Current Concepts on Diagnosis and Prognosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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Abstract: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an uncommon cardiac disease characterized by progressive right ventricular dysfunction due to fibrofatty replacement of myocytes and risk of sudden cardiac death from malignant arrhythmias. ARVC/D is a disease of the cardiac desmosome, with genetic mutations in genes encoding proteins critical to this structure found in the majority of patients. The diagnosis of ARVC/D is based on fulfilling a combination of clinical, imaging, pathologic, and/or genetic criteria set forth by the 2010 modified Task Force Criteria. Cardiac magnetic resonance (CMR) is included in these criteria and plays an important role in the management of ARVC/D, demonstrating pathologic structural changes in the right and left ventricles that provide both diagnostic and prognostic information. The purpose of this article is to provide a background on the pathophysiology and genetics of ARVC/D and focus on the role of CMR in management of ARVC/D including diagnosis, prognosis, and treatment decisions. Common CMR pitfalls that can lead to misdiagnosis will also be reviewed.

Key Words: arrhythmogenic right ventricular cardiomyopathy, diagnosis, Task Force Criteria, cardiac magnetic resonance, prognosis, pitfalls

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare inherited cardiomyopathy characterized by fibrofatty replacement of the right ventricle (RV),[1] which is associated with a high risk for ventricular arrhythmias and sudden cardiac death (SCD).[2] In the classic form of the disease, RV abnormalities are the predominant finding; however, ARVC/D patients may also have variable degrees of involvement of the left ventricle. A left-dominant form of ARVC/D has been recognized.[3] Electrical abnormalities are the most frequent manifestation of disease[4]; however, in a minority of patients, severe right or left ventricular disease can progress to symptomatic heart failure.[5] Classically, ARVC/D presents between the second and fourth decade of life with symptomatic arrhythmias or SCD. There is no single diagnostic test for ARVC/D, but rather the diagnosis is made on the basis of fulfilling a combination of major and minor clinical, electrical, and imaging criteria that have been previously defined by a group of experts. These are known as the Task Force Criteria (TFC) and were initially proposed in 1994 and revised in 2010.[6,7] Cardiac magnetic resonance imaging (CMR) is an important element of the TFC, revealing structural abnormalities in the RV that are the result of fibrofatty replacement of the myocardium. However, evaluation of the RV is challenging, and there are multiple normal variants and disease states that can mimic ARVC/D and lead to misdiagnosis. Accurate diagnosis is critical for initiation of treatment, which in most cases involves prophylactic implantation of internal cardioverter defibrillator (ICD) to prevent SCD. The purpose of this article is to review the diagnosis, prognosis, and treatment of ARVC/D with a focus on the role of CMR in disease management and a discussion of potential pitfalls faced by the imager evaluating a patient for suspected ARVC/D.

PATHOPHYSIOLOGY

The pathophysiological basis for ARVC/D is defects in either cell adhesion proteins or intracellular signaling components that result in desmosomal dysfunction.[4] The desmosome is an important structure for normal cell-cell adhesion and helps provide mechanical strength to tissues. Along with gap junctions and adherin junctions, the desmosome is found in the intercalated disk, serving as a linkage point between one cell and another and also providing an attachment point for structural proteins that make up the internal cytoskeleton of the cell. Mutations of desmosomal molecules represent the primary abnormality in patients with ARVC/D. In the extracellular space, desmosomal cadherins (desmocollin and desmoglein) bind strongly to each other. Cadherins span the cellular membrane, where in the intracellular space, they attach to linker proteins [plakoglobin (JUP), desmoplakin (DSP), and plakophilin-2 (PKP2)], which connect the cadherins to intermediate filaments that provide internal structure to the cell and link to other desmosomes at opposite ends of the cell.[1] Dysfunction of desmosomal proteins and signaling molecules results in weakening of cell-cell junctions, resulting in cellular dysfunction. The degeneration-inflammation model proposes that the resulting cellular damage is accompanied by an inflammatory response, and when the regenerative capacity of the myocardium is exceeded, replacement with fibrous and/or adipose tissue ensues.[8] This cellular damage is found in tissues that are under high mechanical stress,

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such as the myocardium and skin, both of which demonstrate significant abnormalities in the rare autosomal recessive forms of ARVC/D.[1] The importance of mechanical stress in the pathophysiology of ARVC/D is further supported by the association of high intensity exercise with more severe disease expression in ARVC/D mutation carriers.[9]

GENETICS

ARVC/D is inherited in an autosomal dominant pattern with incomplete penetrance and expressivity in the majority of patients. Genetic testing identifies desmosomal mutations in approximately 30% to 60% of ARVC/D cases.[8,10] At least 8 mutations in genes encoding the cardiac desmosomal proteins can be related to ARVC/D (Table 1), the *PKP2* gene has been most frequently associated,[1] with prevalence of 10% to 47% among unrelated probands and 70% to 82% among familiar ARVC/D cases.[4,11] The second most frequent mutated gene is *DSP*.[1] Rare autosomal recessive forms of ARVC/D, Naxos disease and Carvajal syndrome, named after the location of the families discovered with the disease, have also been described.[2] These patients have a more severe arrhythmia phenotype, wooly hair, and abnormal skin thickening in the palms and soles of the feet. The link between desmosomal mutations and ARVC/D was first elucidated in these patients, who have mutations in the genes *JUP* (Naxos) and *DSP* (Carvajal).[15] Interestingly, patients with Naxos disease show a classic right-dominant ARVC/D phenotype, whereas in Carvajal syndrome, patients have a left-sided phenotype, characterized by biventricular dilation and extensive left ventricular fibrosis.[1] This genotype-phenotype correlation has also been described in the more common autosomal dominant forms of the disease, with *PKP2* gene mutations associated with the classical phenotype and *DSP* mutations associated with left-sided disease.[16]

EPIDEMIOLOGY

ARVC/D is a rare disease with an estimated prevalence of approximately 1:1000 to 5000[1,4,10,17,18]; it is more common in the Mediterranean region. This condition is thought to be more prevalent in male individuals with a ratio of 3:1[19,20]; however, some studies have shown an equal prevalence between male and female individuals.[21] ARVC/D is rarely clinically manifested before the age of 12 or after the age of 60.[22] The onset of symptoms is usually in the range of 20 and 40 years.[20] Patients with ARVC/D usually present with palpitations, lightheadedness, and/or syncope. Abnormal rhythms including premature ventricular beats, rapid monomorphic ventricular tachycardia, and ventricular fibrillation may be seen, with SCD from arrhythmia being the presenting symptom in some unfortunate patients.[2,10,23] ARVC/D is present in at least 20% of athletes 35 years of age or younger who presented with SCD in a large series from Italy.[24] It is also present in up to 10% of deaths from undiagnosed cardiac disease in individuals 65 years of age or older.[8] In patients diagnosed with ARVC/D, the annual mortality rate for cardiac death has been reported at 0.08% to 3.6%.[25] Strenuous exercise increases the risk of death; in athletes with ARVC/D the rate of SCD is 5.4 times higher than individuals with sedentary activity.[26]

DIAGNOSTIC CRITERIA

ARVC was first described in 1982, with a case series of 24 patients with recurrent ventricular tachycardia and fibrofatty replacement of the RV wall.[27] However, diagnostic criteria were not established until 1994, when the European Society of Cardiology and Scientific Council of Cardiomyopathies of the International Society and Federation of Cardiology proposed the TFC for the clinical diagnosis of ARVC.[7] The 1994 TFC included major and minor criteria based on structural and functional RV abnormalities at imaging, electrocardiographic (ECG) changes, histopathologic findings, and family history of

TABLE 1. Genetics of ARVC/D[4,11–14]

Gene Codes	Chromosome Locus	Prevalence (%) Unrelated	Prevalence (%) Related	Comments
Desmosomal proteins				
Plakophilin-2 (PKP2)	12p11	10-47	70-81.6	Patients present symptoms earlier compared with the other mutations
Desmoglein-2 (DSG-2)	18q12.1	7-10	6	The Thr335Ala variant is most often reported with a severe and fully penetrant phenotype
Desmocollin-2 (DSC-2)	18q12.1	2	0.5	Heterozygotes have ARVC/D, homozygotes have hair and cutaneous involvement
Desmoplakin (DSP)	6p24	10-16	3.5	Recessive mutations cause Carvajal syndrome. Associated with the biventricular or left-dominant form of arrhythmogenic cardiomyopathy.
Plakoglobin (JUP)	17q21	Rare	0.18	Homozygote recessive mutations cause Naxos disease. Dominant have ARVD/C
Extradesmosomal proteins				
Transmembrane protein-43 (TMEM43)	3p23	Unknown	0.18	Highly lethal condition and fully penetrant. Associated with high incidence of premature SCD
Ryanodine receptor-2 (RYR-2)	1q42-q43	Rare	Unknown	Linked with juvenile SCD and effort-induced polymorphic ventricular tachycardia
Transforming growth factor β-3 (TGFβ3)	14q23-q24	2.50	Unknown	Related with the stimulation of mesenchymal cells to proliferate and produce extracellular matrix components
Phospholamban (PLN)	6q22.31	12	6	Associated with left form of arrhythmogenic cardiomyopathy. Frequent gene in Dutch population

SCD or ARVC/D. Patients are diagnosed with ARVC/D if they have 4 points (2 points for each major criterion and 1 point for each minor criterion). Patients with 3 points are classified as borderline ARVC/D.[2,28] The 1994 criteria did not include the results of genetic testing, limiting sensitivity for early familial disease. In addition, criteria were based on subjective qualitative findings, which resulted in low-specificity and frequent false-positive diagnoses.[6,29] For CMR specifically, major and minor criteria were based on assessment of RV size, function, and wall motion abnormalities. Because of the complexity of RV geometry, assessment of RV size and wall motion is challenging even for experienced imagers. Previous studies showed considerable variability in RV shape and wall motion in normal volunteers that result in a high prevalence of subjective RV dilation and wall motion abnormalities.[30,31] In addition, given the rarity of ARVC/D, the majority of imagers outside of referral centers have little or no experience with true cases of ARVC/D, resulting in false-positive diagnoses. These limitations led to the revision of the TFC in 2010, which was amended to include quantitative assessment of imaging, pathologic, and electrical parameters to improve specificity, and genetic testing to increase sensitivity of diagnosis for familial disease.[6,23] In the 2010 criteria, in order for subject meeting either major or minor criteria for the ARVC/D diagnosis, examinations must demonstrate both regional qualitative and global quantitative RV abnormalities. Specifically, patients must have a localized regional wall motion abnormality, defined as regional akinesia, dyskinesia, or dyssynchrony, and have globally reduced RV ejection fraction (EF) or an increased RV end-diastolic volume (EDV, indexed to body surface area). Quantitative EF and RV end-diastolic volume index (RVEDVI) thresholds are used to determine whether major or minor CMR criteria are fulfilled.

The impact of the 2010 criteria on diagnostic yield was studied by Femia et al,[23] who reported that the positive predictive value for ARVC/D diagnosis was increased to 55% from 23% when comparing patients evaluated using the 1994 and 2010 TFC. In another study by Vermes et al,[29] approximately 300 patients referred for CMR due to suspected ARVC/D, initially scored with the qualitative 1994 major and minor criteria, were reevaluated using the modified 2010 criteria. The effect of the criteria changes was striking; fewer CMR criteria were met under the 2010 TFC, resulting in improved specificity (increased from 78% to 94%), at the expense of decreased sensitivity. The percentage of patients meeting major CMR criteria decreased from 23.5% to 6.5% and minor criteria decreased from 58.5% to 4%. Similar findings were reported by Liu et al,[32] who reviewed nearly 1000 CMR examinations referred for the clinical suspicion of ARVC/D. Application of the 2010 TFC reduced the number of patients meeting major or minor CMR criteria from 23% to 3%. However, despite this reduction in CMR sensitivity, overall global TFC sensitivity has increased with the 2010 criteria due to the inclusion of genetic criteria and increased points for family members with the disease.[33]

IMAGING EVALUATION

Imaging findings in ARVC/D have been well described for 2-dimensional (2D) echocardiography, CMR, RV angiography, and cardiac computed tomography (CCT). CMR, however, is the preferred technique for evaluation of ARVC/D, given its unparalleled ability to image RV structure and function with high spatial and temporal resolution. 2D echocardiography, RV angiography, and CMR findings were included in the 2010 TFC and may be used to fulfill major or minor criteria; however, CCT is not included.

Echocardiography

Echocardiography is typically the first-line test in the evaluation of patients with symptoms that could be attributable to ARVC/D due to its speed, availability, and low cost. However, evaluation of the RV is suboptimal due to near field effects that limit RV wall visualization, operator dependency, and frequently limited imaging windows. Three-dimensional (3D) echocardiography allows for measurement of RV volumes and EF and has been shown to correlate well with CMR.[34] However, 3D echocardiography is a specialized technique with limited availability and is not part of the 2010 criteria. In most centers, use of echocardiography is limited to 2D imaging, which is limited in RV assessment.[35] In a study from Borgquist et al,[35] patients underwent CMR and 2D echocardiography. Using CMR findings as the gold standard, the sensitivity and specificity of 2D echocardiography for TFC criteria were 50% and 70%, respectively.

Computed Tomography (CT)

Multidetector CT imaging has the advantage of high spatial resolution that allows assessment of the morphologic detail of both cardiac chambers (Fig. 1). Retrospective ECG-gating can be used to evaluate wall motion and measure EF and RVEDVI. However, the temporal resolution of CT remains limited for assessment of subtle RV wall motion abnormalities. CCT was not included as a potential diagnostic modality in the 1994 or 2010 TFC. However, CT can be helpful in the differential diagnosis of ARVC/D, providing information on the presence of mediastinal lymphadenopathy that may suggest sarcoidosis. CCT may also be useful in the patient who has a contraindication to CMR due to an implanted device or claustrophobia.[21]

CMR

CMR is the gold standard modality for evaluation of RV structure and function and therefore is the preferred imaging modality for patients with suspected ARVC/D. CMR provides high spatial and temporal resolution images of the heart in any imaging plane. Steady-state free precession cine images are preferred for both quantitative and qualitative evaluation of chamber size, EF, and wall motion (Figs. 2, 3; Video 1, Supplemental Digital Content 1, http://links.lww.com/JTI/A60; Video 2, Supplemental Digital Content 2, http://links.lww.com/JTI/A61). Most institutions also include high-resolution double-inversion or triple-inversion recovery T1-weighted fast-spin echo dark blood sequences for identification of intramyocardial fat in either the RV or the LV (Fig. 4). Late gadolinium enhancement (LGE) images are used to look for cardiac fibrosis, which can occasionally be seen in ARVC/D but can also help suggest alternative diagnoses such as myocarditis or sarcoidosis (Fig. 5). A standard CMR ARVC/D protocol is outlined in Table 2.

ACCURACY OF CMR FOR DIAGNOSIS OF ARVC/D

Using the 2010 revised criteria, sensitivity of major and minor CMR criteria for the diagnosis of ARVC/D is between

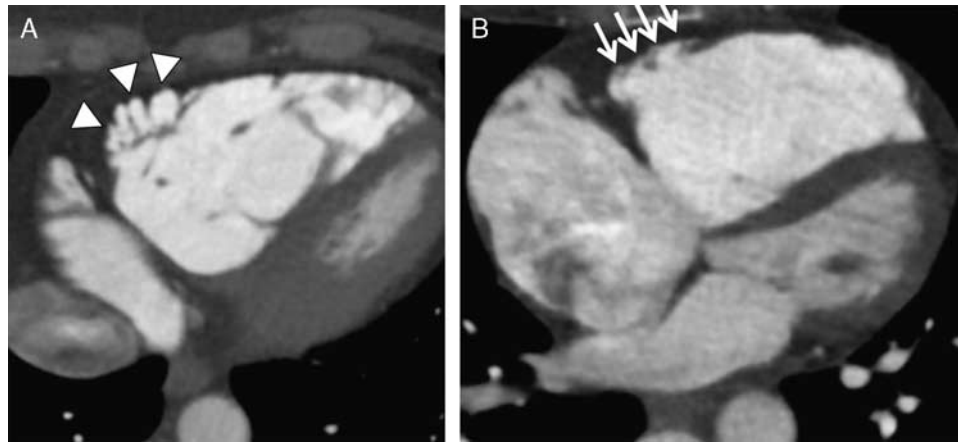

FIGURE 1. CT findings in ARVC/D. A, Axial image from a cardiac CT obtained in a 40-year-old woman with ARVC/D. The RV is dilated, and there are multiple focal areas of outward bulging along the RV free wall, which can be described as microaneurysms (arrowheads). B, More superiorly, the RV is clearly markedly dilated with subtle irregularity of the subtricuspid region of the RV free wall, likely from fat infiltration (arrows).

68% and 76% and 79% and 89%, respectively.[6] Specificity for major and minor criteria is 90% to 98% and 85% to 97%, respectively. It is important to note that these results were based on the evaluation of 108 probands with newly diagnosed ARVC/D in comparison with quantitative values of RV volumes and function from normal subjects. However, in current practice, many patients are family members identified through screening because of a relative diagnosed with ARVC/D. In this patient group there is a higher prevalence of normal CMR examinations and therefore a lower sensitivity and specificity of CMR for the diagnosis. In a recent study by Te Riele and colleagues, 117 relatives of ARVC/D probands were evaluated with CMR. At presentation, 43 (37%) of subjects fulfilled 2010 diagnostic criteria for ARVC/D; however, of these, only 21 (49%) had structural changes on CMR.[37] Evidence suggests that the development of electrical abnormalities precedes structural abnormalities in ARVC/D.[38] These patients, therefore, likely have early or mild disease that predates identifiable RV structural changes. Other patients in this category may have a borderline CMR examination that shows a localized RV wall motion abnormality, for instance, but does not meet the RVEF or volume thresholds for major or minor CMR criteria. Most experts would suggest close follow-up for these patients with serial ECG and Holter monitoring and repeat CMR for patients with new symptoms or electrical abnormalities.[37]

CMR OF RV WALL MOTION ABNORMALITIES IN ARVC/D

As discussed above, major and minor CMR criteria are based upon (1) identification of a regional wall motion abnormality and (2) reduced RVEF and/or increased RV volume. The hallmark of ARVC/D is regional heterogeneity of RV function, which results in localized wall motion abnormalities. Importantly, this is in contrast to the global RV dysfunction that can be seen from various types of dilated cardiomyopathies. Three types of RV regional wall motion abnormalities are described in the 2010 TFC. In *akinesia*, a region of the RV wall shows no evidence of contraction during systole, best seen by complete lack of wall thickening and longitudinal or radial shortening. These

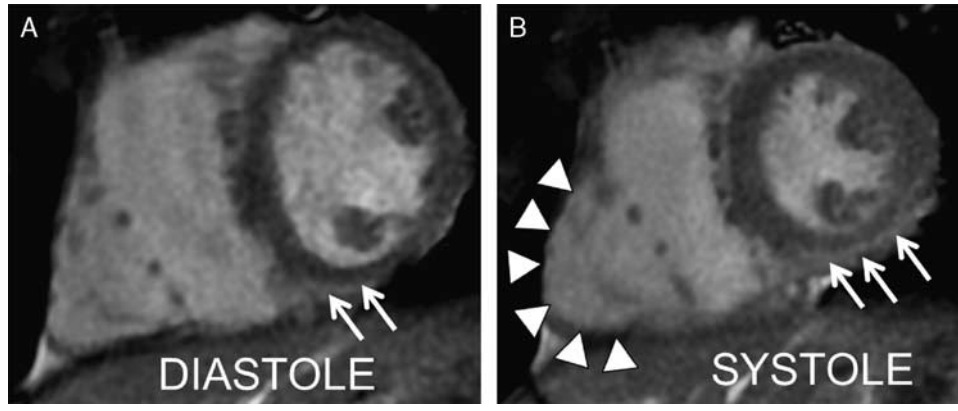

FIGURE 2. Typical RV wall motion abnormalities on short-axis images in RV-predominant ARVC/D. The short-axis diastolic (A) and systolic (B) bright blood images from a CMR obtained in a 16-year-old man with ARVC/D demonstrate focal bulging of the RV wall around the "angle" of the RV (the junction of the anterior and inferior walls) in systole (arrowheads), which is a common site of wall motion abnormalities in ARVC/D. Images were obtained postcontrast, and there is also some subepicardial enhancement of the inferior wall of the LV (arrows).

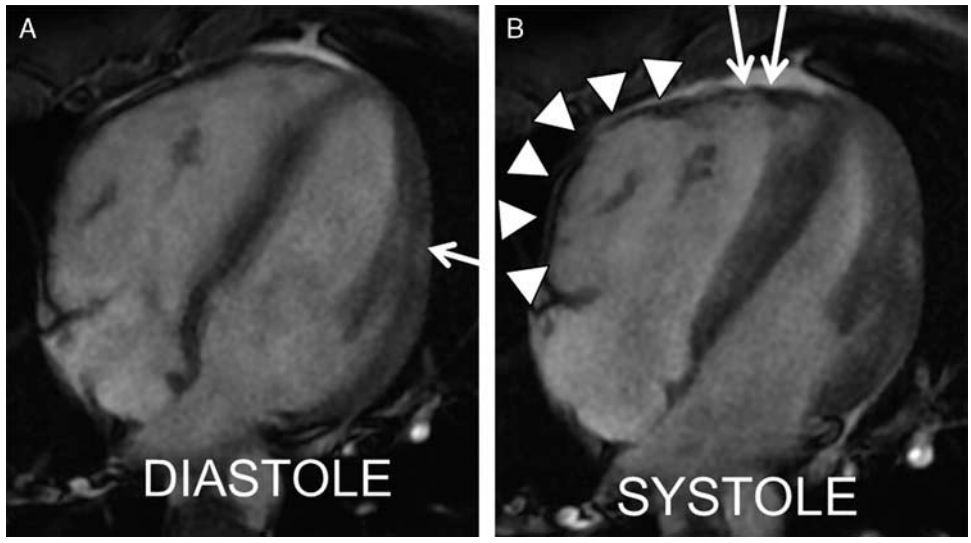

FIGURE 3. Typical RV wall motion abnormalities on long-axis images in RV-predominant ARVC/D. The 4-chamber diastolic (A) and systolic (B) bright blood images from a CMR obtained in a 16-year-old man with ARVC/D demonstrate focal bulging of the mid RV anterior wall in systole (arrowheads), which is a common site of wall motion abnormalities in ARVC/D. Apical contraction (arrows) is preserved. Images were obtained postcontrast, and there is also some subepicardial enhancement of the lateral wall of the LV.

portions of the wall may move inward during systole, however, if they are dragged by adjacent areas with preserved contractile function. In *dyskinesia*, the diseased segment moves in the wrong direction, usually best seen as localized outward bulging that occurs during systole (Figs. 2, 3; Videos 1 and 2, Supplemental Digital Contents 1 and 2, which demonstrate short-axis and long-axis cine imaging of typical ARVC/D RV wall motion abnormalities). Small areas of bulging may also be referred to as microaneurysms. A crinkling pattern of contraction has also been described, coined the accordion sign, which can be visualized on the RV free wall in long-axis images.[39] Finally, in *dyssynchrony*, segments of the RV wall will contract at different times after the onset of systole, with abnormal areas lagging behind the normal myocardium. In practice, most patients show a combination of the above findings in several regions, and differentiation of these kinds of wall motion abnormalities may be challenging, but not essential to the diagnosis. In our experience, outward bulging in the subtricuspid region, at the junction of the RV free wall and inferior wall, and in the RV inferior wall are encountered most often (Fig. 2). The location of RV disease in ARVC/D was traditionally described as conforming to the "triangle of dysplasia," a region extending from the RV inferior wall to the apex and then wrapping around cranially to the RV outflow tract.[27] However, this dogma was established on the basis of early studies in patients with highly advanced disease and may not be applicable today where early diagnosis and familial disease are more commonly encountered. A recent study by Te Riele et al[40] suggested the need for a paradigm shift away from the triangle of dysplasia. In this study of 74 mutation-positive patients with ARVC/D, the apex was the least often segment of the RV involved by disease and was only associated with an advanced phenotype. The basilar inferior wall and anterior walls were most commonly affected in early disease, which was corroborated by electrophysiological findings of low voltage in these regions.

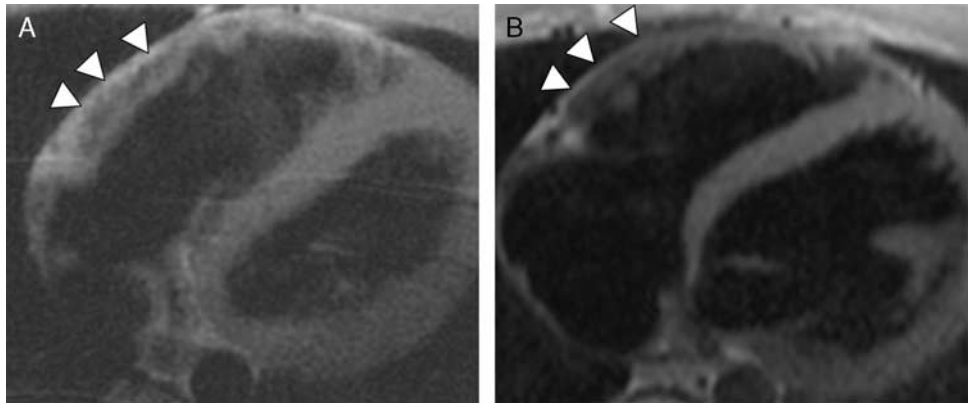

FIGURE 4. Fat infiltration in the RV wall in classical RV-predominant ARVC/D. A, Axial dark blood image from a cardiac CT obtained in a 17-year-old boy with ARVC/D. There is irregular high signal along the epicardial surface of the basilar to mid RV anterior wall due to fat infiltration (arrowheads). B, Normal RV wall for comparison showing a smooth epicardial contour (arrowheads).

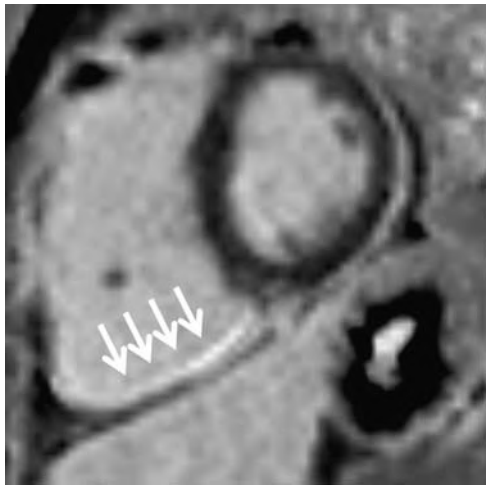

FIGURE 5. RV LGE in ARVC/D. Short-axis LGE image with a 2D phase-sensitive inversion recovery technique obtained in a 40-year-old woman with ARVC/D. Diffuse enhancement of the inferior RV wall is clearly seen (arrows).

CMR OF RV VOLUMES AND FUNCTION IN ARVC/D

In ARVC/D patients, RV myocardial fibrosis and fatty replacement lead to RV wall thinning and dysfunction. Regional wall motion abnormalities eventually result in globally reduced RV systolic function. In addition, the RV will often become dilated. Quantitative measurements of RV volumes and function are generally performed using the Simpson summation of disks method, which adds the volumes designated by endocardial contours that are traced on contiguous short-axis slices obtained in end-systole and end-diastole. Most authors include the RV trabeculations in the blood pool volume. Segmentation of the RV can be challenging, with a previous study showing that 100 training cases were needed to reduce interobserver variability to a reasonable range of 5%,[36] leading some authors to suggest that variability in standard clinical practice is not likely to be better than 10%.[10] This potential variability is of critical importance when considering that a change in EF of 6% (from 40% to 46%) can move a patient from fulfilling none of the CMR TFC criteria to major criteria. Some centers have recommended performing axial or radial stacks through the RV rather than the traditional short-axis views. However, this is not commonly practiced and not recommended, given that the TFC thresholds were established on the basis of short-axis examinations.

NON–TASK FORCE CMR FEATURES

Tissue characterization sequences with CMR can identify intramyocardial fibrosis and fatty replacement that are characteristic of ARVC/D. It is important to note that these findings, although often seen in ARVC/D patients, were not included in the TFC due to concerns over low sensitivity and specificity. However, when identified, they may lend further confidence to the imager when confronted with a possible ARVC/D diagnosis.

Ventricular Fat Infiltration

Fatty replacement of the RV myocardium is the characteristic pathologic abnormality in the classical, right-dominant forms of ARVC/D. CMR has been used to identify these changes in patients with suspected ARVC/D. T1-weighted fast-spin echo dark blood images are used to provide motion-free, high-resolution imaging of cardiac morphology. RV fibrofatty infiltration is seen as finger-like projections of high signal on T1-weighted images that infiltrate the RV myocardium from the epicardial surface[41] (Fig. 4). RV fat infiltration is most often found in the anterior, or free, wall of the RV. It may also be seen in the inferior wall if short-axis dark blood images are obtained. Fat-saturated images can be helpful, as loss of signal in regions of fat infiltration will be confirmatory. On fat-saturated images, the epicardial border of the myocardium has an irregular contour owing to the multiple islands of fat infiltration, in contrast to the smooth outer contour seen in the normal RV (Fig. 4). Several studies have evaluated the utility of fat imaging for the diagnosis of ARVC/D.[41–43] These studies have shown that RV fat infiltration has poor sensitivity for the diagnosis of ARVC/D and has limited reproducibility. This is likely due to the limited spatial resolution of CMR in relation to the thinness of the RV wall. Quantitative measures of RV volumes and function were more sensitive and specific for the diagnosis of ARVC/D in a study of 42 probands with ARVC/D.[43] For these reasons, RV fat infiltration was not included as diagnostic criteria in the 2010 TFC.

RV LGE

RV LGE has been described in patients with ARVC/D. Typical LGE protocols acquire images 10 to 20 minutes after injection of a gadolinium-based contrast agent, typically 0.15 to 0.2 mmol/kg. Fibrotic regions of the myocardium retain contrast due to increased extracellular fluid volume and can be identified as regions of high myocardial signal (Fig. 5). The use of 2D phase-sensitive inversion recovery sequence provides better and more reliable image quality of LGE imaging of the RV compared with magnitude images.[44] The prevalence of RV LGE in ARVC/D has

TABLE 2. Proposed Protocol to Evaluate ARVC/D by CMR[10,13,32,36]

Imaging Sequence	Imaging Plane	Comments
Double-inversion recovery black-blood FSE imaging with and without fat suppression	Axial and short axis	Optimal tissue characterization of the RV free wall. Fat suppression improves reader confidence in diagnosis of RV fat infiltration. Also to evaluate LV fat infiltration
SSFP bright blood cine images	Axial, 4 chamber, and short axis. RV 3 chamber	Assess for RV regional function. RV size and LV function estimation. RV quantitative analysis is performed on the short-axis cine images
LGE (PSIR recommended)	Axial, short-axis, 4-chamber, and vertical long axis	Optimal for imaging fibrosis

been variable in the literature. In 1 small study of 52 subjects with suspected ARVC/D, RV LGE showed high sensitivity and specificity for the diagnosis of ARVC/D, being identified in 7/8 ARVC/D cases (88%) compared with only 6/44 (14%) subjects without ARVC/D.[45] In another small study, 8/12 subjects with ARVC/D (67%) had RV LGE on CMR compared with 0% of 18 patients without ARVC/D.[46] Larger studies of RV LGE prevalence are currently lacking. The presence of RV LGE has been associated with low-voltage scars at electrophysiological studies, which some authors have suggested can serve as a guide for ablation procedures, although RV LGE lacked sensitivity for smaller areas of scar.[47,48] LGE sequences, however, have limitations. Most importantly, the thin RV wall makes it difficult to identify the increased signal from LGE, particularly in the setting of motion artifact. In addition, both normal epicardial fat and RV LGE show high signal on LGE sequences, and it can be difficult to differentiate between the 2. RV LGE, therefore, was not included as part of the 2010 TFC and should be considered only as a confirmatory finding when identified on CMR.

LEFT VENTRICULAR INVOLVEMENT IN ARRHYTHMOGENIC CARDIOMYOPATHY

Left ventricular involvement is common in ARVC/D. Three patterns of ARVC/D have been described: the classical pattern with isolated RV involvement, a biventricular pattern with prominent RV wall motion abnormalities associated with LV fat infiltration or fibrosis, and left-dominant forms that show LV fibrosis and systolic dysfunction with relatively mild RV abnormalities.[3,49,50] The left-dominant form, also known as left-dominant arrhythmogenic cardiomyopathy (LDAC) is characterized by myocardial fibrosis principally in the inferior LV wall and septum[8] and is characterized by myocyte loss with fibrotic or fibrofatty replacement similar to classical ARVC/D (Fig. 6).[51] Likewise, LDAC is associated with ventricular arrhythmia of right block configuration, T-wave inversion in inferior or lateral leads, and left ventricular dilatation and/or systolic impairment.[52] LDAC patients have a more severe disease, with higher rates of malignant arrhythmias.[49] In the past, left ventricle involvement was thought to be only seen in the advanced cases of ARVC/D,[53] but it has become clear that left ventricular involvement can be associated with any stage of the disease.[54] In a cohort of 78 North American ARVC/D mutation carriers, Rastegar and colleagues found that among the 38 patients with abnormal magnetic resonance imaging (MRI), only 45% had isolated RV abnormalities, whereas the majority (55%) had LV abnormalities, 2 patients had isolated LV abnormalities, and the remainder had a biventricular pattern of disease. Patients with classical or biventricular forms of ARVC/D did not differ in quantitative measures of either RV or LV function, only in genotype. These results and others have suggested that the degree of left ventricular involvement is genetically determined.[16] Accordingly, the prevalence of left and right-dominant forms of disease has regional variation, likely due to differences in the genetic make-up of the local populations. Researchers in the United Kingdom were the first to report the left-dominant form of ARVC/D and have found a high rate (approximately 80%) of LV abnormalities in their cohorts.[49] LV-predominant disease is less common in North American cohorts. The importance of LV involvement has led some to suggest changing the name of ARVC/D to more generic "arrhythmogenic cardiomyopathy," to encompass both left and right-dominant forms of the disease.[49] The most recent 2010 TFC did not include LV findings in the diagnostic criteria; however, given increasing recognition of the importance of left-sided disease, it is likely that future revisions of criteria will include left-sided findings. Both fat infiltration and fibrosis can be visualized in the left ventricle in patients with ARVC/D. Increased signal intensity on LGE images, suggestive of fibrosis, is often found in the midwall of the septum or in the midwall or subepicardial region of the inferolateral wall. Fat infiltration in the LV is typically subendocardial in location and found in the mid to apical aspect of the lateral wall.[39]

DIFFERENTIAL DIAGNOSIS

CMR findings in ARVC/D can overlap with other cardiomyopathies, particularly cardiac sarcoidosis and myocarditis. In both conditions, nonischemic LGE can be present in the LV, which can be similar in distribution to that described for biventricular and left-sided forms of ARVC/D. In addition, RV involvement is not uncommon

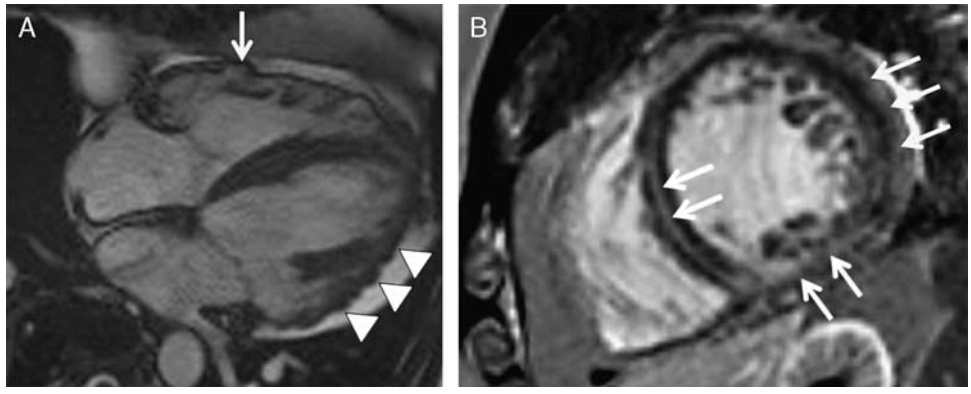

FIGURE 6. Left-dominant ARVC/D. A, Four-chamber bright blood image from a CMR obtained in a 47-year-old woman with the diagnosis of ARVC/D per 2010 TFC. There is marked LV dilation and wall thinning (arrowheads) with relatively normal RV size. A regional wall motion abnormality (bulging) was present in the RV free wall (arrow). B, Short-axis LGE image shows extensive enhancement suggestive of fibrosis in the LV myocardium, involving the midwall of the septum and the subepicardial region of the lateral and inferior walls (arrows).

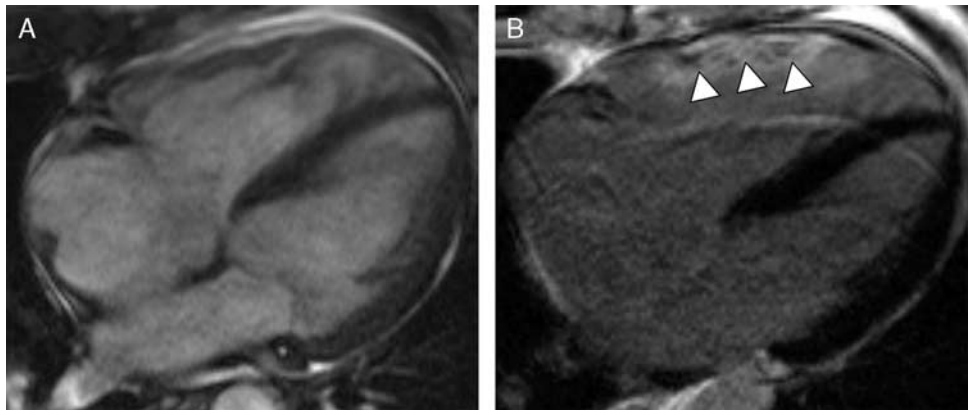

FIGURE 7. Cardiac sarcoidosis. Long-axis LGE images from a CMR obtained in a 65-year-old man who presented with shortness of breath and sustained ventricular tachycardia. The diagnosis of ARVC/D was considered; however, genetics were negative, and the patient was eventually diagnosed with sarcoidosis. A, Four-chamber long-axis view shows dilated right and left ventricles, the RVEF was <30%, and there was global RV and LV hypokinesis. B, Extensive LGE is present involving the RV anterior wall and trabeculations of the RV (arrowheads).

in sarcoidosis, and RV dilation and dysfunction can be a striking feature (Fig. 7). Some features suggestive of cardiac sarcoidosis are left ventricular dysfunction, myocardial delayed enhancement of the septum, mediastinal lymphadenopathy,[55] and clinical manifestations of conduction disease and multisystem involvement.[55,56] In contrast, myocarditis often demonstrates LGE in the lateral and inferior walls of the LV and with a clinical presentation of chest pain and elevated troponins that is unusual for ARVC/D. RV outflow tract tachycardia can be considered one of the principal differential diagnoses of ARVC/D; both diseases are associated with a tachycardia that is very similar, but RV outflow tract tachycardia does not have structural heart disease and is considered a primary electrical disease. CMR is important in these patients to exclude the presence of structural disease that would suggest ARVC/D. Other arrhythmias such as atrioventricular reentry tachycardia and Brugada syndrome can be considered in the differential, as well as alternative causes for RV dilation such as pulmonary hypertension and tricuspid valvulopathy, among others.

MANAGEMENT

The principal goal in the treatment of ARVC/D is to avoid the high-risk event of malignant arrhythmias and sudden death.[2,18] Exercise restriction is an important recommendation because exercise can trigger mechanisms that lead to conduction disorders and SCD.[2,26,57] For this reason, strenuous exercise is strongly discouraged; the recommendation to the patients is to limit their activities to walking and playing golf.[2] Antiarrhythmic medications like β-blockers and class-III antiarrhythmic agents (sotalol, amiodarone) are the most used. For inducible ventricular

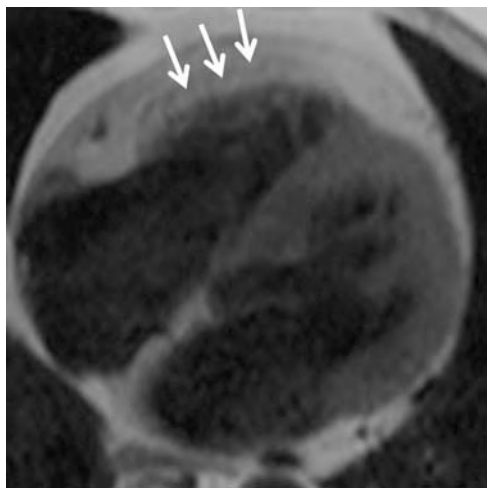

FIGURE 8. Non-ARVC/D fat infiltration in the RV wall on CMR. Axial dark blood T1-weighted CMR images in a 70-year-old man being evaluated for palpitations. There is marked thickening of the wall of the RV secondary to fat infiltration (arrows). This degree of thickening is not typically seen for ARVC/D, which is associated with wall thinning and myocyte replacement.

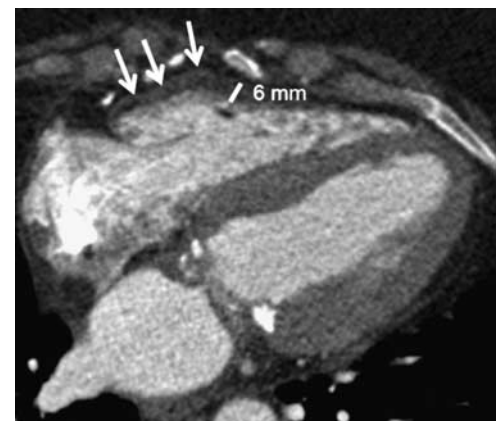

FIGURE 9. Non-ARVC/D fat infiltration in the RV wall on CT. Axial cardiac CT images in a 64-year-old woman being evaluated for tricuspid valve endocarditis. There is marked low-attenuation thickening of the wall of the RV secondary to fat infiltration up to 6 mm (arrows).

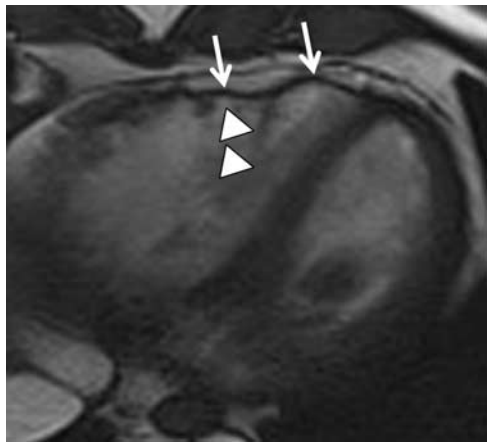

FIGURE 10. ARVC/D pitfall: apicolateral bulging near the moderator band insertion. Axial bright blood cine image from a CMR obtained in a 39-year-old man with a history of cardiac arrest. There was no evidence of ARVC/D on thorough clinical and imaging evaluation. The arrows show bulging of the apical free wall of the RV (arrows) around the moderator band insertion (arrowheads), which is a common finding in normal patients that should not be misinterpreted as a pathologic wall motion abnormality.

tachycardia, the medication most effective is sotalol, and, for nonresponders, the combination of amiodarona with β-blockers is an alternative.[2] The American College of Cardiology, the American Heart Association, and the European Society and Cardiology have recommended ICD implantation for the prevention of SCD in ARVC/D patients with documented sustained ventricular tachycardia or ventricular fibrillation who are receiving adequate pharmacological therapy and have a reasonable expectation of survival.[58] One study reported that the annual cardiac mortality in patients with ARVC/D who were implanted with an ICD was 0.9%.[25] In patients with recurrent arrhythmias despite an optimal medication treatment regimen, catheter ablation may be an option to improve quality of life.[2,18] Heart transplantation is the last treatment option.[18]

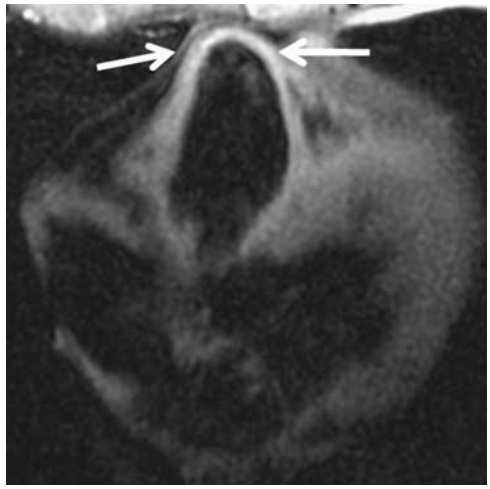

FIGURE 11. ARVC/D pitfall: RV tethering. Axial black-blood images in a 36-year-old man being evaluated for possible ARVC/D. There is triangular outward bulging of the RV outflow tract due to tethering to the posterior wall of the sternum. On cine images, this region demonstrates disordered wall motion but should not be confused for pathologic changes from ARVC/D (Video 3, Supplemental Digital Content 3, http://links.lww.com/JTI/A63).

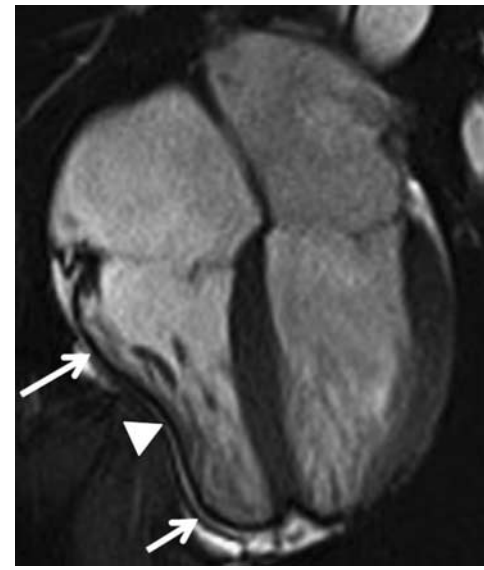

FIGURE 12. ARVC/D pitfall: pectus deformity. Axial bright blood image from a CMR obtained in a 20-year-old man with palpitations and echocardiography concerning for RV enlargement. There was no evidence of ARVC/D on thorough clinical and imaging evaluation. There is a pectus deformity (arrowhead) that results in narrowing of the mid RV anterior wall and relative increase in size of the RV base and apex (arrows). These changes should not be misinterpreted as ARVC/D.

SERIAL MRI EXAMINATIONS AND PROGNOSTIC ROLE OF MRI

An unresolved issue in the management of ARVC/D is the most effective screening strategy for the management of persons who have a relative with ARVC/D and are at risk of developing the disease. Te Riele et al[37] followed at-risk family members of patients with ARCV/D who did not meet ARVC/D diagnostic criteria for an average of 4 years with serial clinical visits, ECG and Holter testing, and CMR examinations. One third of patients progressed over the time interval and eventually met the diagnosis of ARVC/D. However, the progression was almost exclusively electrical in nature; on follow-up CMR examinations, progression of structural disease occurred in only 1 patient, and in this patient the CMR changes were minimal, driven by an increase of RVEDVI by 6 mL and decrease of RVEF from 50% to 45%. These findings lend further support to a growing body of evidence that suggests that, in ARVC/D, electrical changes predate structural defects.[37,38,59] Finding structural abnormalities at CMR, therefore, helps identify patients with a more severe phenotype who are at higher risk for future events. These structural changes on CMR

have important prognostic implications. In a recent study, ARVC/D mutation carriers who had isolated electrical abnormalities but no structural MRI abnormalities had a very low risk for arrhythmia during a mean follow-up period of 7 years.[38] However, patients with both electrical abnormalities and structural disease at MRI were at considerably higher risk, with 11/20 patients in this category experiencing arrhythmic events during the follow-up period, in contrast to 0/48 subjects with no significant CMR abnormalities. These considerations are important given that ICD implantation is not without complication: complications due to lead placement and inappropriate interventions occur at an annual rate of 4.4% and 3.7%, respectively.[25] Therefore, as further data become available, it is likely that CMR abnormalities will play an important role in the management of family members diagnosed with ARVC/D and, in particular, in the decision for prophylactic ICD implantation.

PITFALLS IN CMR FOR SUSPECTED ARVC/D

The evaluation of CMR examinations in patients suspected of ARVC/D can be challenging. As it is a rare diagnosis, many imagers are not familiar with typical CMR findings and potential pitfalls. The 2010 TFC are complex and may be applied incorrectly in centers lacking experience in ARVC/D, often assigning inappropriate weight to non-TFC findings such as RV fat infiltration and RV LGE. In 1 study from a tertiary care center, misdiagnosis of ARVC/D was common with only 27% of 89 patients seeking a second opinion after receiving the diagnosis actually meeting TFC on secondary review.[60] In the majority of cases, CMR examinations were read as abnormal by the referring institution, typically due to qualitative identification of RV fat or wall thinning, none of which was confirmed by expert review. RV fat evaluation is problematic given the thinness of the RV wall and limited CMR spatial resolution. In addition, RV fat infiltration can be seen incidentally in patients without cardiac disease and increases with aging (Figs. 8, 9).[61] In these cases, however, RV wall motion abnormalities should be absent. In addition, the RV wall should be thickened due to the combination of fat and myocytes, unlike ARVC/D, which shows a thinned wall due to myocyte replacement with fat. Other pitfalls in the evaluation of ARVC/D have been described.[21,62] RV free wall contraction can result in areas of subjective bulging near the moderator band insertion, even in normal patients, which can mimic a wall motion abnormality, known as the apicolateral bulge[31] (Fig. 10). In our practice, we have found that tethering of the anterior wall of the RV to the back of the sternum, frequently seen in the region of the RV outflow tract, can also mimic a wall motion abnormality (Fig. 11; Video 3, Supplemental Digital Content 3, which demonstrates axial cine imaging of RV anterior wall tethering).[21] One of the most common pitfalls that can be misinterpreted as RV dilation or wall motion abnormality is cardiac displacement, usually from a pectus disorder, which results in relative increase in the size of the RV apex and narrowing of the base or mid RV that can simulate a regional wall motion abnormality (Fig. 12).[62] In other patients, RV size can be increased in the setting of athletic conditioning[63] or intracardiac shunts,[62] mimicking the RV chamber dilation that can occur with ARVC/D. However, in these cases, wall motion abnormalities should be absent. Strict adherence to the 2010 TFC, which requires a combination of regional wall motion abnormality and global quantitative reduction in systolic function or increase in end-diastolic volume is therefore critical to avoid these pitfalls. For most of these mimics, either a subjective wall motion abnormality or chamber dilation may be seen, although typically not both, as would be required to meet TFC.

SUMMARY

CMR plays a critical role in the diagnosis and management of patients with suspected ARVC/D. Both qualitative regional wall motion abnormalities and quantitative global alterations in RVEF or EDV are necessary to fulfill current CMR diagnostic criteria. Although fat and fibrosis are often seen in ARVC/D, particularly in advanced cases, it is important for imagers to remember that these are not part of the 2010 TFC. Left ventricular abnormalities, particularly fat and fibrosis, are common in ARVC/D, seemed to be linked to genotype, and, in a subset of patients, may be the dominant finding. Familiarity with potential pitfalls in the evaluation of RV size and wall motion is important to avoid misdiagnosis.

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