	…	41 (47)	…	…	10 (7)	NA	8 (53)	NA

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; LV, left ventricular; LV LGE, left ventricular late-gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LWMA, left ventricular wall motion abnormality; NA, not available; RVEDVi, right ventricular end-diastolic volume index; and RVEF, right ventricular ejection fraction.

al[15] described the CMR characteristics of 670 patients with suspected myocarditis, which are also included in Table for comparison.

Rhythm disorders are a major feature of both RV and LV forms of inherited ACM. Classical ARVC is typically characterized by the presence of ventricular tachycardia with a left bundle branch block morphology.[6,7] The diagnosis of arrhythmogenic LV cardiomyopathy relies on documentation of ventricular arrhythmia with a morphology consistent with an LV origin according to the Heart Rhythm Society consensus.[7] On the other hand, conduction system disease such as heart block, bundle branch block, or atrial ventricular delays are rare in ARVC but common in sarcoidosis. It would be interesting to know the proportion of the patients in those ARVC cohorts who have conduction system disease.

The diagnosis of inherited ACM is difficult because of the absence of unique diagnostic criteria and its variable expressivity (ie, RV dominant, biventricular, LV dominant). Bomma et al[17] showed that up to 73% of patients with presumed ARVC referred to their specialized center had the diagnosis ruled out after reevaluation. The authors attributed part of the high frequency of misdiagnosis to an overreliance on CMR findings. Misdiagnosis can be common, particularly in cases where the final diagnosis depends on the presence or absence of imaging criteria, therefore relying on the quality of the study. In the study by Chen and colleagues, all their patients met either a major or minor CMR criterion, which is well above the 72% rate reported by Cipriani, and a 40% rate reported by Aquaro. The Task Force Criteria is not perfect either, as it was found to have a 14% false-positive rate as determined by an experienced expert panel on ARVC.[18] This rate could be even higher because of misinterpretation of CMR studies in less experienced centers.

Another major problem is the lack of uniformity in the definition of LV involvement. Both the 1994 and 2010 Task Force Criteria guidelines were designed to diagnose the classical ARVC, which is RV dominant, and did not include specific criteria for diagnosis of LV involvement.[12,19] Thus, the definition of LV involvement is also highly variable among studies, which hinders the diagnosis and classification of patients with

biventricular forms. Is the presence of LV LGE alone an acceptable definition for LV involvement to classify a patient with RV dyskinesia and RV ejection fraction <40% as having biventricular disease? Or perhaps LV LGE should be accompanied by LV dysfunction to be considered LV involvement? Ideally, the definition of LV involvement should be established upon evidence-based parameters of prognostic relevance.

In the cohort studied by Aquaro, the presence of LV involvement was the strongest predicting variable for the combined end point of sudden cardiac death, implantable cardioverter-defibrillator placement, and aborted cardiac arrest (hazard ratio, 4.2; 95% CI, 2.1–8.4) in a multivariable analysis.[8] Patients with LV involvement had a significantly lower 5-year event-free survival compared with those without LV involvement (≈35% versus 83%; log-rank $P<0.001$). The most important contributing variables for this effect were the presence of LV wall motion abnormality, LV fat infiltration, and LV LGE. LV dysfunction and dilation were rare and not statistically significant prognostic variables. Based on these data, probably the best definition of LV involvement would be the presence of one of the following: LV LGE, LV wall motion abnormality, or LV fat infiltration in the absence of more than mild LV dilation and dysfunction. Unfortunately, LV LGE, LV wall motion abnormality, or LV fat infiltration findings by themselves are nonspecific and can be present in any chronic LV disease with LV dilation and dysfunction. This definition should be tested in a separate validation cohort, which may help the field to identify patients with biventricular and LV-dominant ARVC and to standardize the reporting of data on these individuals. Without any boundary on what the LV-dominant and biventricular ARVC should look like by the LV functional and structural criteria, we are bound to find ourselves in chaos, with any LV cardiomyopathy that presents with an arrhythmia being called LV-dominant ARVC.

In conclusion, some recent studies are reporting a higher prevalence of LV systolic dysfunction in patients with ARVC. These numbers may be explained by differences in the genetic background among patient cohorts and the recent advances in the understanding that the LV is often involved in the disease. Alternatively, some patients with LV cardiomyopathy and arrhythmia may have been misdiagnosed with ARVC. The lack of specific diagnostic criteria for LV-dominant and biventricular forms is challenging, and diagnosis may excessively rely on CMR findings. For this reason, validation of specific criteria to define LV involvement on CMR of patients with ARVC or inherited ACM is urgently needed.

ARTICLE INFORMATION

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