Heart, Lung and Circulation (2019) **28,** 164–177
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.10.013

REVIEW

Arrhythmogenic Cardiomyopathy in 2018–2019: ARVC/ALVC or Both?

Richard G. Bennett, MBChB [a], Haris M. Haqqani, MD, PhD [b], Antonio Berruezo, MD, PhD [c], Paolo Della Bella, MD [d], Francis E. Marchlinski, MD [e], Chi-Jen Hsu, MBBS, PhD [f], Saurabh Kumar, MBBS, PhD [g*]

[a]Bristol Heart Institute, Bristol, UK
[b]Prince Charles Hospital, University of Queensland, Brisbane, Qld, Australia
[c]Cardiology Department, Heart Institute, Teknon Medical Center, Barcelona, Spain
[d]Arrhythmia Unit and Electrophysiology Laboratories, San Raffaele Hospital, Milan, Italy
[e]Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
[f]Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia
[g]Department of Cardiology, Westmead Applied Research Centre, Westmead Hospital, University of Sydney, Sydney, NSW, Australia

Arrhythmogenic cardiomyopathy (ACM) is now commonly used to describe any form of non-hypertrophic, progressive cardiomyopathy characterised by fibrofatty infiltration of the ventricular myocardium. Right ventricular (RV) involvement refers to the classical arrhythmogenic right ventricular cardiomyopathy, but left ventricular, or bi-ventricular involvement are now recognised. ACM is mostly hereditary and associated with mutations in genes encoding proteins of the intercalated disc. ACM classically manifests as ventricular arrhythmias, and sudden death may be the first presentation of the disease. Heart failure is seen with advanced stages of the disease. Diagnosis can be challenging due to variable expressivity and incomplete penetrance, and is guided by established Taskforce criteria that incorporate electrical features (12-lead electrocardiography (ECG), features of ventricular arrhythmias), structural features (on imaging via echo and cardiac magnetic resonance imaging [MRI]), tissue characteristics (via biopsy), and familial/genetic evaluation. Electrical abnormalities may precede structural alterations, which also make diagnosis challenging, especially in differentiating ACM from other conditions such as benign right ventricular arrhythmias, channelopathies such as Brugada, or the Athlete's Heart. Genetic testing is critical in identifying familial mutations and initiating cascade testing, but finds a pathogenic mutation in only ~50% of patients. Some critical genotype-phenotype correlations do exist and may help guide risk stratification and give clues to disease progression. Therapeutic strategies include restriction from high endurance and competitive sports, ß-blockers, antiarrhythmic drugs, heart failure medications, implantable cardioverter-defibrillators and combined endocardial/epicardial catheter ablation. Ablation has emerged as the treatment of choice for recurrent ventricular arrhythmias in ACM. This state-of-the-art review outlines the pathogenesis, diagnosis and treatment of ACM in the contemporary era.

Keywords Arrhythmogenic • Cardiomyopathy • ARVC • ALVC • Sudden cardiac death • Ventricular arrhythmia

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitors; ACM, arrhythmogenic cardiomyopathy; ARB, angiotensin II receptor blockers; ARVC, arrhythmogenic right ventricular cardiomyopathy; CA, catheter ablation; EF, ejection fraction; HF, heart failure; ICD, implanted cardioverter defibrillator; LB, left bundle; LGE, late gadolinium enhancement; LV, left ventricle; mV, millivolts; RB, right bundle; RBBB, right bundle branch block; RV, right ventricle; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; TFC, Taskforce criteria; TWI, T wave inversions; VA, ventricular arrhythmia; VT, ventricular tachycardia; VF, ventricular fibrillation

*Corresponding author at: Associate Professor Saurabh Kumar, Cardiology Department, Westmead Hospital, Westmead Applied Research Centre, University of Sydney, NSW, Australia; Corner Hawkesbury and Darcy Roads, Westmead, New South Wales – 2145; Tel.: +612 8890 8981; Fax: +612 8890 8323., Email: Saurabh.kumar@health.nsw.gov.au

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy that predominantly affects the right ventricle (RV). Given the recent recognition of left dominant and biventricular forms, the term ARVC has been replaced by arrhythmogenic cardiomyopathy (ACM), which encompasses all the phenotypical expressions of the disease [1]. Pathologically, there is progressive myocyte loss with fibrofatty myocardial infiltration, leading to clinical manifestations of ventricular arrhythmias (VA), impaired ventricular systolic function, heart failure (HF) and sudden cardiac death (SCD). Mutation in genes that encode proteins of the intercalated disc, the desmosome as well as non-desmosomal mutations in calcium regulating genes, growth factors and other structural genes underlie the genetic basis of the disease [1–3]. A genetic mutation cannot be identified in up to 50% of ACM patients. However, disease modifiers such as excessive exercise, may play a critical role in phenotypic expression in patients who demonstrate genetic mutations. Indeed, as only 50% of patients have a genetically confirmed disease, it is plausible that the disease may be genetically enabled with other triggers (e.g. inflammation, excessive exercise) perpetuating phenotypic expression, such as viral inflammation and intense exercise [2]. The diagnosis of ACM is difficult due to absence of specific unique diagnostic criteria, its variable expressivity, and its incomplete penetrance in relatives. Taskforce criteria (TFC) incorporating abnormalities detected in cardiac structure (via imaging), histology (via tissue biopsy), myocardial depolarisation and repolarisation (via 12-lead electrocardiograph [ECG]), presence of ventricular arrhythmias, and familial genetic evaluation can increase the specificity of the diagnosis, but it still lacks sensitivity, especially in the early stages of the disease [4]. For the same reason, risk stratification of a proband or asymptomatic relatives is therefore challenging. Left dominant ACM does not follow classic TFC and diagnosis may be entirely genetically mediated. Emerging diagnostic tools in imaging, non-invasive and invasive cardiac mapping, and high throughput genetic sequencing may increase diagnostic yield for early stage disease [1]. Once a symptomatic patient is identified, advocated treatment includes restriction of vigorous or high-intensity exercise, beta blockade, heart failure treatment, prevention of SCD via implantable cardioverter defibrillator (ICD), treatment of recurrent VT with anti-arrhythmic drugs (AAD) with endocardial ± epicardial catheter ablation, and familial evaluation [4]. Although disease progression is thought to occur, the concept lacks clinical evidence as most patients likely do not progress rapidly, and scar progression is thought not to occur [5]. As recently recognised, a combination of endocardial and epicardial ablation in experienced hands, with abolition of all inducible VTs and extensive substrate endo/epicardial modification is a safe and highly effective approach in achieving long-term VT-free survival with limited need for AADs, particularly amiodarone in most patients [6–9]. In particular, as scar progression is thought to be unlikely, this may additionally contribute to the therapeutic efficacy of catheter ablation [5]. The purpose of this state-of-the-art review is to summarise our current understanding and treatment paradigm for ACM.

Epidemiology

The population prevalence of ACM is 1:5,000, however it is reported to be 1:2,000 in some European countries, such as Germany and Italy [2]. In Italy, ACM is the leading cause of death in young athletes, though this is not consistent in other countries, such as the United States or Australia [10]. The prevalence of ACM suggests it is a disease of post-pubertal adults (majority diagnosed at 20–50 years of age; however, age at diagnosis can be highly variable (12–63 years in one study) [11], and diagnosis in the elderly has been recognised. Phenotypic expression is more common in males (2:3–1) [12]; putative reasons include influence of sex hormones on mechanisms involved in the phenotypic expression of disease, or sex-based difference in exercise intensity as a disease modifier [2,3].

Pathogenesis

Progressive loss of ventricular myocardium and fibrofatty infiltration are distinct pathophysiologic features of ACM. Fibro-fatty infiltration has an epicardial to endocardial progression [3]. In its classic sense, ACM involves the RV (right-dominant ACM) with fibrofatty infiltration leading to wall thinning, regional dilatation and aneurysm formation in the classic 'triangle of dysplasia' region bounded by the RV inflow tract (sub-tricuspid region), outflow tract (infundibular RV) and the RV apex, with septal sparing. Although the RV apex may become aneurysmal, there is rarely extensive scarring and, more importantly, VT from the RV apex is extremely rare[13]. Indeed, some studies show that the RV apex is rarely affected in RV ACM [13,14]. Left-dominant is a distinct form of ACM, characterised by the early left ventricular (LV) involvement where arrhythmias precede gross structural alterations, and when global RV function is preserved [2]. Biventricular ACM is characterised by early involvement of both ventricles with disease progression characterised by systolic impairment and biventricular dilation, with clinical features of global congestive heart failure, and ventricular arrhythmias originating from either ventricle at an early stage [2]. Although LV dysfunction, left-sided abnormalities on cardiac magnetic resonance imaging (cMRI) and voltage abnormalities are common (30%) with left dominant or biventricular forms of ACM, LV-related VT is indeed rare, and experience with these subtypes of the disease is still limited—mainly because the diagnosis can no longer be based on TFC and, rather, relies on genetic diagnosis. Recently, it has been suggested that the basal posterolateral LV should be included within the 'triangle of dysplasia', reflecting left dominant or biventricular forms of ACM [15].

Arrhythmogenic cardiomyopathy is caused by mutations in genes that encode proteins of the intercalated disc. The majority (~80%) of the reported ACM-causing mutations are in desmosomal proteins; although non-desmosomal protein mutations have also been recently implicated [1]. Various types of mutations (missense, nonsense, splice site, frameshift and large deletions) are reported, and most are private mutations. Desmosomes provide cell-cell adhesion and play an important role in maintaining structural integrity of tissues subjected to mechanical stress such as the heart and skin. The desmosomal complex comprise of (a) the transmembrane proteins (cadherins) desmocollin-2 (*DSC2*) and desmoglein-2 (*DSG2*); (b) desmoplakin (*DSP*) and (c) the linker armadillo proteins plakoglobin (*JUP*) and plakophilin-2 (*PKP2*), which are mediators between the cadherins and *DSP* (Figure 1) [2].

Mutations in *PKP2*, *DSP*, and *DSG2* are identified in ~80% of confirmed pathogenic mutations. *PKP2* accounts for 36–92% of mutations identified in desmosomal genes [2]. Mutations in desmosomes change their 3D structure, their length and the total amount within the intercalated disc. This may trigger intercalated disc remodelling, altering mechanical stability and electrical coupling between cells, and altering nuclear signalling and transcriptional activity, particularly through pathways regulated by beta-catenin, resulting in increased expression of adipogenic and fibrogenic genes which contribute to the development of fibrofatty myocardial scarring [3]. Fibrofatty myocardial replacement leads to development of slow and circuitous conduction through channels of preserved myocardium within scar, providing the relevant electrophysiological substrate for re-entrant ventricular tachycardia (VT), with the mechanism resembling that of post-infarction VT [16].

Ventricular arrhythmia may also be attributed to a mechanism occurring at a molecular and cellular level. Desmosomes, sodium channels, and gap-junction proteins interact synergistically in a coordinated network of proteins at the intercalated disc, termed the connexome, that regulate adhesion, excitability, and myocyte coupling [3]. Loss of desmosomal protein expression within the connexome may lead to altered amplitude and kinetics of the sodium current, and reduction and restriction of connexin 43, a gap junction protein, contributing to ventricular arrhythmogenesis. In ACM, excessive physical exertion, which increases pressure, afterload and wall stress disproportionately to a greater extent in the RV than the LV, may aggravate mechanical uncoupling of myocytes, leading to disease progression and malignant VAs [1–3].

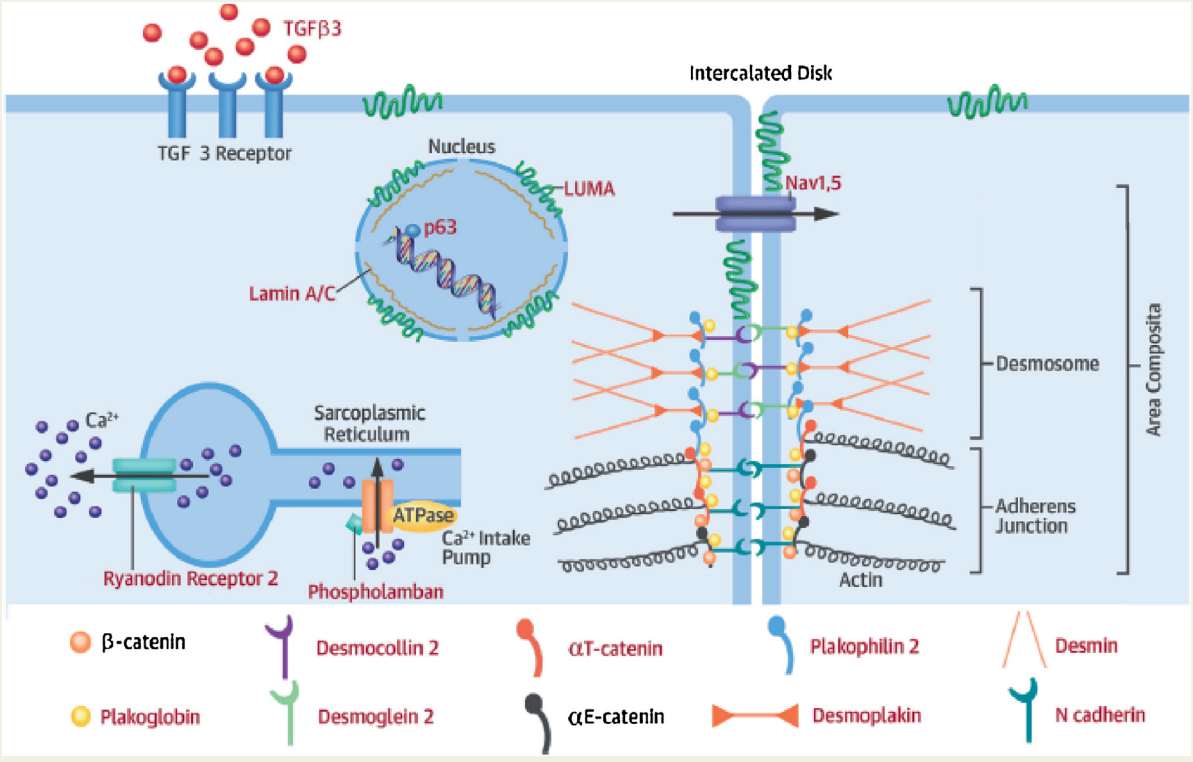

Figure 1 Genetic mutations associated with ACM.
Abbreviations: Plakophilin-2 (PKP2); Desmoglein-2 (DSG2); Desmoplakin (DSP); Desmocollin-2 (DSC2); Plakoglobin (JUP); Alpha-T-catenin (CTNNA3); N-cadherin (CDH2); LUMA (TMEM43); Lamin A/C (LMNA); Desmin (DES); titin (TTN); Phospholamban (PLN); Ryanodine receptor type 2 (RYR2); Nav1.5 (SNC5A); P63 (TP63); TGF-beta 3 (TGFB3). Reproduced, with permissions from Gandjbakhch et al. [1] (license no. 4444320976348).

Genetics

Arrhythmogenic cardiomyopathy is usually of autosomal dominant inheritance. Desmosomal mutations classically exhibit low penetrance, as only one third of mutation-carrying relatives fulfil Taskforce criteria [17]. Recessive mutations lead to severe forms of ACM, such as Naxos disease and Carvajal syndrome. Naxos disease is a plakoglobin mutation (*JUP*) leading to phenotypic co-segregation of abnormalities of the heart (ACM), skin (palmoplantar keratosis), and hair (woolly hair). A recessive mutation in the *DSP* gene can cause another cardio-cutaneous syndrome, the Carvajal syndrome [3]. Gene testing reveals a pathogenic mutation in 50–60% of ACM patients. To date, 16 genes have been associated with ACM [1].

PKP2 mutations account for the vast majority of ACM, leading to the conventional RV dominant ACM phenotype. *DSP* mutations may have phenotypic expression with either RV dominant, isolated LV or biventricular ACM with a proclivity to a more severe phenotype characterised by high risk of VA, SCD, high level of LV involvement, and cardiocutaneous syndromes. Truncating *DSP* mutations are classically associated with higher risk of end stage heart failure (HF) [1]. *DSG2* mutation carriers are characterised by frequent biventricular involvement (20–50%), and a possibly higher risk of end stage HF and transplantation than *PKP2* carriers. Mutations in *JUP* and *DSP* present with cardiocutaneous manifestations and frequent right or biventricular ACM phenotypes. In up to 20% of ACM patients, compound or digenic heterozygosity may be present. Along with homozygous mutations, patients with a complex genetic status present with a more severe phenotype, with higher penetrance, earlier onset VA, higher SCD risk, more frequent LV involvement and higher risk of HF [1].

A number of non-desmosomal genes have been associated with the ACM phenotype. These are worthy of discussion due to their classic presentation, geographical predilection and overlapping phenotypes with cardiomyopathic or channelopathic phenotypes [1]. Briefly, these include (a) mutations in *CTNNA3* (coding for alpha-T-catenin) reported in Italian families; (b) *CDH2* (coding for N-cadherin) reported in South African families; (c) *TMEM43* (founder mutation p.S358L from Newfoundland, Canada encoding the nuclear envelope protein LUMA) which has high penetrance, high risk of SCD, heart failure (especially in men) with poor R-wave progression and frequent LV dilatation, in whom prophylactic ICD implantation should be strongly considered; (d) mutations in *LMNA* (encoding the nuclear envelope protein Lamin) and *DES* (encoding the intermediate filament desmin) presenting with biventricular cardiomyopathy or right dominant ACM, with frequent conduction system disease (sinus and/or AV nodal dysfunction), frequent VA, and/or muscular dystrophy and severe HF; (e) mutations in *PLN* (founder mutation p.R14del, particularly in the Dutch population encoding the calcium regulatory protein phospholamban) presenting as arrhythmogenic biventricular or right dominant ACM; (f) *SCN5A* mutations (encoding the sodium channel NaV1.5) presenting with a ACM phenotype with prolonged QRS duration generally with no QT or Brugada pattern on ECG, but overlapping phenotype between Brugada and right dominant ACM has been reported; and (g) mutations in *RYR2* (coding for classic catecholaminergic polymorphic ventricular tachycardia [CPVT]) in patients with exercise-induced polymorphic ventricular arrhythmias and RV cardiomyopathy in a borderline phenotype with CPVT [1].

Clinical Presentation

Classical right-sided ACM or ARVC can be thought of as occurring in four distinct phases. Initially, there is an asymptomatic or concealed phase characterised by minimal or no structural abnormalities, whereby patients are often undiagnosed, but SCD may be the first presentation of the disease. The electrical phase is the most common clinical presentation with palpitations, exertional syncope in a young adult (age, 20–40 years) with T wave inversion in the right precordial leads (V_1-V_4), VA with a LB pattern in lead V_1 and right ventricular structural abnormalities on imaging (Figure 2). Ventricular arrhythmias are characteristically triggered by adrenergic stimulation, and can range from frequent premature ventricular contractions, sustained monomorphic VT or ventricular fibrillation. Imaging reveals global dilatation and dysfunction and regional wall-motion abnormalities such as systolic akinesia or dyskinesia or diastolic bulging. Ventricular tachycardia with a left bundle (LB) pattern in lead V_1 is the classic pattern of VT seen, and this can be mistaken for the more benign VT originating from the RV outflow tract (RVOT), which has an inferior axis in the limb leads. The presence of a LB superior axis, should raise suspicion of right dominant ACM. Ventricular tachycardias with a RB morphology can be the first presentation of left dominant or biventricular ACM. End stage RV and/or biventricular failure may develop with long standing disease. As mentioned previously, *DSP* mutations may present with a severe left dominant ACM which may exceed or precede any RV abnormalities. Biventricular and LV dominant ACM are again characterised by a significant risk of SCD and the same clinical symptoms. In biventricular variant ACM, there is involvement of both ventricles at the same time. Typically, regional RV dysfunction occurs along with apical-lateral and basal inferior fibrofatty infiltration in the LV, without reduced LV systolic function [18,19]. Patients with LV dominant ACM have only mild RV abnormalities and show regional LV impairment with mid-wall or subepicardial fibrofatty infiltration [18,19]. Premature ventricular complexes or sustained VT typically have a RBBB appearance, originating from the left ventricle [20]. Unexplained inferolateral T-wave inversion can be present. The LV dominant form of ACM is likely to be underrecognised or misdiagnosed, due to the lack of diagnostic criteria and because it can easily be mistaken for myocarditis or sarcoidosis [20].

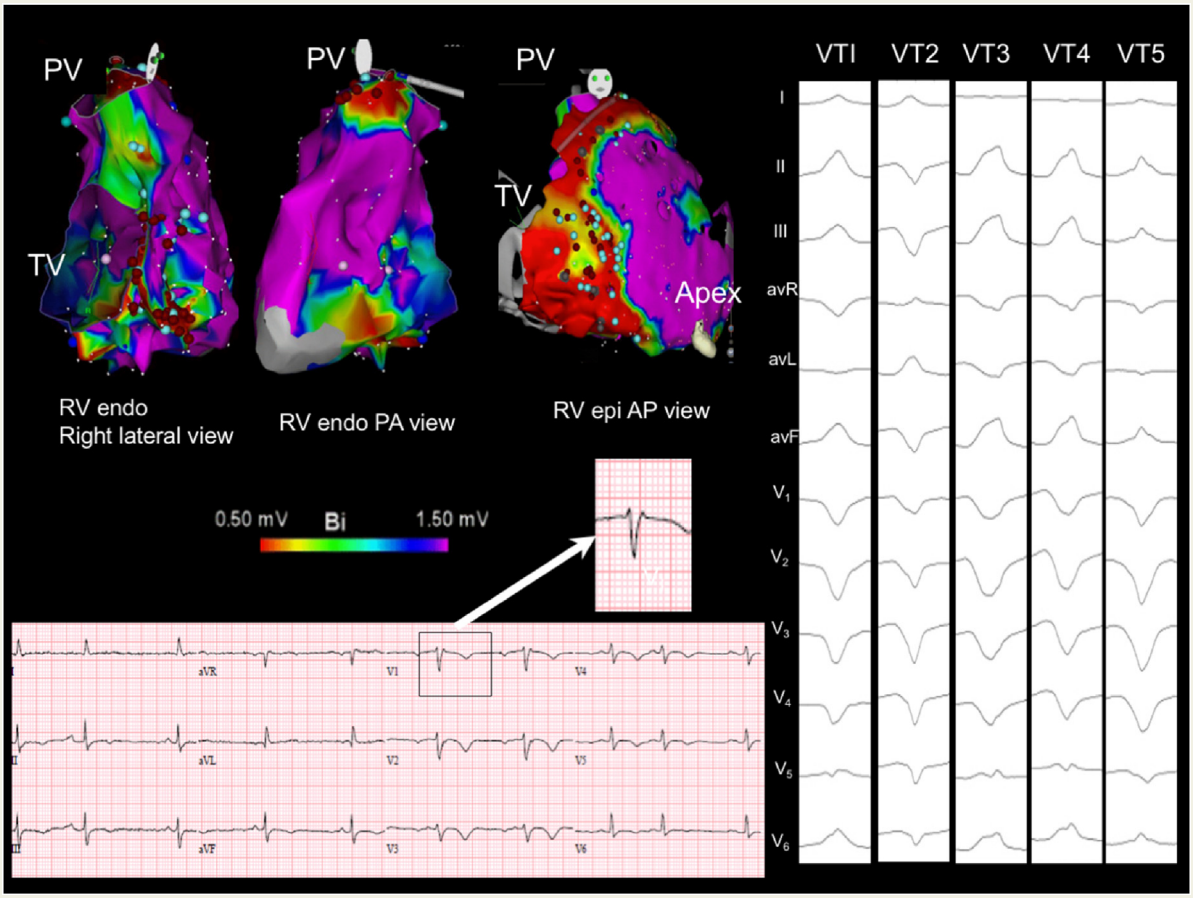

Figure 2 Intra-cardiac voltage mapping, 12-lead ECG and mapping characteristics of a patient with classic RV-ACM. Classic features of RV-ACM (arrhythmogenic right ventricular cardiomyopathy) in a patient with a PKP-2 mutation. Endocardial (endo) and epicardial (epi) intra-cardiac voltage mapping demonstrates low voltage scar (green, yellow, blue and red areas) affecting the RV outflow tract, peri-pulmonic and peri-tricuspid endocardial and epicardial RV. ECG demonstrates TWI V1-V6 and epsilon waves (inset). Multiple inducible VTs were present of LB inferior and superior axes (VT1-5).
Abbreviations: LB, left bundle; TWI, T wave inversions; RV, right ventricular; ECG, electrocardiograph; ACM, arrhythmogenic cardiomyopathy; VT, ventricular tachycardia

Diagnostic Tools

Despite our increasing knowledge about the disease, ACM still presents a significant diagnostic challenge. The concealed, asymptomatic phase of the disease, varying phenotypical expression, and in some cases, only subtle differences from other conditions such as Brugada syndrome, dilated cardiomyopathy, myocarditis, and cardiac sarcoid all play a part in this diagnostic challenge. Diagnostic challenges also include distinguishing right dominant ACM from an athlete's heart or benign RV outflow tract ectopy. Currently, diagnosis of ACM is based on information derived from six diagnostic categories (divided into major and minor subtypes within each category), constituting the revised 2010 Taskforce Criteria (TFC; Table 1) [4]. Categories include (i) global and/or regional myocardial dysfunction and structural abnormalities; (ii) histological characterisation; (iii) repolarisation abnormalities on 12-lead ECG; (iv) depolarisation abnormalities on 12-lead ECG; (v) ventricular arrhythmias and (vi) family history and genetics. A definite diagnosis can be made with two major criteria, one major and two minor criteria, or four minor criteria from different categories; 'borderline' diagnosis is made with one major and one minor criterion, or three minor criteria and a 'possible' diagnosis is made if one major criterion or two minor criteria are present. A higher ACM risk score (two points for major, one point for minor) correlates with higher frequency of major adverse events such cardiovascular death, heart failure hospitalisation, and sustained VA [21]. Despite the classic TFC, other diagnostic tools, particularly additional analyses on 12-lead ECG, imaging, genetics and an use of electroanatomic voltage mapping, may aid diagnosis (Table 2) [1]. However, TFC and additional diagnostic tools do have limitations, particularly if patients present with the left dominant ACM. An important point to note is that left dominant and biventricular forms of the disease may not

Table 1 Taskforce Criteria for ARVC as published by Marcus et al. [4].

Criteria for diagnosis: definite diagnosis: Two major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: One major and 1 minor or 3 minor criteria from different categories; possible: One major or 2 minor criteria from different categories.

I. Global or regional dysfunction and structural alterations

Major *2D TTE*

Regional RV akinesia, dyskinesia or aneurysm and 1 of the following criteria (end diastole):

- PLAX RVOT ≥32 mm (PLAX/BSA] ≥19 mm/m^2)
- PSAX RVOT ≥36 mm (PSAX/BSA] ≥21 mm/m^2)
- or RV fractional area change ≤33%

CMR

Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and 1 of the following criteria (end diastole):

- RV end-diastolic volume/BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
- or RV ejection fraction ≤40%

RV Angiography

- Regional RV akinesia, dyskinesia or aneurysm

Minor *2D TTE*

Regional RV akinesia, or dyskinesia and 1 of the following criteria (end diastole):

- PLAX RVOT ≥29–31 mm ([PLAX/BSA] ≥16–18 mm/m^2)
- PSAX RVOT ≥32–35 mm ([PSAX/BSA] ≥18–20 mm/m^2)
- RV fractional area change >33–39%

CMR

Regional RV akinesia, dyskinesia or dyssynchronous RV contraction and 1 of the following criteria (end diastolic):

- RV end-diastolic volume/BSA ≥100–109 mL/m^2 (male) or ≥90–99 mL/m^2 (female) or RV ejection fraction >40–44%

II. Histological characterisation

Major Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium ≥1 sample, with or without fatty replacement

Minor Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall ≥1 sample, with or without fatty replacement

III. Repolarisation abnormalities

Major T-wave inversions V1–3 or beyond (in absence of complete RBBB)

Minor T-wave inversions V1–2 or V4–6 (in absence of complete RBBB)
T-wave inversions V1–4, if complete RBBB present

IV. Depolarisation abnormalities

Major Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in V1–3

Minor Signal-averaged ECG with late potentials (if QRS on standard surface ECG <110 ms)

V. Ventricular arrhythmias

Major Non-sustained or sustained ventricular tachycardia (VT) of LBBB morphology with superior axis

Minor Non-sustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis or of unknown axis
>500 VES per 24 h (Holter)

VI. Family History and genetics

Major ARVC/D in a first-degree relative who meets current Taskforce Criteria
ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
Identification of a pathogenic mutation categorised as associated with ARVC/D in index patient

Minor Suspected ARVC/D in a first-degree relative (current Taskforce criteria cannot be determined)
Premature SCD (<35 years of age) due to suspected ARVC/D in a first-degree relative
ARVC/D confirmed pathologically or by current Taskforce Criteria in second-degree relatives

Abbreviations: RVOT, right ventricular outflow tract; RV, right ventricular; 2D, two dimensional; TTE, transthoracic echocardiograph; CMR, cardiac magnetic resonance; RBBB, right bundle branch block; LBBB, left bundle branch block; ECG, electrocardiograph; ARVC, arrhythmogenic right ventricular cardiomyopathy; SCD, sudden cardiac death; ARVD, arrhythmogenic right ventricular dysplasia.

Table 2 **Emerging Diagnostic tools for ACM. Derived from Gandjbakhch et al. [1].**

ECG	Imaging	Ventricular Arrhythmias	Tissue Pathology	Genetics
QRS fragmentation	Hypertrophic trabecular or hyper-reflective moderator band	Morphology of VAs: QRSd lead I >120 ms, QRS notching, transition ≥V5	Voltage map guided biopsy	High-throughput sequencing and large panels of genes
V1V2V3 QRS duration ≥110 <ms	Decreased TAPSE and peak systolic RV annular velocity	VAs (PVC, NSVT, VT) originating from multiple RV sites		
V1 + V2 + V3/V4 + V5 + V6 widths ≥1.2	Intra-myocardial fat infiltration in the RV wall	VAs triggered by catecholaminergic stress		
V1V2V3 QRS width ≥25 ms of V6 (parietal block)	LGE of the RV wall	Low sub-epicardial voltage areas in the right ventricle		
S-wave upstroke ≥55 ms	Low peak systolic RV strain	Isoproterenol test		
QRS fragmentation	TTE speckle tracking	RV electroanatomic voltage map		
Inverted T waves in inferior leads (LV extension)	MRI feature tracking			
RBBB with R′/S ratio <1 in V1	MDCT and 4D-cine CT			

Abbreviations: TTE, transthoracic echocardiograph; RV, right ventricular; MRI, magnetic resonance imaging; MDCT, multi-dimensional computed tomography; CT, computed tomography; RBBB, right bundle branch block; LV, left ventricular; LGE, late gadolinium enhancement; VA, ventricular arrhythmia; TAPSE, tricuspid annular plane systolic excursion; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia

exhibit classic TFC and diagnosis may heavily rely on a pathogenic mutation combined with cMRI and voltage abnormalities.

Structural Abnormalities on Imaging

Non-invasive imaging (echo or cMRI) plays a key role in diagnosis of ACM. Major challenges with imaging are accurate detection of abnormities (which requires significant expertise) and in detection of early disease [1]. Diagnosis is made on visual assessment of RV segmental motion abnormalities (akinesia or dyskinesia or dyssynchronous RV contraction) which form a major criterion, and chamber dimension (RVOT dimension, which form another major criterion) and volume, RV fractional area or ejection fraction (extent of reduction determines whether it is a major or a minor criterion (Table 1)) [4]. Other imaging features suggestive of RV ACM include lower tricuspid annular plane systolic excursion and peak systolic RV annular velocity (in advanced RV ACM), and lower peak systolic strain and greater RV mechanical dispersion on speckle tracking echocardiography (which may be useful for early disease detection), which are less well validated (Table 2) [1].

Cardiac MRI is the gold standard for assessing ventricular volumes and regional function independent of geometric assumption, and with high intra-observer and interobserver reproducibility, and for exclusion of other RV ACM mimics. Whilst, initially, cMRI focussed on detection of fat and fibrosis (noted as late gadolinium enhancement [LGE]) as a diagnostic tool for RV ACM, this is technically difficult due to the thin RV wall in terms of the achievable spatial resolution of MRI, fat being a non-specific finding in ACM, and LGE being non-specific (also seen in myocarditis/sarcoidosis). Therefore, cMRI ACM diagnosis is based on demonstrating the consequence of fibrofatty RV replacement manifesting as static morphological abnormalities (aneurysm, bulging) and dynamic morphology (akinesia, dyskinesia, or asynchrony). When mutation-positive ACM patients are examined by cMRI, 96% reveal an abnormal RV with basal inferior RV and basal anterior RV dyskinesia the most prevalent (87–94% of patients); LV involvement (posterolateral LV) was seen in 52% of patients, therefore extending the classic 'triangle of dysplasia' to the LV [15]. A normal cMRI has excellent negative predictive value (99%) for adverse events, whereas an abnormal cMRI has poor predictive value for adverse events (21%); however multiple cumulative abnormalities (morphology, wall motion abnormalities, and fat/fibrosis) independently predicted adverse events [22]. Newer techniques such as regional strain abnormalities on feature-tracking MRI hold promise for early disease detection (Table 2).

ECG Changes

Resting 12-lead ECG is abnormal in most patients with ACM, reflecting progressive loss of RV subepicardial myocytes and

altered conduction; minor abnormalities are present in early stage disease which may progress over time. Electrocardiograph alterations depend on the extent and location of the disease and can be divided into repolarisation and depolarisation abnormalities:

(i) Repolarisation abnormalities: T-wave inversions (TWI) in the right precordial leads are present in up to 87% of adult patients with RV dominant ACM, are directly related to RV dilatation and may extend to the left precordium with time. Inferior lead TWI are related to LV dominant ACM. Notably up to 30% of patients with morphologic criteria for ACM will not have any ECG changes ('ECG concealed' form); this finding is supported by electroanatomic mapping studies showing that marked voltage abnormalities may exist without repolarisation changes on ECG [23]. Extent of TWI is related to the extent of low voltage scar on electroanatomic mapping. For example, TWI extending beyond V_3 is associated with larger endocardial and epicardial scar compared to TWI in V_1-V_3 [23].

(ii) Depolarisation abnormalities (QRS notching, wider QRS, larger S waves, epsilon waves, late potentials, and incomplete, complete or atypical right bundle branch block [RBBB]) correspond to the influence of RV scar on causing delayed RV activation [24]. Epsilon waves correspond to delayed epicardial perivalvular activation. Wider S wave duration reflects delayed endocardial activation in the perivalvular and RV infundibulum. A RBBB block reflects exit block out of the RB as a consequence of scar [24]. Downsloping elevated ST-segment pattern in V_1 and V_2 is associated with more advanced transmural RV disease [23].

Ventricular Arrhythmias

Typically, ACM manifests as re-entrant VT of LB morphology with superior axis; when LB inferior axis forms occur, differentiation from benign RVOT VT is challenging. A point scoring system based on sinus rhythm anterior TWI V_1-V_3 (three points), QRS duration in lead I $\geq$120 ms (two points), notching on any QRS complex (two points), and QRS transition in V_5 or later (one point) is useful for differentiating ACM from benign RVOT VT. A score $\geq$5 is able to distinguish between the conditions with a sensitivity of 84%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 91% [25]. Polymorphic premature ventricular contractions with $\geq$1 couplet, or sustained or non-sustained VT with a LB morphology (excluding an RVOT tachycardia), in response to a continuous infusion of isoproterenol (45 μg/min) for 3 minutes is a useful test for differentiating RV ACM from non ACM-related VT with a sensitivity, specificity, positive, and negative predictive values of 91.4%, 88.9%, 43.2%, and 99.1%, respectively [26].

Biopsy

The diagnostic contribution of endomyocardial biopsy for ACM is generally low due to the patchy nature of fibrofatty replacement (yielding false negative results), subepicardial location of early disease and septal sparing (where the biopsy is generally directed) [1,2]. However, it is useful in excluding other diseases (e.g. sarcoidosis, myocarditis).

Genetic Testing

Guidelines recommend that genetic testing be performed to confirm ACM in patients fulfilling TFC; may be considered in patients with possible ACM (one major or two minor criteria) and in family members and appropriate relatives following the identification of the ACM-causative mutation in an index case. It is not recommended in patients with only a single minor TFC [27]. Genotype/phenotype correlations can be useful for prognostication of future risk of SCD or HF. A classic example is this the *TMEM43* p.S358L (Newfoundland) mutation, which is a fully penetrant mutation with a high risk of lethal VAs, especially in males, which may prompt early prophylactic ICD mutation [2]. Whilst testing for desmosomal mutations will explain the majority of classic RV ACM, the presence of severe or biventricular presentation, or atypical concurrent features (conduction disturbances, early atrial arrhythmias, subclinical or clinical muscular dystrophy, polymorphic VA, LV VA) should prompt search for non-desmosomal gene mutations and lead to broader genetic screening [1]. Due to low penetrance and variable expressivity, clinical diagnosis of relatives is challenging. Moreover, relatives demonstrate age-dependent phenotypic expression such that phenotypically negative relatives can develop symptoms and present years after initial screening [28,29]. Identification of a genetic mutation in the proband with ACM is critical, to allow identification of relatives at risk of developing or transmitting the disease and to facilitate genetic counselling. However, testing can be negative in up to 50% of ACM. Therefore, ***a negative gene test does not exclude ACM***. Repeated phenotypic screening of asymptomatic relatives is recommended, regardless of genotype status, as late expression of disease is not rare [29]. Advances in genetics such as newer throughput genetic sequencing tools (e.g. whole exome sequencing, whole genome sequencing, or targeted capture sequencing), with integration of global integration of large databases and the development of new bioinformatics tools may result in increased diagnostic yield of genetic testing and better understanding of disease pathogenesis.

Voltage Mapping

Although not included in the TFC, there is some evidence that high density endocardial voltage mapping may aid the diagnosis and risk stratification of RV ACM [30–33]. Late gadolinium enhancement on cMRI may miss small scars; indeed one study showed that mapping may be more sensitive than LGE in detecting scars, especially small scars that occupy <20% of the RV area [31]. Mapping may also aid risk stratification. Demonstration and quantification of bipolar RV scar area, and extent of scar-related fractionated electrogram may predict subsequent arrhythmic events [31,32]. However, voltage mapping is invasive, expensive, and

highly operator dependent. Interpretation as low voltage, due to suboptimal contact, may lead to misdiagnosis of scar, and is thus not routinely recommended in the diagnosis of ARVC.

Risk Stratification

The mechanism of SCD in ACM is sustained VT or VF, and may be the first presentation of disease. Real world estimates suggest that overall mortality in ACM is likely <1% per year; higher rates have been reported by tertiary referral centres (up to 3.6%/year) who may have the highest risk patients [34]. A recent meta-analysis reported arrhythmic events from 45 published studies (median 70 patients, median follow-up 5 years). Arrhythmic events occurred in 10.6%/year in patients with definite ACM, 10.0%/year in patients with borderline ACM, and 3.7%/year with mutation carriers [35] Prior cardiac arrest and sustained VT are thought to be the highest risk predictors, along with unexplained syncope, non-sustained VT and severe RV and LV dysfunction [3,34,35]. Other predictors of VA appear to be population dependent: male gender, T wave inversion in lead $>V_3$, RV dysfunction and prior non-sustained VT/VF were consistently predictive in patients with definite ACM. In borderline ACM, additional predictors were inducibility during electrophysiology study and strenuous exercise; in mutation carriers, ventricular ectopy, multiple pathogenic mutations, LV dysfunction and pre-syncope were predictors [35]. Other predictors identified are young age at time of diagnosis, extent of scar on electroanatomic mapping, low QRS amplitude and extent of QRS fragmentation [34]. A useful risk stratification schema is shown in Figure 3 [3].

Treatment

General Principles

Treatment of ACM has the following goals: (i) reduction of arrhythmic and heart-failure related death; (ii) prevention of disease progression that leads to RV, LV or biventricular heart failure; (iii) improvement of quality of life by reducing symptomatic arrhythmic events (palpitations, defibrillator therapies); and, (iv) identification of at-risk individuals in families and prevention of events in high risk individuals [34].

Treatment strategies include lifestyle changes, pharmacological treatment, catheter ablation, ICD, and heart transplantation.

Non-Ablative Approaches

Exercise Restriction

There is strong evidence that intense exercise in ACM patients leads to markedly increased risk of SCD and disease progression. Disease progression is thought to be related to repeated mechanical stress from exercise that may accelerate myocyte cell death due to defective myocyte cell-cell adhesion [34]. Guidelines recommend cessation of competitive and endurance sports in patients with definite ACM (Class I) with the possible exception of recreational low-intensity sports (Class IIa). Restriction from competitive sports may be considered in phenotype-negative family members with a known pathogenic mutation (IIa) or an unknown genotype (IIb) [34]. In general, patients are encouraged to refrain from vigorous high intensity exercise, but up to modest exercise is probably reasonable.

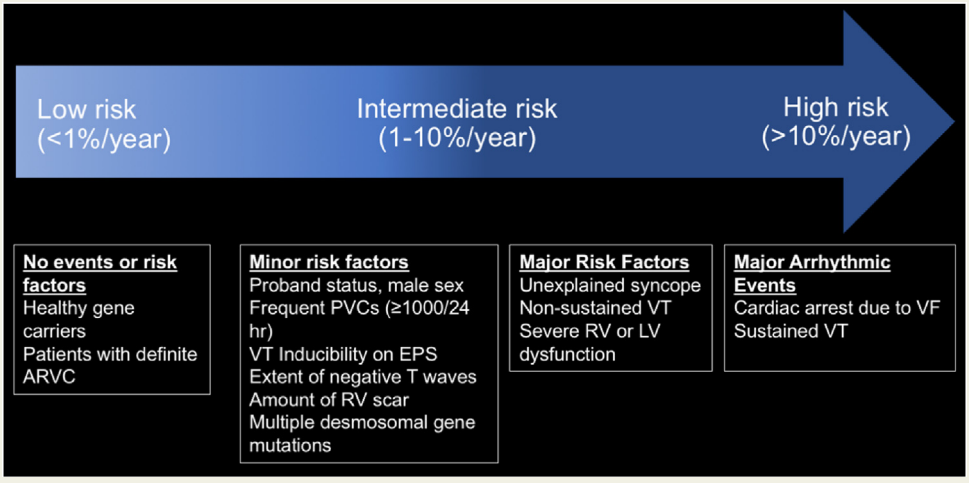

Figure 3 Risk Stratification for ACM.
Patients can be broadly classified into those with high, intermediate and low risk for recurrent VA, to help guide decision for ICD implantation. Derived from Corrado et al. [3].
Abbreviations: ACM, arrhythmogenic cardiomyopathy; VA, ventricular arrhythmia; ICD, implanted cardioverter defibrillator.

Beta Blockers

As VA in ACM are related to adrenergic stress, ß-blockers are recommended for patients with recurrent VT and in patients with supraventricular or atrial arrhythmias (Class I). Prophylactic use in asymptomatic patients for avoiding disease progression is not strong (Class IIa) and is not recommended in healthy gene carriers (Class IIb) [34].

Anti-Arrhythmic Drugs

Given the efficacy of catheter ablation for recurrent VA, the role of anti-arrhythmic agents should be increasingly thought of as adjunctive therapy. Generally, given the young age of patients with ACM, high frequency of arrhythmic events, toxicity profile and poor tolerance of these drugs, they are likely temporising agents to suppress symptoms related to frequent ventricular ectopy, or appropriate defibrillator discharges. No randomised trial data comparing drugs vs. ablation in ACM exist, but clinical experience suggests that breakthrough VA is likely to occurs despite adequate drug therapy. Amiodarone and sotalol are generally used for arrhythmia suppression, though neither should be used prophylactically [34].

Heart Failure Treatment

If RV or LV failure develops, standard drug therapy with angiotensin-converting-enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), β-blockers, and diuretics is recommended (Class I). Prophylactic ACE-I or ARB may be recommended for asymptomatic RV and LV dysfunction (Class IIb) [34].

Implanted Cardioverter Defibrillator

Estimates suggest that 48–78% of ACM ICD patients receive appropriate therapy during a mean follow-up of 2–7 years. However, it is notable that lead-related complications and inappropriate ICD therapies occur between 3.7–4.4%/year. Therefore, a decision for ICD implant should be made after careful risk/benefit assessment [34]. High risk patients are anticipated to have an arrhythmic event rate of >10%/year (sustained VA, resuscitated cardiac arrest, and patients with asymptomatic severe RV dysfunction [RV fractional area change ≤17% or RV ejection fraction, EF ≤35%] or LV dysfunction (LVEF ≤35%) should receive an ICD). Low risk patients such as probands and relatives without risk factors as well as healthy gene carriers should not receive an ICD.[34] The decision for prophylactic ICD implantation in the intermediate risk group is more difficult. By expert consensus, syncope, non-sustained VT, moderate RV dysfunction (RV fractional area change between 17–24% or RV EF 36-40%), or LV dysfunction (LV EF 36–45%) are 'major' risk factors that probably justify a prophylactic ICD. Other risk factors are considered insufficiently strong to justify prophylactic ICD, and an individualised decision should be made (Figure 3) [34].

Catheter Ablation Of ACM

In ACM, fibrofatty myocardial infiltration supports scar-related macro-re-entrant VT, akin to that observed in post-infarction VT, which is suitable for mapping and interruption by catheter ablation (CA) [6–9,14,16,36–38]. Whilst, initially, CA was considered as a palliative treatment for VT in ACM, a number of factors now support ***CA as the treatment of choice***. The disappointing early results of CA (VT recurrence of up to 91% in 3-year follow-up), were predominantly based on endocardial-only approaches to VT [37,38]. Anti-arrhythmic efficacy for VT in ACM is poor and drugs are poorly tolerated. Moreover, advances in our understanding of disease pathogenesis, appreciation of the role of epicardial ablation and advances in gaining epicardial access, high density mapping and ablation technologies have made CA a safer and more efficacious procedure for ACM. Combined endocardial-epicardial ablation, elimination of all inducible VTs, and modification of both endocardial and epicardial substrate leads to improved long-term VT-free survival with minimal requirement for anti-arrhythmic drugs, especially amiodarone, in most patients [7–9]. In a recent study of 62 consecutive patients with ACM and recurrent VT undergoing catheter ablation with a minimum follow-up of 1 year, long-term freedom from VT was 71% at 56 ± 44 months after the last ablation; only 9% of patients experienced a single VT episode after ablation. Endocardial and epicardial ablation was performed in 63% of patients. Before ablation, 87% of patients had failed a mean of 2.4 antiarrhythmic drugs, including amiodarone in 47% of patients. At last follow-up after ablation, 64% of patients were on a ß-blocker or no treatment, and only two patients were on amiodarone for a short time as a bridge to cardiac transplant for refractory right heart failure [9].

Pre-procedural imaging such as computed tomography (CT) or MRI may aid substrate identification (via LGE on cMRI, especially in LV dominant ACM), identification of fibrofatty infiltration (via contrast-enhanced multi-detector computed tomography) and direct visualisation of the coronary arteries for avoidance during epicardial ablation [39,40]. General anaesthesia is preferred due to anticipated long procedure duration and need for epicardial access. Real time image-integration with intra-cardiac echo and 3D mapping (CARTOSOUND, Biosense Webster, La Jolla, CA, USA) allows complete reconstruction of endocardial and epicardial geometry and identification and delineation of endocavitary structures even before catheter mapping begins. It also facilitates tissue contact, and monitoring for complications. Epicardial access may be obtained at the outset, or after endocardial mapping, although up-front access is the preferred option. The needle-in-needle technique of telescoping a small 21 gauge (G) micro-puncture needle that gains access to the pericardial space over a larger 18G Cook needle for stability may improve safety of access by reducing the rate of pericardial bleeding [41]. Due to a dilated RV, a posterior approach is preferred due to risks associated with an anterior needle entry.

Induction of VT is generally performed first using programmed ventricular stimulation with a drive train of 350–400 ms, and 1–4 extra-stimuli introduced at progressively shorter coupling intervals until they do not capture the

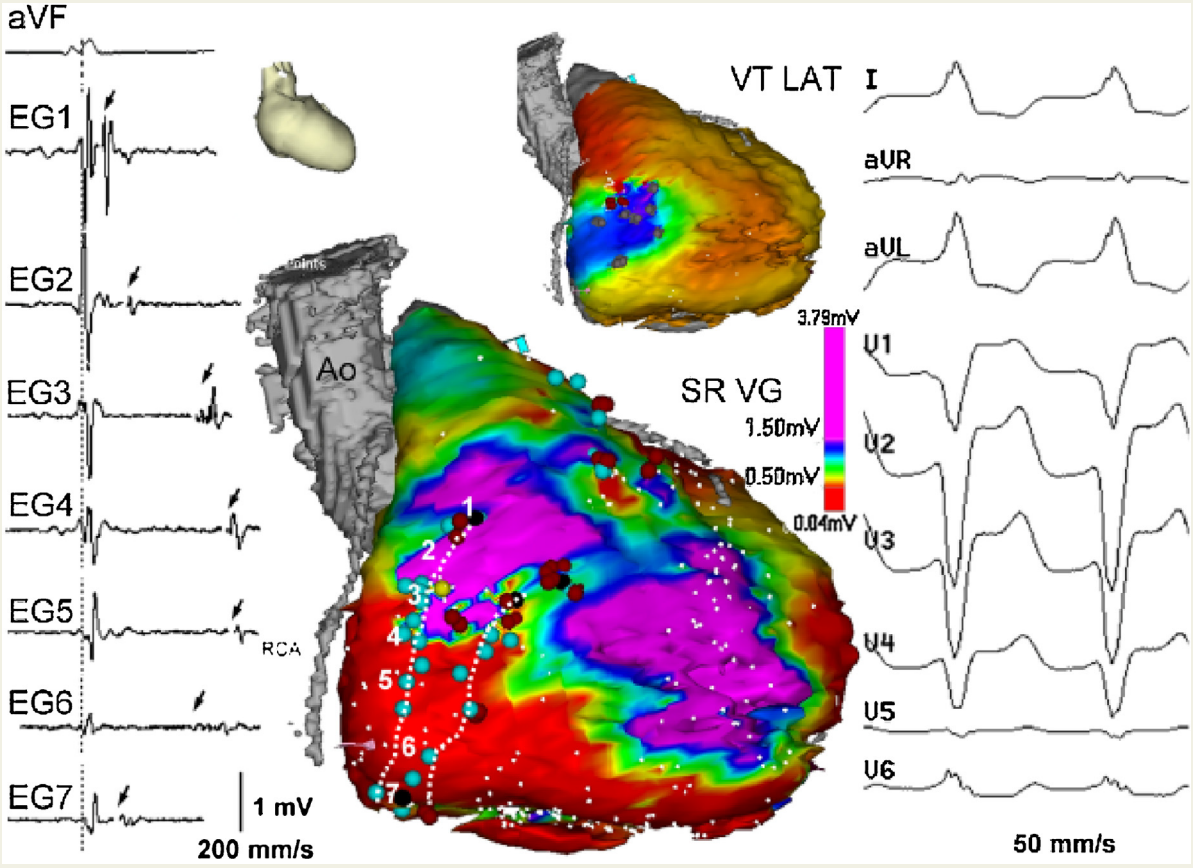

Figure 4 Identifying conducting channels during substrate mapping.
Epicardial voltage map (bottom, larger heart model) of a patient with RV ACM. Dotted lines represent a conducting channel identified during substrate mapping in sinus rhythm with red areas representing dense scar, purple areas representing normal voltage and blue/green/yellow areas representing the border zone between scar and normal voltage. In sinus rhythm, epicardial isolated late potentials (left panel) are tracked (arrows) showing early-to-late, to even later, activation followed by convergence to progressively earlier activation relative to the tall electrogram (EG). This represents signals recorded along a conducting channel with EG1-7 correlating with sites marked 1-7 on the voltage map. VT was induced (right panel) and activation map (small heart model at top of figure) showed that the VT exit site (converge of red, yellow, and blue signals) was at the top of the channel identified during sinus rhythm (yellow dot on the large heart model). Ablation here abolished the induced VT. Derived from Fernandez-Armenta et al, with permissions [14] (license number 4444331076595).
Abbreviations: EG, electrogram; LAT, local activation time; Ao, aorta; VT, ventricular tachycardia

myocardium (refractoriness). This allows confirmation of the diagnosis of VT, and establishment of endpoints and to facilitate ablation targets. Some groups do not routinely perform VT induction, instead using high density substrate mapping for scar channel identification and abolishment of substrate as the primary endpoint with at least equivalent outcomes compared with routine induction [14,42]. A number of mapping approaches are feasible: Activation mapping where the entire VT circuit is mapped whilst the patient remains in sustained VT during the procedure, with the intention of interrupting the re-entrant VT within a critical area of slowed conduction (the ''diastolic isthmus''); and, entrainment mapping, where pacing manoeuvres are performed to determine the critical area of slowed conduction through the circuit, which is used to complement activation mapping and to identify a small region serving as the ''critical isthmus'' where energy can be delivered to interrupt the VT [16]. However, VTs in ACM may not be haemodynamically tolerated for sufficiently long periods under general anaesthesia to allow activation mapping. Inducibility may be unreliable, one VT may change to another, and sometimes no VT is inducible at the outset. These factors limit the utility of activation and entrainment mapping alone.

Due to the limitations outlined above, the most widely used method for VT ablation in ACM in the contemporary era is substrate mapping. Substrate mapping refers to identification of critical electrophysiologic substrate for VT in stable sinus or paced rhythm, using qualitative and

quantitative features of electrical signals recorded during intra-cardiac mapping. These components represent surviving myocytes within fibro-fatty infiltration that are capable of slow conduction that supports re-entry. Voltage mapping allows identification of scar versus normal tissue based on electrical signal amplitude (electrograms) recorded directly underneath a catheter roved within the heart (bipolar mapping with a mapping catheter). Areas of bipolar low voltage scar (<0.5 millivolts [mV]), scar border zone (0.5–1.5 mV) with normal tissue (>1.5 mV) are identified on a 3D reconstruction of RV or LV chamber geometry using a 3D mapping system (Figure 2, 4). These bipolar scar areas occur under the endocardial surface. Mid-myocardial or epicardial scar can be inferred indirectly using unipolar recordings using voltage cut-offs of 5.5 mV and 8.3 mV for the RV and LV, respectively [43,44]. Epicardial mapping follows the same strategy, however scar is defined as voltage <1.0 mV [45]. Qualitatively, abnormal electrograms represent areas of slow conduction, which may be critical components of one or more re-entrant VT circuits (Figure 4). Abnormal electrograms include fractionated potentials and late potentials (signals recorded after the end of the QRS complex) [46] which tend to cluster within scar or scar border zones, but may be evident within normal voltage tissue. High density mapping allows the conducting channels within scar that may support VT to be identified (Figure 4) [7]. Pace mapping is an additional technique that complements substrate mapping, and is used to localise VT isthmii [47]. A recorded 12-lead ECG of the induced VT is used as a reference. Pacing the heart within the scar, border zones, and/or at sites of fractionated or late potentials may produce a 12-lead ECG morphology that resembles the clinical or inducible VT(s). Sites where pacing has a delay, between the electrical stimulus and the QRS onset, suggests local slow conduction that may represent potential substrates for re-entrant VT [47].

After mapping data is collected, a number of ablation strategies are feasible: Targeting of fractionated and late potentials or other abnormal electrograms, and/or sites of long stimulus to QRS delays and/or conduction channels using linear or clustered lesions; linear lesions may be anchored to the valve annulus or normal myocardium. A similar strategy is used in the epicardium, taking care to avoid the coronary arteries (angiographic localisation) and the phrenic nerve (pace mapping to avoid targeting areas of phrenic nerve capture before ablation). Radiofrequency is the energy source applied, using irrigated tip catheters with power of 30–40 Watts for 30–60 seconds at each site. Ablation within 1 cm of an epicardial coronary is avoided during epicardial ablation. Extensive ablation may be necessary due to the thickened RV endocardium. Some VT circuits can be entirely constrained within the epicardial surface [48] and cannot be abolished with endocardial ablation alone, hence combined endocardial and epicardial ablation yields good outcomes [6–9]. Intra-pericardial steroids (triamcinolone) can be given to avoid pericarditis. Acute procedural success is assessed by repeating the same initial programmed ventricular stimulation. Inducibility of the clinical VT is deemed procedural failure, and complete non-inducibility of any VT deemed complete success, with abolition of the clinical VT with residual non-clinical VT deemed as incomplete success. This directly relates to future clinical outcome with best prognosis noted in those without any inducible VT. Non-invasive programmed stimulation performed through the ICD in the days following ablation may identify patients at high risk of recurrence that may need more extensive future ablation [49,50]. Generally, anti-arrhythmic drugs are discontinued after successful ablation, but ß-blockers may be continued as per general management guidelines [34].

Conclusions

Arrhythmogenic cardiomyopathy is a genetic form of progressive non-ischaemic cardiomyopathy characterised by fibrofatty replacement of the ventricular myocardium progressing from the epicardial to endocardial RV (right dominant ACM), LV (left dominant ACM) or both ventricles (biventricular ACM). ACM is inherited in an autosomal dominant fashion, but classic cardio-cutaneous forms are recognised. Fibrosis predisposes to slow conduction and ventricular arrhythmias which may precede overt structural change, predisposing to sudden death. Diagnosis can be challenging and should be made by contextualising systematic phenotyping data using the TFC. Newer imaging techniques such as strain imaging and cMRI may improve phenotypic detection of asymptomatic or minimal symptomatic patients. Genetic testing yields a pathogenic mutation in only 50% of patients, with *PKP2* being the most common mutation recognised. Classical genotype-phenotype correlation does exist, allowing early identification of the disease. Treatment goals are restriction of high intensity exercise, ß-blockade, assessing sudden death risk, risk stratification for ICD implantation for prevention of sudden death. Recurrent VT can be temporised with anti-arrhythmic drugs, although recent advances in catheter mapping and ablation mean that ablation is feasible, safe and effective, and is generally preferred over anti-arrhythmic drugs which tend to be poorly tolerated in this young population. Outcomes are optimised by combined endocardial and epicardial ablation approaches. Further advances in genomics may allow better understanding of the disease pathogenesis and progression.

Disclosures

No disclosures.

Acknowledgements

Dr. Della Bella is a Consultant for Abbott and Biosense, and has received research grants from Abbott, Biosense, and Boston Scientific; Dr Berruezo has received a research grant

from Biosense Webster. Dr. Kumar is supported by a NSW Health Early to Mid Career Fellowship, the Westmead Hospital Charitable Trust Grant, Sylvia and Charles Viertel Charitable Foundation Clinical Investigator Award.

References

[1] 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.
[2] Akdis D, Brunckhorst C, Duru F, Saguner AM. Arrhythmogenic cardiomyopathy: electrical and structural phenotypes. Arrhythm Electrophysiol Rev 2016;5:90–101.
[3] Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med 2017;376:61–72.
[4] Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–41.
[5] Riley MP, Zado E, Bala R, Callans DJ, Cooper J, Dixit S, et al. Lack of uniform progression of endocardial scar in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy and ventricular tachycardia. Circ Arrhythm Electrophysiol 2010;3:332–8.
[6] Bai R, Di Biase L, Shivkumar K, Mohanty P, Tung R, Santangeli P, et al. Ablation of ventricular arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy: arrhythmia-free survival after endo-epicardial substrate based mapping and ablation. Circ Arrhythm Electrophysiol 2011;4:478–85.
[7] Berruezo A, Fernandez-Armenta J, Mont L, Zeljko H, Andreu D, Herczku C, et al. Combined endocardial and epicardial catheter ablation in arrhythmogenic right ventricular dysplasia incorporating scar dechanneling technique. Circ Arrhythm Electrophysiol 2012;5:111–21.
[8] Kirubakaran S, Bisceglia C, Silberbauer J, Oloriz T, Santagostino G, Yamase M, et al. Characterization of the arrhythmogenic substrate in patients with arrhythmogenic right ventricular cardiomyopathy undergoing ventricular tachycardia ablation. Europace 2017;19:1049–62.
[9] Santangeli P, Zado ES, Supple GE, Haqqani HM, Garcia FC, Tschabrunn CM, et al. Long-term outcome with catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2015;8:1413–21.
[10] Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med 2016;374:2441–52.
[11] Marcus FI, Zareba W, Calkins H, Towbin JA, Basso C, Bluemke DA, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American multidisciplinary study. Heart Rhythm 2009;6:984–92.
[12] Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation 2005;112:3823–32.
[13] Marchlinski FE, Zado E, Dixit S, Gerstenfeld E, Callans DJ, Hsia H, et al. Electroanatomic substrate and outcome of catheter ablative therapy for ventricular tachycardia in setting of right ventricular cardiomyopathy. Circulation 2004;110:2293–8.
[14] Fernandez-Armenta J, Andreu D, Penela D, Trucco E, Cipolletta L, Arbelo E, et al. Sinus rhythm detection of conducting channels and ventricular tachycardia isthmus in arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm 2014;11:747–54.
[15] Te Riele ASJM, James CA, Philips B, Rastegar N, Bhonsale A, Groeneweg JA, et al. Mutation-positive arrhythmogenic right ventricular dysplasia/cardiomyopathy: the triangle of dysplasia displaced. J Cardiovasc Electrophysiol 2013;24:1311–20.
[16] Ellison KE, Friedman PL, Ganz LI, Stevenson WG. Entrainment mapping and radiofrequency catheter ablation of ventricular tachycardia in right ventricular dysplasia. J Am Coll Cardiol 1998;32:724–8.
[17] Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, 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;8:437–46.
[18] Dalal D, Tandri H, Judge DP, Amat N, Macedo R, Jain R, et al. Morphologic variants of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy a genetics-magnetic resonance imaging correlation study. J Am Coll Cardiol 2009;53:1289–99.
[19] Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 1997;30:1512–20.
[20] Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. J Am Coll Cardiol 2008;52:2175–87.
[21] Kikuchi N, Yumino D, Shiga T, Suzuki A, Hagiwara N. Long-term prognostic role of the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia. JACC Clin Electrophysiol 2016;2:107–15.
[22] Deac M, Alpendurada F, Fanaie F, Vimal R, Carpenter JP, Dawson A, et al. Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy. Int J Cardiol 2013;168:3514–21.
[23] Kubala M, Pathak RK, Xie S, Casado Arroyo R, Tschabrunn CM, Hayashi T, et al. Electrocardiographic repolarization abnormalities and electroanatomic substrate in arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2018;11:e005553.
[24] Tanawuttiwat T, Te Riele ASJM, Philips B, James CA, Murray B, Tichnell C, et al. Electroanatomic correlates of depolarization abnormalities in arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Cardiovasc Electrophysiol 2016;27:443–52.
[25] Hoffmayer KS, Bhave PD, Marcus GM, James CA, Tichnell C, Chopra N, et al. An electrocardiographic scoring system for distinguishing right ventricular outflow tract arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy from idiopathic ventricular tachycardia. Heart Rhythm 2013;10:477–82.
[26] Denis A, Sacher F, Derval N, Lim HS, Cochet H, Shah AJ, et al. Diagnostic value of isoproterenol testing in arrhythmogenic right ventricular cardiomyopathy. Circ: Arrhythmia Electrophysiol 2014;7:590–7.
[27] Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. 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;13:1077–109.
[28] te Riele AS, James CA, Groeneweg JA, Sawant AC, Kammers K, Murray B, et al. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Eur Heart J 2016;37:755–63.
[29] Bhonsale A, Te Riele A, Sawant AC, Groeneweg JA, James CA, Murray B, et al. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation. Heart Rhythm 2017;14:883–91.
[30] Corrado D, Basso C, Leoni L, Tokajuk B, Bauce B, Frigo G, et al. Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2005;111:3042–50.
[31] Santangeli P, Hamilton-Craig C, Dello Russo A, Pieroni M, Casella M, Pelargonio G, et al. Imaging of scar in patients with ventricular arrhythmias of right ventricular origin: cardiac magnetic resonance versus electroanatomic mapping. J Cardiovasc Electrophysiol 2011;22:1359–66.
[32] Migliore F, Zorzi A, Silvano M, Bevilacqua M, Leoni L, Marra MP, et al. Prognostic value of endocardial voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circ Arrhythm Electrophysiol 2013;6:167–76.
[33] Santangeli P, Dello Russo A, Pieroni M, Casella M, Di Biase L, Burkhardt JD, et al. Fragmented and delayed electrograms within fibrofatty scar predict arrhythmic events in arrhythmogenic right ventricular cardiomyopathy: results from a prospective risk stratification study. Heart Rhythm 2012;9:1200–6.
[34] Corrado D, Wichter T, Link MS, Hauer RN, Marchlinski FE, Anastasakis A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. Circulation 2015;132:441–53.
[35] Bosman LP, Sammani A, James CA, Cadrin-Tourigny J, Calkins H, van Tintelen JP, et al. Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. Heart Rhythm 2018;15:1097–107.
[36] Garcia FC, Bazan V, Zado ES, Ren JF, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2009;120:366–75.

[37] Dalal D, Jain R, Tandri H, Dong J, Eid SM, Prakasa K, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2007;50:432–40.
[38] Verma A, Kilicaslan F, Schweikert RA, Tomassoni G, Rossillo A, Marrouche NF, et al. Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia. Circulation 2005;111:3209–16.
[39] Komatsu Y, Jadidi A, Sacher F, Denis A, Daly M, Derval N, et al. Relationship between MDCT-imaged myocardial fat and ventricular tachycardia substrate in arrhythmogenic right ventricular cardiomyopathy. J Am Heart Assoc 2014;3.
[40] Xie S, Desjardins B, Kubala M, Liang J, Yang J, van der Geest RJ, et al. Association of regional epicardial right ventricular electrogram voltage amplitude and late gadolinium enhancement distribution on cardiac magnetic resonance in patients with arrhythmogenic right ventricular cardiomyopathy: implications for ventricular tachycardia ablation. Heart Rhythm 2018;15:987–93.
[41] Kumar S, Bazaz R, Barbhaiya CR, Enriquez AD, Helmbold AF, Chinitz JS, et al. "Needle-in-needle" epicardial access: preliminary observations with a modified technique for facilitating epicardial interventional procedures. Heart Rhythm 2015;12:1691–7.
[42] Fernandez-Armenta J, Penela D, Acosta J, Andreu D, Evertz R, Cabrera M, et al. Substrate modification or ventricular tachycardia induction, mapping, and ablation as the first step? A randomized study. Heart Rhythm 2016;13:1589–95.
[43] Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, et al. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2011;4:49–55.
[44] Polin GM, Haqqani H, Tzou W, Hutchinson MD, Garcia FC, Callans DJ, et al. Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm 2011;8:76–83.
[45] Cano O, Hutchinson M, Lin D, Garcia F, Zado E, Bala R, et al. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. J Am Coll Cardiol 2009;54:799–808.
[46] Vergara P, Trevisi N, Ricco A, Petracca F, Baratto F, Cireddu M, et al. Late potentials abolition as an additional technique for reduction of arrhythmia recurrence in scar related ventricular tachycardia ablation. J Cardiovasc Electrophysiol 2012;23:621–7.
[47] Stevenson WG, Sager PT, Natterson PD, Saxon LA, Middlekauff HR, Wiener I. Relation of pace mapping QRS configuration and conduction delay to ventricular tachycardia reentry circuits in human infarct scars. J Am Coll Cardiol 1995;26:481–8.
[48] Haqqani HM, Tschabrunn CM, Betensky BP, Lavi N, Tzou WS, Zado ES, et al. Layered activation of epicardial scar in arrhythmogenic right ventricular dysplasia: possible substrate for confined epicardial circuits. Circ Arrhythm Electrophysiol 2012;5:796–803.
[49] Frankel DS, Mountantonakis SE, Zado ES, Anter E, Bala R, Cooper JM, et al. Noninvasive programmed ventricular stimulation early after ventricular tachycardia ablation to predict risk of late recurrence. J Am Coll Cardiol 2012;59:1529–35.
[50] Oloriz T, Baratto F, Trevisi N, Barbaro M, Bisceglia C, D'Angelo G, et al. Defining the Outcome of Ventricular Tachycardia Ablation: Timing and Value of Programmed Ventricular Stimulation. Circ Arrhythm Electrophysiol 2018;11:e005602.