Circulation: Cardiovascular Imaging

ADVANCES IN CARDIOVASCULAR IMAGING

Multimodality Imaging in Arrhythmogenic Right Ventricular Cardiomyopathy

Nitin Malik, MD; Monica Mukherjee, MD, MPH; Katherine C. Wu, MD; Stefan L. Zimmerman, MD; Junzhen Zhan, MD; Hugh Calkins, MD; Cynthia A. James, PhD; Nisha A. Gilotra, MD; Farooq H. Sheikh, MD; Harikrishna Tandri, MD; Shelby Kutty, MD, PhD; Allison G. Hays, MD

ABSTRACT: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare, heritable myocardial disease associated with the development of ventricular arrhythmias, heart failure, and sudden cardiac death in early adulthood. Multimodality imaging is a central component in the diagnosis and evaluation of ARVC. Diagnostic criteria established by an international task force in 2010 include noninvasive parameters from echocardiography and cardiac magnetic resonance imaging. These criteria identify right ventricular structural abnormalities, chamber and outflow tract dilation, and reduced right ventricular function as features of ARVC. Echocardiography is a widely available and cost-effective technique, and it is often selected for initial evaluation. Beyond fulfillment of diagnostic criteria, features such as abnormal tricuspid annular plane excursion, increased right ventricular basal diameter, and abnormal strain patterns have been described. 3-dimensional echocardiography may also expand opportunities for structural and functional assessment of ARVC. Cardiac magnetic resonance has the ability to assess morphological and functional cardiac features of ARVC and is also a core modality in evaluation, however, tissue characterization of the right ventricle is limited by spatial resolution and low specificity for detection of pathological changes. Nonetheless, the ability of cardiac magnetic resonance to identify left ventricular involvement, offer high negative predictive value, and provide a reproducible structural evaluation of the right ventricle enhance the ability and scope of the modality. In this review, the prognostic significance of multimodality imaging is outlined, including the supplemental value of multidetector computed tomography and nuclear imaging. Strengths and weaknesses of imaging techniques, as well as future direction of multimodality assessment, are also described.

Key Words: death, sudden, cardiac ■ echocardiography ■ heart failure ■ magnetic resonance imaging ■ prognosis

Arrhythmogenic right ventricular cardiomyopathy (ARVC), the most well-recognized heritable arrhythmogenic cardiomyopathy (ACM), is a rare genetic disease characterized by myocyte loss and fibrofatty replacement, primarily of the right ventricle. It is associated with ventricular arrhythmias and an increased risk of sudden cardiac death and heart failure, and it has been recognized as an underlying cause of exercise-induced sudden cardiac death in young patients.[1] A broader understanding of ARVC has led to the development of diagnostic criteria,[2] identification of associated genotypes,[3] and publication of consensus statements to guide management.[4]

The earliest case series to describe ARVC identified increased right ventricular diastolic dimension in patients with 2-dimensional echocardiograms.[5] Since then, there has been an evolving role for multimodality imaging in diagnosis, family screening, and prognostication. Given the morbidity of the illness and risk of sudden death, as well as lack of clinical symptoms at a young age, identification and monitoring for disease phenotype by noninvasive methods are increasingly relevant for the management of ARVC. The following sections provide a clinical overview of ARVC and the role of multimodality imaging in the evaluation and management of patients with ARVC.

Correspondence to: Allison G. Hays, MD, Johns Hopkins University, 600 N. Wolfe St, Halstead 565, Baltimore, MD 21287. Email ahays2@jhmi.edu
This manuscript was sent to Linda D. Gillam, MD, MPH, Senior Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at: https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.121.013725.
For Sources of Funding and Disclosures, see page 118.

Circulation: Cardiovascular Imaging is available at www.ahajournals.org/journal/circimaging

Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
CMR	cardiac magnetic resonance imaging
LGE	late gadolinium enhancement
LV	left ventricle
MDCT	multidetector computed tomography
RV-FAC	right ventricular fractional area change
RVOT	right ventricular outflow tract
TAPSE	tricuspid annular plane systolic excursion

BACKGROUND

The prevalence of ARVC is reported at ≈1 in 5000.[1,6] Patients tend to present with symptoms in the second to fifth decade of life.[1,6] In general, the preclinical phase of the disease exhibits minimal or no structural abnormalities. However, the first manifestation of the disease may be sudden cardiac death,[6] noted in 11% of patients diagnosed with ARVC in one study,[7] and a family history of the disease is present in over 30% to 50% of cases.[6] The most common presenting symptoms include palpitations, followed by syncope, atypical chest pain, dyspnea, and heart failure.[8]

The disease is believed to result from genetically mediated disruption of desmosomes, which are critical for maintaining normal intercellular junctions as well as intracellular and intercellular signal transduction.[1] However, a genetic cause is unknown in one-third of the patients.[9] Myocyte detachment and uncoupling because of mechanical stress is thought to promote the pathological changes seen in ARVC, particularly because intense aerobic exercise is associated with higher risk of disease progression.[1,10,11]

Histopathologic samples from biopsy and autopsy studies suggest that desmosomal disruption promotes myocyte death, fibrofatty replacement of the myocardium, and scattered foci of inflammation.[1,10] Macroscopically, wall thinning and aneurysmal dilation are seen in the right ventricle, traditionally in the region enclosed by the subtricuspid region of the right ventricle, right ventricular outflow tract at the infundibulum, and right ventricular apex, known as the triangle of dysplasia.[1] However, it has recently been recognized that the RV apex is only impacted in the most severe forms of the disease and that the third arm of the triangle is the posterolateral left ventricle (LV).[12,13]

Diagnostic criteria were initially proposed by an international task force in 1994 using a scoring system with major and minor criteria.[14] These criteria were revised in 2010 (Table 1) to improve sensitivity by including quantitative imaging measurements and genotype.[1,2] In summary, structural, pathological, electrocardiographic, and genetic/family history criteria are used to establish a definite, borderline, or possible diagnosis of ARVC according to fulfillment of major and/or minor criteria. Challenges in diagnosis include poor specificity of ECG findings, multiple possible causes for right ventricular arrhythmias, difficulty in assessing the right ventricle using imaging, and at times inconclusiveness of the pathogenicity of genetic variants detected.[1]

ARVC has a mortality estimated at 0.08% to 3.6% per year, and the clinical course is predominately dictated by ventricular arrhythmias and development of heart failure in advanced disease.[15] The prevalence of left ventricular or biventricular dysfunction is variably reported, which is thought to be because of discrepancies in selection criteria for analyses, variable sensitivity of imaging used, differences in the genetic basis of ARVC, and referral bias.[1,15] Broadly, ARVC is typically managed first by assessment of sudden death risk and implantable cardioverter defibrillator implantation in high-risk patients.[16,17] Other components of therapy include avoidance of high-intensity physical activity, beta blocker therapy, treatment of symptomatic ventricular arrhythmias with antiarrhythmic medications and/or catheter ablation, and heart failure therapies as appropriate. Cascade screening of family members is vital.[4,15]

While ARVC has been traditionally characterized by dysfunction of the RV, pathological involvement of the LV is well-described.[18–21] LV-dominant and biventricular pathological changes have also been demonstrated by cardiac magnetic resonance imaging (CMR).[12,22] Because of frequent involvement of the left ventricle, several experts have suggested retitling the disease entity as ACM instead of ARVC to more broadly describe the spectrum of phenotypic variants.[18–21] Recognizing a lack of diagnostic criteria for left-dominant disease in the 2010 Task Force Criteria, new diagnostic criteria to redefine right-dominant, biventricular, and left-dominant disease phenotypes of ACM have recently been proposed ("the Padua Criteria").[20,23]

The Heart Rhythm Society (HRS), conversely, has defined ACM as a term for arrhythmogenic disorders of the myocardium not secondary to ischemic, hypertensive, or valvular heart disease, which includes ARVC as well as other illnesses such as cardiac amyloidosis, sarcoidosis, Chagas disease, and LV noncompaction.[4] Arrhythmogenic left ventricular cardiomyopathy is also included, although the authors acknowledge a lack of validated diagnostic criteria for this disease entity.[4] The following sections refer to ARVC and ACM in accordance with HRS definitions, which is endorsed by multiple cardiovascular societies; however, our authors recognize the ongoing debate regarding the diagnostic characterization of ARVC.

Table 1. 2010 Modified Task Force Criteria for Diagnosis of ARVC

Major	Minor
I. Global or regional dysfunction and structural alterations	
By 2D echocardiogram	By 2D echocardiogram
Regional RV akinesia, dyskinesia, or aneurysm *and* 1 of the following (end-diastole):	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end-diastole):
PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m²)	29 mm ≤PLAX RVOT <32 mm (16 ≤PLAX/BSA <19 mm/m²)
PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m²)	32 ≤PSAX RVOT <36 mm (18 ≤PSAX/BSA <21 mm/m²)
Or RV-FAC ≤33%	Or 33% <RV-FAC ≤40%
By MRI	By MRI
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
RV end-diastolic volume/BSA ≥110 mL/m² (male) or ≥100 mL/m² (female)	100 mL/m² ≤RV end-diastolic volume/BSA <110 mL/m² (male) or 90 mL/m² ≤RV end-diastolic volume/BSA <100 mL/m² (female)
Or RV ejection fraction ≤40%	Or 40% <RV ejection fraction ≤45%
By RV angiography	
Regional RV akinesia, dyskinesia, or aneurysm	
II. Tissue characterization of RV wall	
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 y of age (in the absence of complete RBBB)	Inverted T waves in leads V_1 and V_2 in individuals >14 y of age (in the absence of complete RBBB) or in V_4, V_5, or V_6
	Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 y of age in the presence of complete RBBB
IV. Depolarization/conduction abnormalities	
Epsilon wave in the right precordial leads (V_1 to V_3)	Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration ≥110 ms on the standard ECG:
	Filtered QRS duration ≥114 ms
	Duration of terminal QRS <40 µV (low-amplitude signal duration) ≥38 ms
	Root mean square voltage of terminal 40 ms ≤20 µV
	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S-wave to the end of the QRS, including R', in V_1, V_2, or V_3, in the absence of complete RBBB
V. Ventricular arrhythmias	
Nonsustained or sustained VT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	Nonsustained or sustained RVOT VT of LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or with unknown axis
	>500 ventricular extrasystoles per 24 h (Holter)
VI. Family history	
ARVC confirmed in a first-degree relative who meets current TFC	History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current TFC
ARVC confirmed pathologically at autopsy or surgery in a first-degree relative	Premature sudden death (<35 y of age) due to suspected ARVC in a first-degree relative
Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient	ARVC confirmed pathologically or by current TFC in second-degree relative
Diagnosis	
Definite: 2 major OR 1 major and 2 minor criteria OR 4 minor from different categories.	
Borderline: 1 major and 1 minor OR 3 minor criteria from different categories.	
Possible: 1 major OR 2 minor criteria from different categories.	

2D indicates 2-dimensional; ARVC, arrhythmogenic right-ventricular cardiomyopathy; aVF, augmented Vector Foot; aVL, augmented Vector Left; BSA, body surface area; ECG, electrocardiography; LBBB, left bundle branch block; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RBBB, right bundle branch block; RV, right ventricular; RV-FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; SAECG, signal-averaged electrocardiography; TFC, Task Force Criteria; and VT, ventricular tachycardia.

Adapted from Marcus et al[2] with permission. Copyright ©2010, Wolters Kluwer Health, Inc.

ECHOCARDIOGRAPHY

As a noninvasive, widely available, and inexpensive imaging modality, echocardiography is often selected in initial evaluation of ARVC, although CMR imaging is also usually pursued if resources and expertise are available. The modality also serves an important role for serial assessment of RV and LV size and function and recommended by the an international expert report[13] especially in patients in whom CMR imaging may be obscured because of the presence of an implantable cardioverter defibrillator. Qualitative parameters outlined in the 2010 Task Force Criteria for diagnosis of ARVC include identification of wall motion abnormalities such as right ventricular akinesia, dyskinesia, or aneurysm, while quantitative parameters rely on RV chamber dimensions such as right ventricular outflow tract (RVOT) diameter from the parasternal long axis and parasternal short axis (PSAX) views, as well as measurement of right ventricular fractional area change (RV-FAC).[2] Criteria are summarized in Table 1, noting that one of the described wall motion abnormalities is necessary to satisfy major or minor criteria by echocardiography. While specific, these criteria lack sensitivity,[24] and several other echocardiographic features and findings have been identified to further support diagnosis or predict clinical progression.

More detailed structural evaluation of ARVC beyond Task Force Criteria includes identification of other metrics of regional and global right heart dilation and dysfunction. Several studies have identified abnormal right-sided chamber sizes in patients with ARVC, including right atrial and right ventricular enlargement, in addition to RVOT enlargement from the parasternal long and short axis views, compared with those of controls.[25–28] Morphological abnormalities such as hyper-reflective moderator band, trabecular derangement, and sacculations have also been described.[25] Contrast-enhanced studies can improve delineation of the endocardium and evaluation of structural abnormalities.[29]

Regarding valvular assessment, tricuspid regurgitation is associated with poor prognosis.[30,31] There are limited data regarding surgical correction of functional tricuspid regurgitation in patients with ARVC; however, a case series of 3 patients suggested it could have a therapeutic role in selected patients.[32]

In addition to decreased RV-FAC, as identified by the 2010 Task Force Criteria,[2] other indices of right ventricular dysfunction have been reported. Compared with controls, tricuspid annular motion in the lateral, septal, and posterior locations, as well as tissue Doppler velocity patterns in diastole in all locations, were decreased in patients with ARVC.[27] In addition, patients with ARVC had a decreased lateral systolic annular velocity.[27] Abnormal tricuspid annular plane systolic excursion (TAPSE) <17 millimeters (mm) has been associated with major adverse cardiovascular events in an observational study, although reduced RV-FAC was determined to be the strongest echocardiographic predictor of adverse outcomes.[33] TAPSE, RV-FAC, and peak systolic tricuspid annular velocity (S') have also been found to be predictive of reduced right ventricular ejection fraction of <45% by CMR[34,35]; however, measurement of S' was found to be more reproducible and feasible in comparison to RV-FAC.[35] In addition, a meta-analysis found TAPSE and S' to be significantly lower in patients with ARVC compared with healthy controls.[36] These findings suggest a potential diagnostic role for TAPSE and S', although TAPSE and S' are not included in the 2010 Task Force Criteria and further validation of these markers is needed. A summary of select echocardiographic features that may be useful in diagnostic evaluation or for prediction of adverse events is given in Table 2.

Echocardiography is also useful for the detection of pathological involvement of the left ventricle. On echocardiography, the presence of left ventricular dysfunction, as defined by left ventricular ejection fraction <50%, added predictive value for death or heart transplantation above that of baseline RV dysfunction.[31] However, LV systolic dysfunction is not always appreciated by conventional echocardiography despite abnormalities seen on CMR, which could lead to undetected LV involvement.[38] Left ventricular deformation imaging was shown to improve identification of LV involvement in ARVC, using CMR as the reference standard.[38] Identification of LV involvement was also shown to have prognostic implications and may precede RV involvement.[38,49]

A limitation of RV evaluation by transthoracic echocardiography is the complexity of the RV geometry and a narrow acoustic window.[19] Emerging nontraditional techniques for evaluation of the RV in ARVC may play a role and include 3-dimensional (3D) echocardiography and RV strain. Compared with 2-dimensional (2D) echocardiography, 3D echocardiography may provide more accurate volume assessment of the RV by comparison to CMR, which is considered the gold standard.[50,51] However, standardized cutoff values and risk stratification from 3D echocardiography measures have yet to be established through prospective studies.[4,19] Transesophageal echocardiography, another nontraditional technique, while only studied to a limited extent in ARVC, may allow enhanced detection of right ventricular structural abnormalities compared with transthoracic echocardiography.[52]

Right ventricular strain, which can be assessed on both echocardiography and CMR, is the measurement of myocardial deformation as a percentage change in dimension, whereas strain rate is its time derivative.[53] Multiple studies have identified abnormal right ventricular strain and strain rate, particularly of the RV free wall and subtricuspid region, in ARVC.[26,36,54–57] Abnormal right ventricular strain and strain rate have also been associated with structural progression of ARVC.[39] Furthermore,

Table 2. Diagnostic and Prognostic Performance of Select Echocardiographic, CMR, and MDCT Imaging Markers in ARVC

Markers for diagnosis			Markers for prognosis		
Parameter	**End point**	**Citation**	**Parameter**	**End point**	**Citation**
Echocardiography					
RV-FAC <48%	Se 100%, Sp 73% for RVEF <45% by CMR	Wang et al[35]	RV-FAC ≤33%	MACE, median 5.3 y (IQR, 1.8–9.8): HR, 3.12 (95% CI, 1.42–6.87; *P*=0.005)	Saguner et al[33]
TAPSE <16.8 mm	Se 80%, Sp 87% for RVEF <45% by CMR	Wang et al[35]	TAPSE <17 mm	MACE, median 5.3 y (IQR, 1.8–9.8): HR, 2.15 (95% CI, 1.10–4.17; *P*=0.02)	Saguner et al[33]
S' <8.8 cm/s	Se 80%, Sp 79% for RVEF <45% by CMR	Wang et al[35]	RVEDA ≥28 cm^2	MACE, median 5.3 y (IQR, 1.8–9.8): HR, 2.96 (95% CI, 1.48–5.91; *P*=0.002)	Saguner et al[33]
RVGLS >-20.4%	Se 52.6%, Sp 100% for definite ARVC by 2010 TFC in adolescents	Pieles et al[37]	LVPSS of posterolateral wall >−12.5%	MACE, mean 5.9 y±2.3: HR, 4.9 (95% CI, 1.7–14.2; *P*=0.01)	Mast et al[38]
RVFWS >-17%	Se 96%, Sp 93% for RVEF <45% by CMR	Focardi et al[34]	RVFWS >−20%	Structural progression of RVOT-PSAX at median 3.6 y (IQR, 1.3–6.8): OR, 18.4 (95% CI, 2.7–125.8; *P*=0.003)	Malik et al[39]
			RV-FAC <33% and LVEF <50%	MACE, mean 10.7 y±7.7: HR, 6.3 (95% CI, 2.17–17.45; *P*<0.001)	Pinamonti et al[31]
			TR jet area >4 cm^2	MACE, mean 10.7 y±7.7: HR, 7.60 (95% CI, 2.60–22.0; *P*<0.001)	Pinamonti et al[31]
CMR					
Any RV wall motion abnormality (excluding hypokinesia) plus any pre- or post-contrast signal abnormality	Se 96%, Sp 100% for definite ARVC by 2010 TFC	Aquaro et al[40]	Normal CMR	MACE, median 4.3 y (IQR, 2.8–6.1): NPV of 96.9%	Aquaro et al[41]
				MACE, median 5 y (IQR, 2–8): NPV of 100%	Aquaro et al[42]
				MACE, mean 4.3 y±1.5: NPV of 98.8%	Deac et al[43]
RV or LV LGE	Concordance of 92% with endomyocardial biopsy for detection of myocardial fibrosis in patients with possible, borderline, or definite ARVC by 2010 TFC	Perazzolo Marra et al[44]	RVEF, per % decrease	Ventricular arrhythmia, median 4.83 y (IQR, 2.44–9.33), HR, 1.03 (95% CI, 1.01–1.04; *P*=0.002)	Cadrin-Tourigny et al[16]
Annular subepicardial LV-LGE pattern	Association with a nondesmosomal mutation vs desmosomal mutation vs negative genotype (76.5% vs 23.5% vs 0%, *P* = 0.02)	Segura-Rodriguez et al[45]	LV Involvement by CMR	MACE, median 5 y (IQR, 2–8): HR, 4.2 (95% CI, 2.1–8.4; *P*=0.0001)	Aquaro et al[42]
			LV-GLS >−12.65%	MACE, mean 4.10 y ± 1.77: HR, 3.578 (95% CI, 1.139–11.245; *P*=0.029)	Shen et al[46]
MDCT					
CT scoring system	Se 87%, Sp 94.4%, PPV 87% for definite ARVC by 2010 TFC	Nakajima et al[47]			
Fat extent >8.5% of RV free wall	Se 94%, Sp 92% for definite ARVC by 2010 TFC	Cochet et al[48]			

Citation	Definition of marker/outcome
Saguner et al[33]	MACE: cardiac death, heart transplantation, survived sudden cardiac death, VF, sustained VT, and arrhythmogenic syncope
Mast et al[38]	MACE: spontaneous sustained monomorphic ventricular tachycardia, sudden cardiac death, aborted sudden cardiac death, appropriate ICD intervention for a ventricular arrhythmia, and heart transplantation
Pinamonti et al[31]	MACE: death and heart transplantation
Aquaro et al[41]	MACE: sudden cardiac death, appropriate ICD shock, and resuscitated cardiac arrest
Aquaro et al[42]	MACE: sudden cardiac death, appropriate ICD intervention, and aborted cardiac arrest LV involvement: defined as at least 1 of the following–LVEF <50%, LV-WMA, LV fat infiltration, nonischemic pattern LV-LGE
Deac et al[43]	MACE: cardiac death, sustained VT, VF, and appropriate ICD discharge
Shen et al[46]	MACE: sustained VT or VF, cardiac death, resuscitated cardiac arrest, heart transplantation, and appropriate ICD shock
Nakajima et al[47]	CT scoring system: fulfillment of major and/or minor criteria based on fatty infiltration of the RV and interventricular septum, bulging of the RV free wall, and dilatation of the RV

A summary of select imaging markers and relationship to prognostic and diagnostic end points are shown for echocardiography, CMR, and MDCT. These parameters are not explicitly included in the 2010 Task Force Criteria, other than RV-FAC and RVEF. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; CT, computed tomography; GLS, global longitudinal strain; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LVPSS, left ventricular peak systolic strain; MACE, major adverse cardiovascular events; MDCT, multidetector computed tomography; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RV, right ventricle; RV-FAC, right ventricular fractional area change; RVEDA, right ventricular end diastolic area; RVEF, right ventricular ejection fraction; RVFWS, peak RV free wall systolic strain; RVOT-PSAX, right ventricular outflow tract diameter on parasternal short axis view; Se, sensitivity; Sp, specificity; TAPSE, tricuspid annular plane systolic excursion; TFC, Task Force Criteria; TR, tricuspid regurgitation; VF, ventricular fibrillation; VT, ventricular tachycardia; and WMA, wall motion abnormalities.

mechanical dispersion, which is defined as the SD of the time-to-peak strain in a multisegmented RV model,[19] was more pronounced in early phase (nondefinite) ARVC patients[58] compared with those of patients with ventricular tachycardia originating from the RVOT, and was also found to be a marker of prior arrhythmia events in early phase ARVC patients.[59] Combining information from RV mechanical dispersion with RV deformation patterns has shown incremental improvement in identifying patients with a history of life-threatening ventricular arrhythmia.[60] Echocardiographic deformation imaging has also demonstrated a role in computational modeling of cardiac tissue properties in patients with ARVC.[61]

The presence of abnormal RV strain by echocardiography as an early marker of disease has been suggested in the adolescent population.[37] In one study of adolescent patients investigated for ARVC, abnormal RV strain was associated with likelihood of ARVC diagnosis despite the fact that the majority of patients in the cohort did not meet echocardiographic Task Force Criteria.[37] An example of assessment for RV strain is given in Figure 1C.

Stress imaging may be useful for assessing prognosis, given the link between exercise activity and disease progression,[1,11] although the additive value is currently uncertain. One study compared 19 patients with ARVC with age- and sex-matched subjects and endurance athletes using strain echocardiography both at rest and after stress and found that 3-dimensional RV ejection fraction and strain were lower in patients with ARVC than in control subjects.[62] Furthermore, RV strain after exercise did not change significantly in patients with ARVC, whereas RV strain increased in magnitude in the comparison groups.[62]

In recognition of the value for a more comprehensive echocardiographic assessment of ARVC, an expert consensus from the European Heart Society recently suggested routine evaluation of RV basal diameter and TAPSE (conventional echocardiographic parameters) as well as RV and LV strain and mechanical dispersion, in addition to the listed features in the 2010 Task Force Criteria[19] for patients with suspected or established ARVC. Furthermore, they recommended the addition of 3D echocardiography for qualitative structural assessment and quantitation of ejection fraction when available, noting that the value of 3D echocardiography and cutoff thresholds need to be established.[19] The HRS, however, suggests that further validation is needed before recommending parameters beyond the 2010 Task Force Criteria for routine use.[4]

Regarding long-term monitoring, there is considerable heterogeneity in the structural progression of ARVC[63] and presence of progression has been shown to predict clinical outcomes,[64] suggesting the importance of serial monitoring in patients with ARVC. A 2020 international expert report recommends an echocardiogram on initial evaluation as well as follow-up imaging every 1 to 3 years according to age, genetic status, and clinical features.[13] Specific recommendations by the European Association of Cardiovascular Imaging are further outlined in Haugaa et al.[19]

CARDIAC MAGNETIC RESONANCE IMAGING

CMR is the preferred initial test for evaluation of patients with suspected ARVC. It is also of value in serial follow up of ARVC patients or at-risk patients such as relatives of ARVC probands. The modality has the ability to assess a variety of structural and functional cardiac features, including biventricular chamber morphology, chamber volumes, wall thickness, myocardial mass, regional motion, fibrosis, adipose content, interstitial and cellular edema, and flow, and is not subject to acoustic window or body size limitations.[24] CMR thus is uniquely capable of comprehensive evaluation of the known structural manifestations of ARVC, which include RV outflow tract enlargement, RV ventricular dilation, fibrofatty replacement of the myocardium, and global or regional systolic dysfunction.[65] According to the 2010 Task Force Criteria, qualitative CMR identification of RV akinesia, dyskinesia,

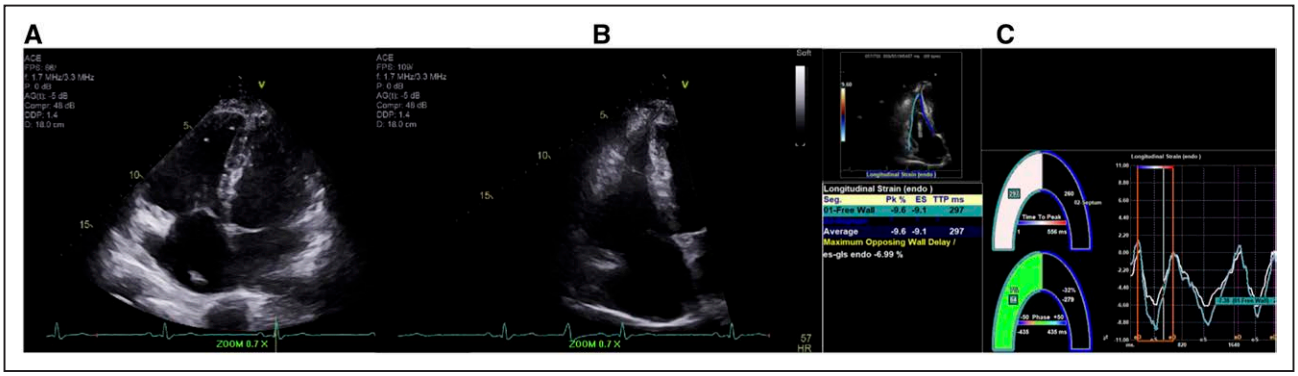

Figure 1. Echocardiography and right ventricle (RV) strain in arrhythmogenic right ventricular cardiomyopathy (ARVC). Representative echocardiographic images in a patient with ARVC. A dilated RV is seen on the apical 4-chamber view in (**A**) end-diastole and (**B**) end-systole. **C**, RV free wall strain is markedly reduced in magnitude at −9.6% (normal is <−20%).

or dyssynchronous RV contraction are required to satisfy either major or minor diagnostic criteria.[2] Additionally, abnormal RV end-diastolic volume indexed to body surface area or RV ejection fraction by CMR are required quantitative parameters to assign CMR criteria.[2] Features are summarized in Table 1.

Of note, the reference ranges reported in the 2010 Task Force Criteria are derived from controls in the multiethnic study of atherosclerosis (MESA), which specified ventricular volumes in patients aged 45 to 85 years of age using an older gradient-echo cine MRI technique, while steady-state free precession (SSFP) sequences are now more contemporarily used for chamber volume assessment.[2,66] As such, some experts feel the 2010 Task Force Criteria may need to be updated to include SSFP normal ranges.[67] Others note that screening for ARVC often occurs during teenage years, and normal RV dilatation of the athletic heart may reduce the specificity of current RV volume thresholds.[66,68] Additionally, the requirement of regional wall motion abnormalities with RV dilation or systolic dysfunction to satisfy 2010 Task Force Criteria has been found to have low sensitivity, and some experts recommend using isolated RV wall motion abnormalities on CMR as a freestanding criterion that could be combined with presence of underlying fatty or fibrotic infiltration.[13,66] Furthermore, high inter-observer variability in assessment of RV regional and global contractile function has been observed.[65,69]

In addition to RV chamber dilation and reduced RV ejection fraction, atrial abnormalities are increasingly recognized. When compared with controls, enlarged left and right atria and decreased biatrial function using atrial ejection fraction and strain rate have been noted.[28,70] Furthermore, parameters of atrial chamber enlargement and dysfunction are predictive of incident atrial arrhythmias, suggesting atrial involvement of ARVC.[28]

With regards to myocardial tissue characterization, early CMR evaluations of ARVC described fatty infiltration of the RV using T1 spin-echo sequences.[71] However, intramyocardial fat has also been seen in older, obese patients without ARVC, and this finding is thus nonspecific.[65] In addition, despite the accepted pathological mechanism of fibrofatty infiltration predisposing for arrhythmic events and ventricular dysfunction, fatty infiltration has been seen in a high proportion of autopsy cases in non-ARVC patients dying of noncardiac causes.[65] Furthermore, tissue characterization of the RV is difficult because of the presence of a thin free wall, which reduces spatial resolution.[24]

Late gadolinium enhancement (LGE) imaging is an established marker of fibrosis in contrast-enhanced imaging[24] and is well-described in ARVC in both the left and right ventricles,[24,65] with RV involvement in as many as 88% of patients[72] and LV involvement in as many as 61% of patients.[73] In a study of 36 patients with possible, borderline, and definite ARVC who underwent both contrast-enhanced CMR and endomyocardial biopsy during the same hospital admission, CMR demonstrated a 92% concordance with endomyocardial biopsy for detection of myocardial fibrosis.[44] It should be noted that a majority of patients in this study had either isolated LV LGE or biventricular LGE (8 patients and 18 patients, respectively), thus, LV fibrosis could have been collected on biopsy specimens particularly if obtained from the apical septal wall. A relationship between genotype and patterning on LGE imaging has also been suggested, with one study identifying an association between desmin gene mutation and circumferential subepicardial LGE of the LV.[45] The addition of fibrofatty infiltration or LGE to regional RV wall motion abnormalities may also provide incremental improvement in identifying patients with ARVC, as one study demonstrated high diagnostic accuracy within a cohort of ARVC patients and matched healthy controls when these markers were combined.[40] However, LGE itself is a nonspecific finding and may not distinguish between ARVC and ischemic or other nonischemic right ventricular cardiomyopathies.[24] Moreover, some experts consider LGE to be a feature of late stage ARVC, as concomitant findings of advanced disease, such as RV dilation or dysfunction, are often present.[65] It is thus important to emphasize that although both fatty infiltration and LGE can be detected by CMR in ARVC, they have been excluded from the Task Force Criteria due to poor reproducibility and a lack of both sensitivity and specificity. Characteristic findings of ARVC by CMR are depicted in Figure 2A through 2C (and Videos S1 and S2).

While the conventional description of pathological involvement of the RV inflow tract, outflow tract, and apex (Triangle of Dysplasia) was initially described, the presence of LGE involving the LV (Figure 3), most prominently of the inferolateral or apicolateral segments (the so-called displaced triangle of dysplasia),[12,22] has prompted expert opinion to redefine the classically affected region of ARVC.[12,65] Additionally, the presence of LV involvement has been observed independently of the stage of RV disease, refuting the traditional notion that LV involvement appears in late-stage disease.[74]

Outcome prediction in ARVC using CMR is an evolving area of investigation. Multiple studies have identified a high negative predictive value for cardiac events with a normal cardiac MRI, nearing 100% in patients with suspected or definitive ARVC.[41–43] A recent prediction model identified reduced RV ejection fraction as a risk factor for sustained ventricular arrhythmias in a population of patients with ARVC without sustained arrhythmias at baseline,[16] although a follow-up study suggested risk underestimation for patients with LV involvement (defined as left ventricular ejection fraction <50%, wall motion abnormalities, fat infiltration, and/or LGE with a nonischemic pattern).[42] Furthermore, one meta-analysis

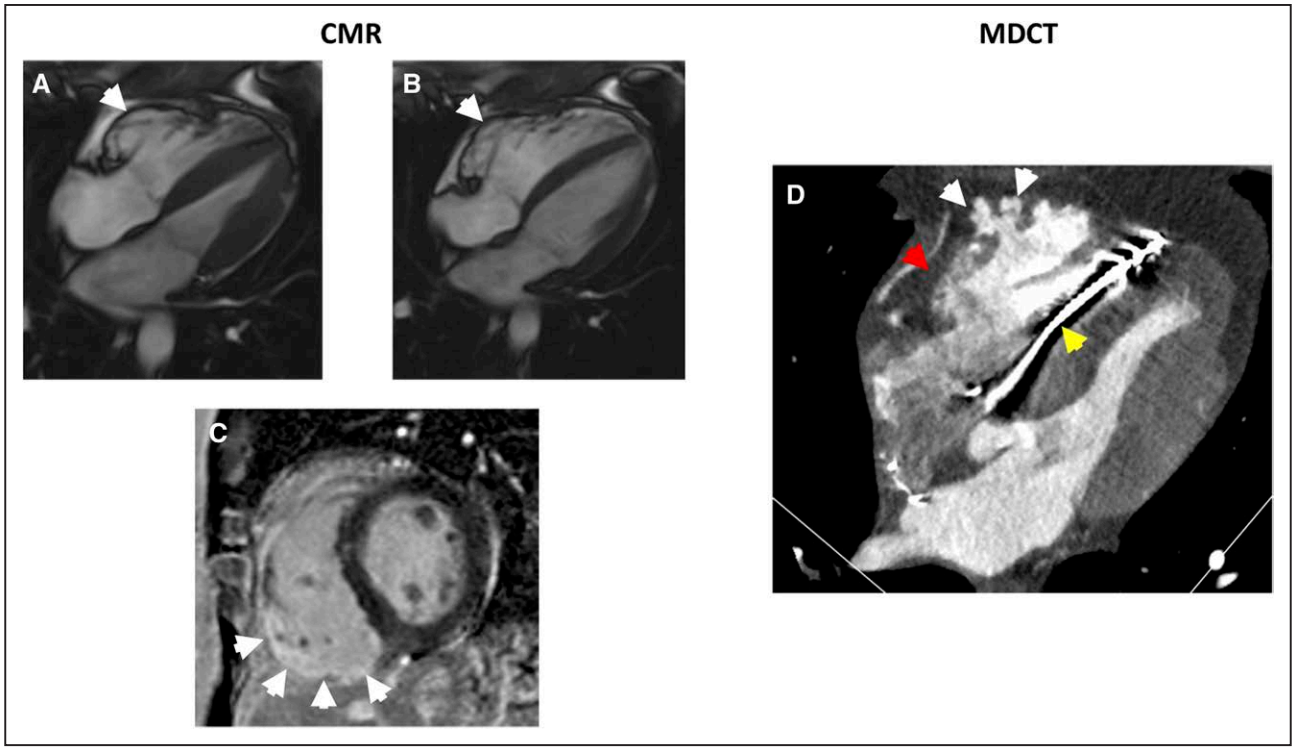

Figure 2. Features of arrhythmogenic right ventricular cardiomyopathy (ARVC) on cardiac magnetic resonance (CMR) and multidetector computed tomography (MDCT).
Cine 4-chamber images in systole (**A**) and diastole (**B**) in a 47-y-old female with ARVC, showing a dyskinetic segment of the basal right ventricular free wall (arrow). **C**, Short-axis late gadolinium enhancement image in the same patient showing right ventricle (RV) inferior and anterior wall late enhancement (arrows). **D**, Fifty-four-year-old male with ARVC who underwent preablation MDCT. Imaging shows multiple microaneurysms (white arrows) of the RV free wall and fatty infiltration (red arrow). An implanted cardioverter defibrillator lead is also present (yellow arrow).

found the presence of LGE on CMR to be a predictor for major adverse cardiovascular events with a relative risk of 2.48 in comparison to LGE-negative ARVC patients.[75] A summary of selected CMR parameters for diagnostic evaluation and outcome prediction is shown in Table 2.

A recent international expert consensus report does not identify a role for serial CMR studies in ARVC patients, primarily due to cost and time-consuming nature of the exam.[13] Furthermore, many ARVC patients have ICDs implanted, which may compromise CMR image quality. However, repeat CMR could be considered in patients with definitive ARVC who develop worsening clinical symptoms or new ECG abnormalities, arrhythmias, or echocardiographic findings.[13] Additionally, patients with ARVC and clinical heart failure were more likely to have features of RV dysfunction by echocardiogram and CMR compared with ARVC patients without clinical heart failure,[76] suggesting value for serial functional assessment of the RV for prediction of heart failure symptom development. Fast CMR sequences can also be utilized to lower acquisition times, particularly in the context of serial scans; however, such protocols require compressed sensing algorithms for acceleration of cine acquisitions, which is feasible but requires the appropriate equipment and is not universally available.

In the future, CMR tissue deformation and strain analysis (Figure 4) may provide diagnostic and prognostic information. Strain imaging has demonstrated promise in differentiating ARVC and borderline ARVC from healthy volunteers as well as other disease entities, such as right ventricular outflow-tract ventricular tachycardia (RVOT-ventricular tachycardia) and Brugada syndrome, through the presence of impaired LV and RV strain.[46,77–80] In addition, CMR has demonstrated the ability to distinguish ARVC from athlete's heart using strain and strain rate of the mid-ventricular RV free wall.[81] Such assessments may allow objective identification of RV dysfunction, which are otherwise based on qualitative assessment in the 2010 Task Force Criteria.[2] Novel techniques to perform water and fat separation[82] and high resolution 3D LGE[83,84] may allow incremental improvement in identification of ARVC, however, further development and validation of these techniques are needed.[24] Moreover, development of enhanced pulse sequences for T1 mapping may allow for improved quantification of RV myocardial fibrosis, which is largely restricted to the LV currently due to limited spatial resolution.[65]

RECOMMENDED ASSESSMENT BY CMR

Assessment of right ventricular regional wall motion is challenging in ARVC and sometimes subject to inter-reader variability. We previously published a

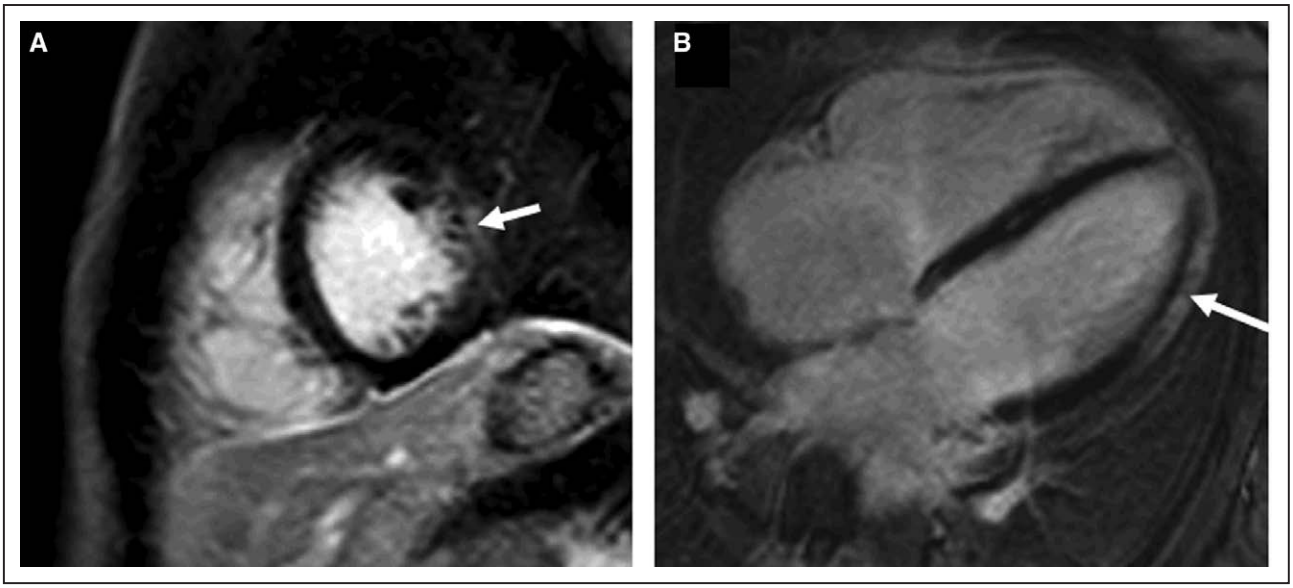

Figure 3. Example of left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy (ARVC). Cardiac magnetic resonance example in a 19-year-old runner with a history of ventricular tachycardia after a race, and a subsequent diagnosis of ARVC and variant of uncertain significance in the PKP2 gene. Late gadolinium enhancement (LGE) images show enhancement in the apicolateral left ventricular wall (**A**, short axis view, **B**, 4 chamber view, white arrows pointing to area of LGE), the so-called displaced triangle of dysplasia.

comprehensive review on this topic summarizing many of the findings and pitfalls we have encountered in clinical practice.[85] In patients with ARVC, the basal inferior and lateral walls of the RV are often the first to show structural abnormalities, and structural abnormalities seem to progress from base to apex.[12] Isolated apical wall motion abnormalities are rare in true cases of ARVC, and the presence of an RV apicolateral bulge near the moderator band insertion may lead to misdiagnosis.[85] Long axis cine views of the RV, both in the 4-chamber and axial plane, are important to include in any ARVC CMR protocol, however, it is important to note that RV shape is variable, particularly in the axial plane, and any wall motion abnormalities in the long axis plane should ideally be confirmed in the short axis plane as well. Additionally, tethering of the anterior wall of the RV to the posterior sternum is a normal variant that can be mistaken for a wall motion abnormality.[85,86]

In the short axis plane, outward bulging of the myocardium in early systole of the inferior wall and the angle of the RV is commonly encountered in ARVC. In addition, lifting of the RV inferior wall from the diaphragmatic surface in systole is classically absent in ARVC owing to dyskinesis of the inferior wall but is present in normal patients. In our experience, systole is the most important part of the cardiac cycle for identification of wall motion abnormalities in ARVC. We have found that irregular diastolic relaxation patterns in the RV are common across various types of patients and may be misleading. Finally, we find that that a common source of misdiagnosis is the presence of RV fatty infiltrates. RV fat is not specific to ARVC and difficult to assess reliably, hence its absence from the 2010 Task Force Criteria. We strongly discourage use of RV fat on imaging to influence clinical decision making.

As an additional note, implantable cardioverter defibrillator implantation may obscure the ability to interpret CMR in patients with ARVC. However, several strategies may be used to enhance image quality. Gradient-echo (GRE) sequences may be used to improve image quality in favor of standard SSFP images. Additionally, wideband filtering algorithms may further improve image quality in the vicinity of an implanted device, including LGE images. In-depth recommendations are described elsewhere.[87]

Comprehensive ARVC Exam

1. Cine imaging: 2-chamber, 4-chamber, short axis stack, RVOT, and axial stack
2. Tissue characterization: axial stack of dark blood T1-weighted images, optional axial stack of fat-saturated dark blood T1-weighted images, and late gadolinium enhancement images in the same planes as cine imaging

INVASIVE MODALITIES AND MODALITIES USING IONIZING RADIATION

The 2010 Task Force Criteria include findings by RV angiography (regional RV akinesia, dyskinesia, or aneurysm)

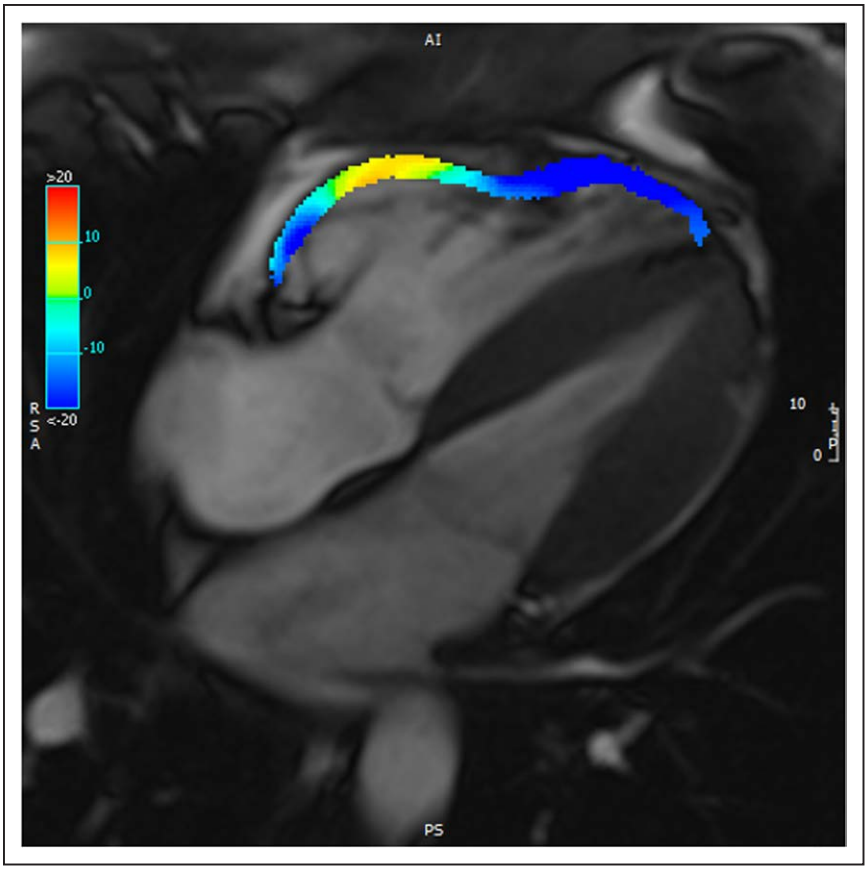

Figure 4. Example of right ventricular strain imaging using cardiac magnetic resonance (CMR) in arrhythmogenic right ventricular cardiomyopathy (ARVC).
Example of long axis strain imaging of the right ventricle (RV) using CMR showing reduced basal strain and preserved apical RV strain in a 47-y-old woman with ARVC.

as major criteria for diagnosis of ARVC.[2] However, owing to the widespread availability and noninvasive nature of alternative modalities, this technique is not frequently used for evaluation or diagnosis.

Multidetector computed tomography (MDCT) does not currently have a defined role in the diagnosis of ARVC by the 2010 Task Force Criteria.[2] While not generally used for initial testing, CT may provide potential diagnostic utility. The technique offers accurate quantitation of RV and LV volumes and function, as well as the ability to identify and quantitate fatty tissue.[48,65] CT also offers high temporal and spatial resolution (0.5 mm)[24] at low-dose radiation levels of 1 to 2 millisieverts[19,24,65] and much shorter scan times compared with CMR.

In terms of diagnostic performance, one study using CT created a scoring system using fatty tissue, bulging appearance of the RV, and dilatation of the right ventricle and compared it against the 2010 Task Force Criteria as the reference standard in 77 patients with diagnosed or suspected ARVC, and cited a sensitivity, specificity and positive predictive value of 87%, 94.4%, and 87%, respectively for definite ARVC.[47] Another study of 36 patients with ARVC by 2010 Task Force Criteria that included matched controls and patients with ischemic cardiomyopathy determined that a fat extent threshold of 8.5% of the RV free wall had a 94% sensitivity and 92% specificity of diagnosing ARVC.[48] Fat content also correlated to RV size, dysfunction, presence of epsilon waves, T wave inversions in V1-V3, and presence of *PKP2* mutations.[48] Additional studies have suggested a role for identifying myocardial fat and tissue heterogeneity by MDCT and integration with catheter mapping to localize regions of ventricular tachycardia substrate.[88,89] Nonetheless, further validation is needed to establish the utility of this modality for routine clinical care in ARVC patients. A representative MDCT image of a patient with ARVC is shown in Figure 2D.

Current recommendations suggest utilization of MDCT for evaluation of structural RV and/or LV remodeling particularly in patients in whom echocardiographic information is insufficient and CMR is contraindicated or not available.[4,19] Such patients may include those with significant arrhythmia, claustrophobia, ICDs, or patients with suspected focal ARVC.[24]

Similar to MDCT, nuclear imaging techniques are also not included in the 2010 Task Force Criteria for diagnosis of ARVC.[2] Therefore, the role in screening and prognostication for these modalities continues to evolve. Radionuclide angiography is capable of quantitating RV ejection fraction, and the SD of regional times of end systole has been identified as a possible marker of diffuse or localized ARVC.[90] Studies by ^{123}I-labeled norepinephrine analog on metaiodobenzylguanidine (^{123}I-MIBG) single-photon emission computed tomography have suggested abnormal sympathetic innervation in patients with ARVC, and abnormal tracer uptake by ^{123}I-MIBG

single-photon emission computed tomography has been associated with a higher incidence of ventricular tachyarrhythmias.[91,92] These studies suggest a potential role for ^{123}I-MIBG single-photon emission computed tomography in arrhythmia risk stratification. Another study retrospectively evaluated 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with ARVC and found evidence for active myocardial inflammation, suggesting a role for myocarditis in the pathogenesis of ARVC.[93] Furthermore, myocardial beta-adrenergic receptor density, as assessed by PET, was found to be lower in patients with ARVC compared with age-matched controls.[94] Expert consensus by the European Association of Cardiovascular Imaging assert that while nuclear imaging modalities may have the ability to provide risk assessment, further investigation is needed.[19]

Three-dimensional endocardial voltage mapping is an invasive modality that may also have a role in diagnosis and management of ARVC by identifying electroanatomic regions of scar within the RV.[13] Although the 2010 Task Force Criteria[2] do not define a specific role for 3D endocardial voltage mapping, the 2019 HRS guidelines state that voltage mapping may improve yield of endomyocardial biopsy by identifying regions of low voltage.[4] Furthermore, the technique may provide guidance in catheter ablation of recurrent ventricular tachycardia.[19] However, the technique is limited by procedure availability, and a 2020 expert consensus report suggests using endocardial voltage mapping only for select patients undergoing catheterization for arrhythmia management and not for routine diagnosis.[13]

DIFFERENTIATION FROM OVERLAP DIAGNOSES

Several cardiomyopathies and arrhythmogenic syndromes share clinical features with ARVC. As such, the role of multimodality imaging in distinguishing ARVC from other cardiomyopathies is critical, particularly in gene and histopathologic elusive cases. It is important to note that certain diagnoses, such as sarcoidosis, myocarditis, and athlete's heart, may not be easily distinguished from ARVC. For example, a recent study suggested that the 2010 Task Force Criteria may not reliably distinguish cardiac sarcoid from ARVC as patients with cardiac sarcoidosis may fulfill ARVC diagnostic criteria.[95] However, extensive left ventricular involvement, lower left ventricular ejection fractions, and positive PET scans were more commonly seen in sarcoidosis, whereas larger RVOT measurements were seen in ARVC.[95] Similarly, the physiological stresses of exercise are known to disproportionately affect the right-sided cardiac chambers,[96] and though LGE on CMR is nonspecific for ARVC, up to 40% of athletes may demonstrate fibrosis of the RV insertion points.[97] However, the right atrium is often disproportionately affected in patients with ARVC, and a recent study has utilized this feature by designing a scoring system that incorporates the ratio of RA to LA volume to distinguish athlete's heart from ARVC.[98] The spectrum of clinical and diagnostic overlap between ARVC and other diseases underscores the importance of reader familiarity with imaging findings of overlap diagnoses and why findings by multimodality imaging must be integrated into clinical context. Table 3 summarizes the characteristic findings of overlap diagnoses by multimodality imaging.

ROLE OF CARDIAC IMAGING IN FAMILY SCREENING

The optimal timing and frequency of screening for relatives of probands using multimodality imaging is unknown, particularly in context of variable genotype expression and penetrance of ARVC.[64] In one study evaluating the penetrance of ARVC, 47% of mutation-positive family members without signs of ARVC at inclusion ultimately fulfilled criteria for diagnosis after a median of 5.7 years of follow-up.[64] Of note, structural progression was monitored largely by echocardiography in this study. Another study identified new-onset definite ARVC by serial CMR in a subset of patients who did not meet the 2010 Task Force Criteria but had RV dysfunction and a family history of ARVC or an ARVC-associated gene mutation at baseline.[99] Though limited, these studies provide some evidence for periodic monitoring for structural progression in at-risk relatives without a definite diagnosis of ARVC. While the decision, timing, and modality for serial imaging in at-risk family members is often individualized, our authors will generally seek repeat imaging every 2 to 5 years in this patient population. When technically feasible, our authors prefer serial imaging by CMR given its ability to perform a more comprehensive examination compared with echocardiography.

Per the 2019 HRS guidelines,[4] all first-degree relatives are recommended to undergo clinical evaluation every 1 to 3 years, starting at 10 to 12 years of age, though it may be reasonable for asymptomatic members who do not have a familial variant and also have a normal cardiovascular evaluation to be released from regular screening unless symptoms occur. The guidelines further recommend cardiovascular evaluations to include a 12-lead EKG, ambulatory EKG, and cardiac imaging, but do not specifically describe the frequency of serial imaging.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

The ability to identify ARVC early in its disease course is vital, as it allows for the opportunity to extend screening

Table 3. Comparison of Imaging Findings in Overlap Diagnoses

	Imaging modality			
Overlap diagnosis	Echocardiography	CMR	MDCT	PET
Athlete's heart	Balanced dilation of cardiac chambers	Same structural findings as echocardiography	…	…
		LGE, if present, is generally limited to the RV insertion points		
	Wall thickness <15 mm			
	Absence of RWMA			
Sarcoidosis	Reduced LV function	Characteristic nonischemic LGE pattern of the interventricular septum and/or lateral wall, often basal	Mediastinal lymphadenopathy may be detected	Heterogenous tracer uptake in active cardiac sarcoid
	RWMA may be seen			
Myocarditis	Reduced LV function	Reduced LV function	…	May demonstrate and localize active myocardial inflammation
		RWMA may be seen		
		Tissue edema		
	RWMA may be seen	Patchy subepicardial myocardial LGE (nonischemic pattern)		
		May show pericardial involvement		
Dilated cardiomyopathy	Dilated LV cavity	Dilated LV cavity	…	…
		Reduced LV function		
	Reduced LV function	Mid-wall septal LGE on CMR		
RVOT-VT	Normal imaging findings	Normal imaging findings	…	…
Brugada syndrome	Normal imaging findings	Normal imaging findings	…	…
Uhl's anomaly (total absence of right ventricular myocardium)	Apposition of endocardium and epicardium	Apposition of endocardium and epicardium	…	…

A summary of diagnoses that may be mistaken for arrhythmogenic right ventricular cardiomyopathy and associated characteristic imaging findings is given. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle; MDCT, multidetector computed tomography; PET, positron emission tomography; RV, right ventricular; RVOT-VT, right ventricular outflow tract ventricular tachycardia; and RWMA, regional wall motion abnormalities.

to relatives, implement therapeutic and preventative measures (such as implantable cardioverter defibrillator implantation), and provide a platform for illness counseling. Despite the advancement of multimodality imaging in the diagnosis of ARVC, several challenges remain. Because ARVC is rare, nearly all studies of noninvasive imaging techniques are retrospective in design. Additionally, most studies evaluate the performance of imaging modalities in patients who ultimately fulfill the 2010 Task Force Criteria, which may artificially inflate reported specificities in diagnosis or prediction of adverse events. The onset of disease in early adulthood highlights the value for identification of ARVC in late childhood and adolescence, before symptom manifestation. Identification of imaging markers of disease in the pediatric population could enhance the role of early noninvasive imaging in at-risk populations; however, relatively few studies have evaluated patients in this age group. Ongoing multicenter registries that follow high-risk patients from childhood on may help identify and establish these imaging markers.

The widespread use of noninvasive imaging modalities in the diagnosis of ARVC, particularly contrast-enhanced CMR, has led to a growing recognition for biventricular and left-ventricular involvement.[20,21,23] As mentioned previously, new diagnostic criteria have been proposed ("the Padua criteria") to combine these clinical entities as disease variants under an umbrella diagnosis of ACM, noting overlap in the genetic bases of left-dominant, right-dominant, and biventricular phenotypes.[18,20,21,23,100] As the links between genotypes and phenotypes are further elucidated, our understanding for how to characterize this spectrum of illnesses, and more importantly, the implications of diagnosis on management and prognosis, will continue to evolve.

Finally, diagnosis of definite ARVC by the 2010 Task Force Criteria requires fulfillment of nonimaging criteria (see Table 1). As noted previously, current imaging techniques are unable to definitively distinguish ARVC from other disease entities without additional clinical information, and findings must be considered within clinical and pathological contexts. Nonetheless, the development and understanding of novel techniques in ARVC, such as 3D echocardiography, RV strain imaging by echocardiography and CMR, and high resolution 3D LGE using CMR, may provide incremental predictive value for symptom and disease course in the future.

CONCLUSIONS

The role of multimodality imaging in ARVC has evolved since the earliest case series described the disease.[5] Potential for early recognition and treatment of ARVC will depend on improved accessibility of current imaging modalities, as well as further advancement and innovation of established techniques. Less established modalities, such as MDCT and nuclear imaging, also have potential to supplement standard techniques by providing

prognostic information and modifying how ARVC is followed and managed.

ARTICLE INFORMATION

Affiliations

MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC (N.M., F.H.S.). Georgetown University, Washington, DC (N.M., F.H.S.). Johns Hopkins University Department of Medicine, Division of Cardiology, Baltimore, MD (M.M., K.C.W., H.C., C.A.J., N.A.G., H.T., A.G.H.). Johns Hopkins University Department of Radiology, Baltimore, MD (S.L.Z.). Johns Hopkins University Department of Pediatrics, Division of Pediatric Cardiology, Baltimore, MD (J.Z., S.K.).

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

None.

Supplemental Material

Videos S1 and S2

REFERENCES

1. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med.* 2017;376:61–72. doi: 10.1056/NEJMra1509267
2. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* 2010;121:1533–1541. doi: 10.1161/CIRCULATIONAHA.108.840827
3. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, et al; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace.* 2011;13:1077–1109. doi: 10.1093/europace/eur245
4. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, Daubert JP, de Chillou C, DePasquale EC, Desai MY, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm.* 2019;16:e301–e372. doi: 10.1016/j.hrthm.2019.05.007
5. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation.* 1982;65:384–398. doi: 10.1161/01.cir.65.2.384
6. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation.* 2017;136:2068–2082. doi: 10.1161/CIRCULATIONAHA.117.030792
7. Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, Murray B, Wiesfeld AC, Sawant AC, Kassamali B, et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet.* 2015;8:437–446. doi: 10.1161/CIRCGENETICS.114.001003
8. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation.* 2004;110:1879–1884. doi: 10.1161/01.CIR.0000143375.93288.82
9. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. *Circ Genom Precis Med.* 2021;14:e003273. doi: 10.1161/CIRCGEN.120.003273
10. James CA, Syrris P, van Tintelen JP, Calkins H. The role of genetics in cardiovascular disease: arrhythmogenic cardiomyopathy. *Eur Heart J.* 2020;41:1393–1400. doi: 10.1093/eurheartj/ehaa141
11. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol.* 2013;62:1290–1297. doi: 10.1016/j.jacc.2013.06.033
12. Te Riele AS, James CA, Philips B, Rastegar N, Bhonsale A, Groeneweg JA, Murray B, Tichnell C, Judge DP, Van Der Heijden JF, et al. Mutation-positive arrhythmogenic right ventricular dysplasia/cardiomyopathy: the triangle of dysplasia displaced. *J Cardiovasc Electrophysiol.* 2013;24:1311–1320. doi: 10.1111/jce.12222
13. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, Basso C, Bauce B, Brunckhorst C, Bucciarelli-Ducci C, et al; International Experts. Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J.* 2020;41:1414–1429. doi: 10.1093/eurheartj/ehz669
14. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task force of the working group myocardial and pericardial disease of the European society of cardiology and of the scientific council on cardiomyopathies of the international society and federation of cardiology. *Br Heart J.* 1994;71:215–218. doi: 10.1136/hrt.71.3.215
15. Corrado D, Wichter T, Link MS, Hauer RN, Marchlinski FE, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Circulation.* 2015;132:441–453. doi: 10.1161/CIRCULATIONAHA.115.017944
16. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, Bourfiss M, Fortier A, Lie ØH, Saguner AM, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J.* 2019;40:1850–1858. doi: 10.1093/eurheartj/ehz103
17. Cadrin-Tourigny J, Bosman LP, Wang W, Tadros R, Bhonsale A, Bourfiss M, Lie ØH, Saguner AM, Svensson A, Andorin A, et al. Sudden cardiac death prediction in arrhythmogenic right ventricular cardiomyopathy: a multinational collaboration. *Circ Arrhythm Electrophysiol.* 2021;14:e008509. doi: 10.1161/CIRCEP.120.008509
18. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. *Circ Res.* 2017;121:784–802. doi: 10.1161/CIRCRESAHA.117.309345
19. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, Galderisi M, Habib G, Knuuti J, Lancellotti P, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy–an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J - Cardiovasc Imaging.* 2017;18:237–253. doi: 10.1093/ehjci/jew229
20. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari M, Migliore F, Pilichou K, Rampazzo A, Rigato I, et al. Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria. *Int J Cardiol.* 2020;319:106–114. doi: 10.1016/j.ijcard.2020.06.005
21. Corrado D, Basso C. Arrhythmogenic left ventricular cardiomyopathy. *Heart.* [epub ahead of print 13 July 2021]. doi: 10.1136/heartjnl-2020-316944
22. Cipriani A, Bauce B, De Lazzari M, Rigato I, Bariani R, Meneghin S, Pilichou K, Motta R, Aliberti C, Thiene G, et al. Arrhythmogenic right ventricular cardiomyopathy: characterization of left ventricular phenotype and differential diagnosis with dilated cardiomyopathy. *J Am Heart Assoc.* 2020;9:e014628. doi: 10.1161/JAHA.119.014628
23. Corrado D, Zorzi A, Cipriani A, Bauce B, Bariani R, Beffagna G, De Lazzari M, Migliore F, Pilichou K, Rampazzo A, et al. Evolving diagnostic criteria for arrhythmogenic cardiomyopathy. *J Am Heart Assoc.* 2021;10:e021987. doi: 10.1161/JAHA.121.021987
24. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical diagnosis, imaging, and genetics of arrhythmogenic right ventricular cardiomyopathy/dysplasia: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2018;72:784–804. doi: 10.1016/j.jacc.2018.05.065
25. Yoerger DM, Marcus F, Sherrill D, Calkins H, Towbin JA, Zareba W, Picard MH; Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia. *J Am Coll Cardiol.* 2005;45:860–865. doi: 10.1016/j.jacc.2004.10.070
26. Teske AJ, Cox MG, De Boeck BW, Doevendans PA, Hauer RN, Cramer MJ. Echocardiographic tissue deformation imaging quantifies abnormal regional right ventricular function in arrhythmogenic right ventricular

dysplasia/cardiomyopathy. *J Am Soc Echocardiogr.* 2009;22:920–927. doi: 10.1016/j.echo.2009.05.014
27. Lindström L, Wilkenshoff UM, Larsson H, Wranne B. Echocardiographic assessment of arrhythmogenic right ventricular cardiomyopathy. *Heart.* 2001;86:31–38. doi: 10.1136/heart.86.1.31
28. Zghaib T, Bourfiss M, van der Heijden JF, Loh P, Hauer RN, Tandri H, Calkins H, Nazarian S, Te Riele ASJM, Zimmerman SL, et al. Atrial dysfunction in arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Imaging.* 2018;11:e007344. doi: 10.1161/CIRCIMAGING.117.007344
29. López-Fernández T, García-Fernández MA, Pérez David E, Moreno Yangüela M. Usefulness of contrast echocardiography in arrhythmogenic right ventricular dysplasia. *J Am Soc Echocardiogr.* 2004;17:391–393. doi: 10.1016/j.echo.2003.11.013
30. Jeong H, Song S, Seo J, Cho I, Hong GR, Ha JW, Shim CY. Characteristics and prognostic implications of tricuspid regurgitation in patients with arrhythmogenic cardiomyopathy. *ESC Heart Fail.* 2020;7:2933–2940. doi: 10.1002/ehf2.12906
31. Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, Di Lenarda A, Morgera T, Mestroni L, Sinagra G. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. *Eur Heart J.* 2011;32:1105–1113. doi: 10.1093/eurheartj/ehr040
32. Katritsis G, Shah AS, James CA, Murray B, Tichnell C, Judge DP, Calkins H, Tedford RJ. Surgical correction of tricuspid regurgitation in patients with ARVD/C. *HeartRhythm Case Rep.* 2015;1:326–330. doi: 10.1016/j.hrcr.2015.05.001
33. Saguner AM, Vecchiati A, Baldinger SH, Rüeger S, Medeiros-Domingo A, Mueller-Burri AS, Haegeli LM, Biaggi P, Manka R, Lüscher TF, et al. Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ Cardiovasc Imaging.* 2014;7:230–239. doi: 10.1161/CIRCIMAGING.113.000210
34. Focardi M, Cameli M, Carbone SF, Massoni A, De Vito R, Lisi M, Mondillo S. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *Eur Heart J Cardiovasc Imaging.* 2015;16:47–52. doi: 10.1093/ehjci/jeu156
35. Wang J, Prakasa K, Bomma C, Tandri H, Dalal D, James C, Tichnell C, Corretti M, Bluemke D, Calkins H, et al. Comparison of novel echocardiographic parameters of right ventricular function with ejection fraction by cardiac magnetic resonance. *J Am Soc Echocardiogr.* 2007;20:1058–1064. doi: 10.1016/j.echo.2007.01.038
36. Qasem M, Utomi V, George K, Somauroo J, Zaidi A, Forsythe L, Bhattacharrya S, Lloyd G, Rana B, Ring L, et al. A meta-analysis for echocardiographic assessment of right ventricular structure and function in ARVC. *Echo Res Pract.* 2016;3:95–104. doi: 10.1530/ERP-16-0028
37. Pieles GE, Grosse-Wortmann L, Hader M, Fatah M, Chungsomprasong P, Slorach C, Hui W, Fan CS, Manlhiot C, Mertens L, et al. Association of echocardiographic parameters of right ventricular remodeling and myocardial performance with modified task force criteria in adolescents with arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Imaging.* 2019;12:e007693. doi: 10.1161/CIRCIMAGING.118.007693
38. Mast TP, Teske AJ, vd Heijden JF, Groeneweg JA, Te Riele AS, Velthuis BK, Hauer RN, Doevendans PA, Cramer MJ. Left ventricular involvement in arrhythmogenic right ventricular dysplasia/cardiomyopathy assessed by echocardiography predicts adverse clinical outcome. *J Am Soc Echocardiogr.* 2015;28:1103–13.e9. doi: 10.1016/j.echo.2015.04.015
39. Malik N, Win S, James CA, Kutty S, Mukherjee M, Gilotra NA, Tichnell C, Murray B, Agafonova J, Tandri H, et al. Right ventricular strain predicts structural disease progression in patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Heart Assoc.* 2020;9:e015016. doi: 10.1161/JAHA.119.015016
40. Aquaro GD, Barison A, Todiere G, Grigoratos C, Ait Ali L, Di Bella G, Emdin M, Festa P. Usefulness of combined functional assessment by cardiac magnetic resonance and tissue characterization versus task force criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol.* 2016;118:1730–1736. doi: 10.1016/j.amjcard.2016.08.056
41. Aquaro GD, Pingitore A, Di Bella G, Piaggi P, Gaeta R, Grigoratos C, Altinier A, Pantano A, Strata E, De Caterina R, et al. Prognostic role of cardiac magnetic resonance in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol.* 2018;122:1745–1753. doi: 10.1016/j.amjcard.2018.08.007
42. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N, Lesizza P, Grigoratos C, Minati M, Dell'Omodarme M, et al. Prognostic value of magnetic resonance phenotype in patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol.* 2020;75:2753–2765. doi: 10.1016/j.jacc.2020.04.023
43. Deac M, Alpendurada F, Fanaie F, Vimal R, Carpenter JP, Dawson A, Miller C, Roussin I, di Pietro E, Ismail TF, et al. Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiol.* 2013;168:3514–3521. doi: 10.1016/j.ijcard.2013.04.208
44. Perazzolo Marra M, Cipriani A, Rizzo S, De Lazzari M, De Gaspari M, Akrami N, Bariani R, Zorzi A, Migliore F, Rigato I, et al. Myocardial tissue characterization in arrhythmogenic cardiomyopathy: comparison between endomyocardial biopsy and cardiac magnetic resonance. *JACC Cardiovasc Imaging.* 2021;14:1675–1678. doi: 10.1016/j.jcmg.2021.02.015
45. Segura-Rodríguez D, Bermúdez-Jiménez FJ, Carriel V, López-Fernández S, González-Molina M, Oyonarte Ramírez JM, Fernández-Navarro L, García-Roa MD, Cabrerizo EM, Durand-Herrera D, et al. Myocardial fibrosis in arrhythmogenic cardiomyopathy: a genotype–phenotype correlation study. *Eur Heart J - Cardiovasc Imaging.* 2020;21:378–386. doi: 10.1093/ehjci/jez277
46. Shen MT, Yang ZG, Diao KY, Jiang L, Zhang Y, Liu X, Gao Y, Hu BY, Huang S, Guo YK. Left ventricular involvement in arrhythmogenic right ventricular dysplasia/cardiomyopathy predicts adverse clinical outcomes: a cardiovascular magnetic resonance feature tracking study. *Sci Rep.* 2019;9:14235. doi: 10.1038/s41598-019-50535-z
47. Nakajima T, Kimura F, Kajimoto K, Kasanuki H, Hagiwara N. Utility of ECG-gated MDCT to differentiate patients with ARVC/D from patients with ventricular tachyarrhythmias. *J Cardiovasc Comput Tomogr.* 2013;7:223–233. doi: 10.1016/j.jcct.2013.05.004
48. Cochet H, Denis A, Komatsu Y, Jadidi AS, Aït Ali T, Sacher F, Derval N, Relan J, Sermesant M, Corneloup O, et al. Automated quantification of right ventricular fat at contrast-enhanced cardiac multidetector CT in arrhythmogenic right ventricular cardiomyopathy. *Radiology.* 2015;275:683–691. doi: 10.1148/radiol.14141140
49. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation.* 2007;115:1710–1720. doi: 10.1161/CIRCULATIONAHA.106.660241
50. Prakasa KR, Dalal D, Wang J, Bomma C, Tandri H, Dong J, James C, Tichnell C, Russell SD, Spevak P, et al. Feasibility and variability of three dimensional echocardiography in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol.* 2006;97:703–709. doi: 10.1016/j.amjcard.2005.11.020
51. Knight DS, Grasso AE, Quail MA, Muthurangu V, Taylor AM, Toumpanakis C, Caplin ME, Coghlan JG, Davar J. Accuracy and reproducibility of right ventricular quantification in patients with pressure and volume overload using single-beat three-dimensional echocardiography. *J Am Soc Echocardiogr.* 2015;28:363–374. doi: 10.1016/j.echo.2014.10.012
52. Cismaru G, Grosu A, Istratoaie S, Mada L, Ilea M, Gusetu G, Zdrenghea D, Pop D, Rosu R. Transesophageal and intracardiac ultrasound in arrhythmogenic right ventricular dysplasia/cardiomyopathy: two case reports. *Medicine (Baltimore).* 2020;99:e19817. doi: 10.1097/MD.0000000000019817
53. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23:685–713; quiz 786. doi: 10.1016/j.echo.2010.05.010
54. Prakasa KR, Wang J, Tandri H, Dalal D, Bomma C, Chojnowski R, James C, Tichnell C, Russell S, Judge D, et al. Utility of tissue Doppler and strain echocardiography in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol.* 2007;100:507–512. doi: 10.1016/j.amjcard.2007.03.053
55. Sarvari SI, Haugaa KH, Anfinsen OG, Leren TP, Smiseth OA, Kongsgaard E, Amlie JP, Edvardsen T. Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *Eur Heart J.* 2011;32:1089–1096. doi: 10.1093/eurheartj/ehr069
56. Teske AJ, Cox MG, Te Riele AS, De Boeck BW, Doevendans PA, Hauer RN, Cramer MJ. Early detection of regional functional abnormalities in asymptomatic ARVD/C gene carriers. *J Am Soc Echocardiogr.* 2012;25:997–1006. doi: 10.1016/j.echo.2012.05.008
57. Mast TP, Taha K, Cramer MJ, Lumens J, van der Heijden JF, Bouma BJ, van den Berg MP, Asselbergs FW, Doevendans PA, Teske AJ. The prognostic value of right ventricular deformation imaging in Early arrhythmogenic

right ventricular cardiomyopathy. *JACC Cardiovasc Imaging.* 2019;12:446–455. doi: 10.1016/j.jcmg.2018.01.012
58. Saberniak J, Leren IS, Haland TF, Beitnes JO, Hopp E, Borgquist R, Edvardsen T, Haugaa KH. Comparison of patients with early-phase arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract ventricular tachycardia. *Eur Heart J Cardiovasc Imaging.* 2017;18:62–69. doi: 10.1093/ehjci/jew014
59. Leren IS, Saberniak J, Haland TF, Edvardsen T, Haugaa KH. Combination of ECG and echocardiography for identification of arrhythmic events in Early ARVC. *JACC Cardiovasc Imaging.* 2017;10:503–513. doi: 10.1016/j.jcmg.2016.06.011
60. Kirkels FP, Lie ØH, Cramer MJ, Chivulescu M, Rootwelt-Norberg C, Asselbergs FW, Teske AJ, Haugaa KH. Right ventricular functional abnormalities in arrhythmogenic cardiomyopathy: association with life-threatening ventricular arrhythmias. *JACC Cardiovasc Imaging.* 2021;14:900–910. doi: 10.1016/j.jcmg.2020.12.028
61. van Osta N, Kirkels FP, van Loon T, Koopsen T, Lyon A, Meiburg R, Huberts W, Cramer MJ, Delhaas T, Haugaa KH, et al. Uncertainty quantification of regional cardiac tissue properties in arrhythmogenic cardiomyopathy using adaptive multiple importance sampling. *Front Physiol.* 2021;12:738926. doi: 10.3389/fphys.2021.738926
62. Vitarelli A, Cortes Morichetti M, Capotosto L, De Cicco V, Ricci S, Caranci F, Vitarelli M. Utility of strain echocardiography at rest and after stress testing in arrhythmogenic right ventricular dysplasia. *Am J Cardiol.* 2013;111:1344–1350. doi: 10.1016/j.amjcard.2013.01.279
63. Mast TP, James CA, Calkins H, Teske AJ, Tichnell C, Murray B, Loh P, Russell SD, Velthuis BK, Judge DP, et al. Evaluation of structural progression in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *JAMA Cardiol.* 2017;2:293–302. doi: 10.1001/jamacardio.2016.5034
64. Chivulescu M, Lie ØH, Popescu BA, Skulstad H, Edvardsen T, Jurcut RO, Haugaa KH. High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy. *Eur Heart J.* 2020;41:1401–1410. doi: 10.1093/eurheartj/ehz570
65. Te Riele ASJM, Tandri H, Sanborn DM, Bluemke DA. Noninvasive multimodality imaging in ARVD/C. *JACC Cardiovasc Imaging.* 2015;8:597–611. doi: 10.1016/j.jcmg.2015.02.007
66. Corrado D, Cipriani A, De Lazzari M, Perazzolo Marra M. Right ventricular dilatation in arrhythmogenic right ventricular cardiomyopathy: need for a revision of the 2010 International Task Force criteria. *Eur Heart J.* 2020;41:1452–1453. doi: 10.1093/eurheartj/ehaa003
67. Khanji MY, Chahal AA, Lopes LR, Petersen SE. Cardiovascular magnetic resonance imaging volume criteria for arrhythmogenic right ventricular cardiomyopathy: need for update? *Eur Heart J.* 2020;41:1451. doi: 10.1093/eurheartj/ehz965
68. D'Ascenzi F, Anselmi F, Piu P, Fiorentini C, Carbone SF, Volterrani L, Focardi M, Bonifazi M, Mondillo S. Cardiac magnetic resonance normal reference values of biventricular size and function in male Athlete's heart. *JACC Cardiovasc Imaging.* 2019;12:1755–1765. doi: 10.1016/j.jcmg.2018.09.021
69. Etoom Y, Govindapillai S, Hamilton R, Manlhiot C, Yoo SJ, Farhan M, Sarikouch S, Peters B, McCrindle BW, Grosse-Wortmann L. Importance of CMR within the task force criteria for the diagnosis of ARVC in children and adolescents. *J Am Coll Cardiol.* 2015;65:987–995. doi: 10.1016/j.jacc.2014.12.041
70. Wu L, Guo J, Zheng L, Chen G, Ding L, Qiao Y, Sun W, Yao Y, Zhang S. Atrial remodeling and atrial tachyarrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol.* 2016;118:750–753. doi: 10.1016/j.amjcard.2016.06.003
71. Blake LM, Scheinman MM, Higgins CB. MR features of arrhythmogenic right ventricular dysplasia. *AJR Am J Roentgenol.* 1994;162:809–812. doi: 10.2214/ajr.162.4.8140995
72. Pfluger HB, Phrommintikul A, Mariani JA, Cherayath JG, Taylor AJ. Utility of myocardial fibrosis and fatty infiltration detected by cardiac magnetic resonance imaging in the diagnosis of arrhythmogenic right ventricular dysplasia–a single centre experience. *Heart Lung Circ.* 2008;17:478–483. doi: 10.1016/j.hlc.2008.03.085
73. Marra MP, Leoni L, Bauce B, Corbetti F, Zorzi A, Migliore F, Silvano M, Rigato I, Tona F, Tarantini G, et al. Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance. *Circ Arrhythm Electrophysiol.* 2012;5:91–100. doi: 10.1161/CIRCEP.111.964635
74. Rastegar N, Zimmerman SL, Te Riele ASJM, James C, Burt JR, Bhonsale A, Murray B, Tichnell C, Judge D, Calkins H, et al. Spectrum of biventricular involvement on CMR among carriers of ARVD/C-associated mutations. *JACC Cardiovasc Imaging.* 2015;8:863–864. doi: 10.1016/j.jcmg.2014.09.009
75. Liu Y, Yu J, Liu J, Wu B, Cui Q, Shen W, Xia S. Prognostic value of late gadolinium enhancement in arrhythmogenic right ventricular cardiomyopathy: a meta-analysis. *Clin Radiol.* 2021;76:628.e9–628.e15. doi: 10.1016/j.crad.2021.04.002
76. Gilotra NA, Bhonsale A, James CA, Te Riele ASJ, Murray B, Tichnell C, Sawant A, Ong CS, Judge DP, Russell SD, et al. Heart failure is common and under-recognized in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ Heart Fail.* 2017;10:e003819. doi: 10.1161/CIRCHEARTFAILURE.116.003819
77. Heermann P, Fritsch H, Koopmann M, Sporns P, Paul M, Heindel W, Schulze-Bahr E, Schülke C. Biventricular myocardial strain analysis using cardiac magnetic resonance feature tracking (CMR-FT) in patients with distinct types of right ventricular diseases comparing arrhythmogenic right ventricular cardiomyopathy (ARVC), right ventricular outflow-tract tachycardia (RVOT-VT), and Brugada syndrome (BrS). *Clin Res Cardiol.* 2019;108:1147–1162. doi: 10.1007/s00392-019-01450-w
78. Heermann P, Hedderich DM, Paul M, Schülke C, Kroeger JR, Baeßler B, Wichter T, Maintz D, Waltenberger J, Heindel W, et al. Biventricular myocardial strain analysis in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) using cardiovascular magnetic resonance feature tracking. *J Cardiovasc Magn Reson.* 2014;16:75. doi: 10.1186/s12968-014-0075-z
79. Prati G, Vitrella G, Allocca G, Muser D, Buttignoni SC, Piccoli G, Morocutti G, Delise P, Pinamonti B, Proclemer A, et al. Right ventricular strain and dyssynchrony assessment in arrhythmogenic right ventricular cardiomyopathy: cardiac magnetic resonance feature-tracking study. *Circ Cardiovasc Imaging.* 2015;8:e003647; discussion e003647. doi: 10.1161/CIRCIMAGING.115.003647
80. Bourfiss M, Vigneault DM, Aliyari Ghasebeh M, Murray B, James CA, Tichnell C, Mohamed Hoesein FA, Zimmerman SL, Kamel IR, Calkins H, et al. Feature tracking CMR reveals abnormal strain in preclinical arrhythmogenic right ventricular dysplasia/ cardiomyopathy: a multisoftware feasibility and clinical implementation study. *J Cardiovasc Magn Reson.* 2017;19:66. doi: 10.1186/s12968-017-0380-4
81. Czimbalmos C, Csecs I, Dohy Z, Toth A, Suhai FI, Müssigbrodt A, Kiss O, Geller L, Merkely B, Vago H. Cardiac magnetic resonance based deformation imaging: role of feature tracking in athletes with suspected arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiovasc Imaging.* 2019;35:529–538. doi: 10.1007/s10554-018-1478-y
82. Kellman P, Hernando D, Shah S, Zuehlsdorff S, Jerecic R, Mancini C, Liang ZP, Arai AE. Multiecho dixon fat and water separation method for detecting fibrofatty infiltration in the myocardium. *Magn Reson Med.* 2009;61:215–221. doi: 10.1002/mrm.21657
83. Basha TA, Akçakaya M, Liew C, Tsao CW, Delling FN, Addae G, Ngo L, Manning WJ, Nezafat R. Clinical performance of high-resolution late gadolinium enhancement imaging with compressed sensing. *J Magn Reson Imaging.* 2017;46:1829–1838. doi: 10.1002/jmri.25695
84. Hennig A, Salel M, Sacher F, Camaioni C, Sridi S, Denis A, Montaudon M, Laurent F, Jais P, Cochet H. High-resolution three-dimensional late gadolinium-enhanced cardiac magnetic resonance imaging to identify the underlying substrate of ventricular arrhythmia. *Europace.* 2018;20(FI2):f179–f191. doi: 10.1093/europace/eux278
85. Rastegar N, Burt JR, Corona-Villalobos CP, Te Riele AS, James CA, Murray B, Calkins H, Tandri H, Bluemke DA, Zimmerman SL, et al. Cardiac MR findings and potential diagnostic pitfalls in patients evaluated for arrhythmogenic right ventricular cardiomyopathy. *Radiographics.* 2014;34:1553–1570. doi: 10.1148/rg.346140194
86. Zimmerman SL. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: an updated imaging approach. *Magn Reson Imaging Clin N Am.* 2015;23:69–79. doi: 10.1016/j.mric.2014.09.001
87. Indik JH, Gimbel JR, Abe H, Alkmim-Teixeira R, Birgersdotter-Green U, Clarke GD, Dickfeld TL, Froelich JW, Grant J, Hayes DL, et al. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. *Heart Rhythm.* 2017;14:e97–e153. doi: 10.1016/j.hrthm.2017.04.025
88. Venlet J, Tao Q, de Graaf MA, Glashan CA, de Riva Silva M, van der Geest RJ, Scholte AJ, Piers SRD, Zeppenfeld K. RV tissue heterogeneity on CT: a novel tool to identify the VT substrate in ARVC. *JACC Clin Electrophysiol.* 2020;6:1073–1085. doi: 10.1016/j.jacep.2020.04.029

89. Komatsu Y, Jadidi A, Sacher F, Denis A, Daly M, Derval N, Shah A, Lehrmann H, Park CI, Weber R, et al. Relationship between MDCT-imaged myocardial fat and ventricular tachycardia substrate in arrhythmogenic right ventricular cardiomyopathy. *J Am Heart Assoc.* 2014;3:e000935. doi: 10.1161/JAHA.114.000935
90. Mariano-Goulart D, Déchaux L, Rouzet F, Barbotte E, Caderas de Kerleau C, Rossi M, Le Guludec D. Diagnosis of diffuse and localized arrhythmogenic right ventricular dysplasia by gated blood-pool SPECT. *J Nucl Med.* 2007;48:1416–1423. doi: 10.2967/jnumed.107.041129
91. Paul M, Wichter T, Kies P, Gerss J, Wollmann C, Rahbar K, Eckardt L, Breithardt G, Schober O, Schulze-Bahr E, et al. Cardiac sympathetic dysfunction in genotyped patients with arrhythmogenic right ventricular cardiomyopathy and risk of recurrent ventricular tachyarrhythmias. *J Nucl Med.* 2011;52:1559–1565. doi: 10.2967/jnumed.111.088997
92. Wichter T, Hindricks G, Lerch H, Bartenstein P, Borggrefe M, Schober O, Breithardt G. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy. An analysis using 123I-meta-iodobenzylguanidine scintigraphy. *Circulation.* 1994;89:667–683. doi: 10.1161/01.cir.89.2.667
93. Protonotarios A, Wicks E, Ashworth M, Stephenson E, Guttmann O, Savvatis K, Sekhri N, Mohiddin SA, Syrris P, Menezes L, et al. Prevalence of 18F-fluorodeoxyglucose positron emission tomography abnormalities in patients with arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiol.* 2019;284:99–104. doi: 10.1016/j.ijcard.2018.10.083
94. Wichter T, Schäfers M, Rhodes CG, Borggrefe M, Lerch H, Lammertsma AA, Hermansen F, Schober O, Breithardt G, Camici PG. Abnormalities of cardiac sympathetic innervation in arrhythmogenic right ventricular cardiomyopathy: quantitative assessment of presynaptic norepinephrine reuptake and postsynaptic beta-adrenergic receptor density with positron emission tomography. *Circulation.* 2000;101:1552–1558. doi: 10.1161/01.cir.101.13.1552
95. Gasperetti A, Rossi VA, Chiodini A, Casella M, Costa S, Akdis D, Büchel R, Deliniere A, Pruvot E, Gruner C, et al. Differentiating hereditary arrhythmogenic right ventricular cardiomyopathy from cardiac sarcoidosis fulfilling 2010 ARVC Task Force Criteria. *Heart Rhythm.* 2021;18:231–238. doi: 10.1016/j.hrthm.2020.09.015
96. La Gerche A, Rakhit DJ, Claessen G. Exercise and the right ventricle: a potential Achilles' heel. *Cardiovasc Res.* 2017;113:1499–1508. doi: 10.1093/cvr/cvx156
97. Gati S, Sharma S, Pennell D. The role of cardiovascular magnetic resonance imaging in the assessment of highly trained athletes. *JACC Cardiovasc Imaging.* 2018;11(2 Pt 1):247–259. doi: 10.1016/j.jcmg.2017.11.016
98. Rossi VA, Niederseer D, Sokolska JM, Kovacs B, Costa S, Gasperetti A, Brunckhorst C, Akdis D, Tanner FC, Duru F, et al. A novel diagnostic score integrating atrial dimensions to differentiate between the Athlete's heart and arrhythmogenic right ventricular cardiomyopathy. *J Clin Med.* 2021;10:4094. doi: 10.3390/jcm10184094
99. Femia G, Semsarian C, McGuire M, Sy RW, Puranik R. Long term CMR follow up of patients with right ventricular abnormality and clinically suspected arrhythmogenic right ventricular cardiomyopathy (ARVC). *J Cardiovasc Magn Reson.* 2019;21:76. doi: 10.1186/s12968-019-0581-0
100. Mattesi G, Cipriani A, Bauce B, Rigato I, Zorzi A, Corrado D. Arrhythmogenic left ventricular cardiomyopathy: genotype-phenotype correlations and new diagnostic criteria. *J Clin Med.* 2021;10:2212. doi: 10.3390/jcm10102212