Published in final edited form as:

Eur J Heart Fail. 2019 August ; 21(8): 955–964. doi:10.1002/ejhf.1534.

Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report

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Abstract

It is 35 years since the first description of arrhythmogenic right ventricular cardiomyopathy (ARVC) and more than 20 years since the first reports establishing desmosomal gene mutations as a major cause of the disease. Early advances in the understanding of the clinical, pathological and genetic architecture of ARVC resulted in consensus diagnostic criteria, which proved to be sensitive but not entirely specific for the disease. In more recent years, clinical and genetic data from families and the recognition of a much broader spectrum of structural disorders affecting both ventricles and associated with a propensity to ventricular arrhythmia have raised many questions about pathogenesis, disease terminology and clinical management. In this paper, we present the conclusions of an expert round table that aimed to summarise the current state of the art in arrhythmogenic cardiomyopathies and to define future research priorities.

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Keywords

Arrhythmogenic cardiomyopathy; Arrhythmogenic right ventricular cardiomyopathy; Ventricular arrhythmias

Introduction

In recent years, the clinical paradigm of arrhythmogenic right ventricular cardiomyopathy (ARVC) has moved on from a focus on severe right ventricular disease and malignant arrhythmia to a broader disease spectrum that includes concealed or subclinical phenotypes and biventricular disease. This has led to the development of a new concept–arrhythmogenic cardiomyopathy (AC) – that embraces a confusing array of disease terms and quite different pathologies. In November 2017, a group of international experts met in Athens, Greece, to discuss current knowledge about ACs with the aim of defining future research priorities. The meeting format was that of a moderated round table discussion (edited highlights of which can be viewed at http://www.fondazione-menarini.it/Home/Eventi/International-Closed-Workshop-on-ArrhythmogenicCardiomyopathy/Presentazione). This document summarizes the content of the meeting. A brief summary of each section is presented in Table 1.

What is arrhythmogenic cardiomyopathy?

The term ‘arrhythmogenic cardiomyopathy’ is used to describe a family of diseases that feature structural myocardial abnormalities (identified by macroand microscopic pathological examination besides cardiac imaging) and ventricular arrhythmia. In Figure 1, we show how the most commonly used terms in the literature (including ARVC) can be organised by the patterns of ventricular involvement within the rubric of AC.[1–3] Inclusion of entities such as hypertrophic and restrictive cardiomyopathy is not considered appropriate as their aetiology and management rarely overlap with the conceptual model of AC as conceived in this paper.

Accepting that a precise definition for AC has yet to be agreed upon, its diagnosis should follow a systematic approach that builds on the existing ARVC concept. Fundamental aspects include the following:

- **i.** *Arrhythmia*: frequent ventricular ectopy, from either ventricle, sustained or non-sustained ventricular tachycardia, or unexplained cardiac arrest are essential manifestations of the AC phenotype.
- **ii.** *Electrical abnormalities*: in addition to the classical ECG changes of ARVC, other abnormalities such as conduction disease, atrial arrhythmia, small voltage complexes and the pattern of left ventricular disease provide diagnostic clues to specific aetiologies.
- **iii.** *Structural abnormalities*: abnormalities of myocardial structure and dysfunction on non-invasive imaging are important but not essential criteria for AC, whereas tissue characterisation with cardiac magnetic resonance imaging, and if

necessary nuclear imaging and cardiac histopathology, is essential for the definition of sub-phenotypes.

iv. *Heritability*: family history (including clinical evaluation of first-degree relatives and at least a three-generation pedigree) is one of the principal diagnostic tools in AC. Genetic analysis is central to the diagnosis in probands and defines carrier status in relatives. Family history of other relevant traits such as premature conduction disease or extra-cardiac manifestations (skin, hair and neuromuscular phenotypes) helps to orient and interpret diagnostic tests.

v. *Phenocopy exclusion*: in all cases of AC, it is important to exclude mimics of the AC phenotype such as congenital anomalies, pulmonary hypertension, cardiac sarcoidosis and myocarditis.

What is the genetic architecture of arrhythmogenic cardiomyopathy?

Pathogenic mutations in desmosomal genes (*JUP*, *DSP*, *PKP2*, *DSG2*, *DSC2*) account for disease in over 50% of patients with classical ARVC.[4–9] Non-desmosomal pathogenic variants are described in *DES*, *LMNA*, *SCN5A*, *CDH2*, *CTNNA3*, *FLNC*, *PLN*, *TGFB3*, *TMEM43*, *RYR2*, *TJP1* and *TTN*[10–21] and reports describe a disproportionately high burden of ventricular arrhythmia in dilated cardiomyopathy caused by pathogenic variants in *RBM20*, *TNNT2*, and *BAG3*.[22–24] The possible relation between the main causative genes and the relative involvement of the left and right ventricles are shown in Table 2.[4,6,8–16,19,25–31]

Despite the prominence given to gene mutations in the Task Force diagnostic criteria for ARVC, many pathogenic variants classified as ‘pathogenic’ or ‘likely pathogenic’ are also seen in people without AC. In part, this reflects the challenge of accurately classifying missense variants due to the limitations of current methods of variant calling (functional studies, in-silico methods, etc.). Nevertheless, even within affected families the penetrance of most pathogenic desmosome gene variants is relatively low (approximately 30%), suggesting that disease expression is influenced by other genetic or environmental factors.[32] For example, endurance athletes with desmosomal variants have earlier disease onset, are more likely to meet ARVC Task Force criteria, and have lower lifetime-free survival from ventricular tachycardia/fibrillation and heart failure.[33]

Many questions and challenges remain regarding the genetics of AC. In particular, the increasing number of variants identified by continuously evolving genomic methods has raised the need for more extensive and better curated controls. There is a growing focus on deep intronic variants that alter splicing in genes already known to be associated with the disorder and the use of approaches such as RNA sequencing or assessment of long non-coding RNAs that may improve diagnostic yield. The need for functional assays that can provide quantitative assessment of novel variants and their potential role in disease becomes ever more pressing.

What is the role of the desmosome in arrhythmogenic cardiomyopathy?

Arrhythmogenic cardiomyopathy is associated with mutations in desmosome genes, and thus it has been assumed that the inability to effectively withstand mechanical stress is a major contributing factor to disease pathogenesis. However, many other functions for desmosomes and their components are emerging and may turn out to have role in the pathogenesis of AC (Figure 2). Postnatally in vertebrates, an intermingling of desmosome and other junction components occurs, creating a specialised form of junctions called ‘area compositae’.[34] This mixed junction may provide additional strength to the junction by distributing intermediate filament connections throughout the junctional interface. For instance, desmosomes play critical roles in trafficking and stability of the gap junction protein connexin 43[35,36] and other membrane channels including Na_v 1.5.[37] Thus, impaired desmosome function also leads to loss of efficient electrical coupling and conduction that could be linked to arrhythmias. Desmosomes also help localize the actin-regulatory machinery including Rho-GTPases,[38] which might further impact the organisation and function of the adherens junctions associated actin cytoskeleton and contractile apparatus. Desmosome components also regulate multiple other signalling pathways including GSK3beta/Wnt,[39,40] p38/TGFbeta[41] and Ras/Erk2.[42] Coupling with these pathways regulates multiple endpoints in skin and heart, including cell fate, differentiation, and fibrotic gene expression.

The first genetic studies of AC arose from the study of autosomal recessive AC syndromes associated with a skin disease (palmoplantar keratoderma) and woolly hair.[4,5,42,43] Better understanding of desmosomal function and disease mechanisms in the skin from AC patients may provide insights into AC pathogenesis and potential therapeutic strategies. Further insights come from studying molecules that regulate desmosomes including the iRhom2/ADAM17 pathway that cleaves membrane bound cytokines, growth factors and desmoglein 2.[44–47] Also, there is emerging evidence of links between systemic inflammatory stress and perturbed desmosome function in both heart and skin.[48]

What is the role of inflammation in the pathogenesis of arrhythmogenic cardiomyopathy?

Evidence from autopsy and endomyocardial biopsy in classic ARVC suggests that cell death is largely the result of apoptosis.[49,50] The adipocytes seen on histology appear not to result from cardiomyocyte transdifferentiation,[51–54] but are instead derived from interstitial mesenchymal fibroblasts. Cardiomyocyte loss is usually patchy, but can rarely occur as acute segmental pathology with clinical manifestations of angina, ECG ST-segment elevation and release of troponin mimicking myocardial infarction.[54]

Autopsy studies show that myocardial inflammation in the form of T-cell infiltrates is present in approximately two-thirds of ARVC cases[53,55] (Figure 3); the absence of neutrophils rules out ischaemic injury. The search for cardiotropic viruses in the myocardium has yielded conflicting results[56,57] with adenovirus, cytomegalovirus, hepatitis C virus, parvovirus and even enterovirus present in some specimens. Whether viruses are by-standers or true pathogenetic viral particles remains an unsolved issue.

Immunohistochemistry has shown a reduced signal for plakoglobin at the intercalated disc,[58] but other studies indicate that a reduced desmosomal protein signal is found also in patients with giant cell myocarditis and sarcoidosis.[59] The latter is a peculiar form of chronic myocarditis that can mimic AC.[60]

It remains unclear if myocarditis in AC is a primary phenomenon or reactive to spontaneous cardiomyocyte death. The hypothesis that a genetically[61] vulnerable myocardium may predispose to myocarditis has been advanced[62] and local myocardial production of selected cytokines and alterations in the balance between circulating pro-inflammatory and anti-inflammatory cytokines in patients with AC has been demonstrated.[59] In one study, cytokines implicated in granulomatous inflammation promoted rapid intracellular translocation of junctional plakoglobin in cultured neonatal rat ventricular myocytes, suggesting that inflammatory mediators might play a role in AC, even in the absence of infiltrating inflammatory cells.[59] Furthermore, the increasing understanding of the interplay between immune response and exercise might provide further insights in the mechanisms of exercise promoted disease progression in AC.[61]

How can sudden cardiac death prediction be improved in arrhythmogenic cardiomyopathy?

Most evidence suggests that in AC caused by desmosomal mutations, the degree of structural remodelling is a key determinant of ventricular arrhythmia. Data on arrhythmia risk in non-desmosomal forms of AC are still emerging, but there are already compelling findings for some genetic subtypes. For example, registry data in AC caused by *LMNA* mutations suggest that male sex, non-sustained ventricular tachycardia, reduced ejection fraction and non-missense mutations define the patient at risk of ventricular tachycardia/fibrillation.[63] Other genetic causes of AC are less well studied, but data suggest that for mutations in *TMEM43*, *RBM20*, the founder R14del in phospholamban and *FLNC*, sudden death risk relates to the severity of structural and functional abnormalities, although anecdotal reports and familial evaluation suggest that sudden death can be the initial presenting feature.[16,30] Several novel disease biomarkers that might aid risk prediction are under study, such as testosterone, BIN-1, soluble ST2 and anti-desmoglein-2 autoantibodies.[64–67] However, these have not been compared with conventional risk factors. The dynamic nature of the disease and inflammatory hot phases may promote a temporary increased vulnerability to ventricular fibrillation. Anti-inflammatory agents may provide a means for reducing arrhythmic risk but require sensitive and specific biomarkers of disease activity and therapeutic response.

The diversity of causes for AC, together with phenotypic variability and age-related penetrance of genetic mutations, means that risk assessment needs to be tailored to aetiology and stage of disease (Figure 4). For patients fulfilling current Task Force criteria for ARVC, high- and low-risk cohorts have been identified, but there are many individuals who fall into an intermediate category for whom clear guidance on management is lacking. Moreover, most approaches to risk estimation are based on a relatively crude assessment of relative risk rather than absolute risk prediction. The challenge of optimal risk modelling might be

addressed through the integration of large deeply phenotyped and genotyped cohorts with sufficient follow-up to permit development and validation of risk models that integrate genetic, ECG, electrophysiological and imaging data.

What are the prospects for trials in arrhythmogenic cardiomyopathy?

Prospective treatment trials focused on novel therapeutic approaches for the treatment of AC are lacking. This reflects the challenges for conventional trial design in diseases that are rare, heterogeneous in presentation, associated with prominent arrhythmia, and slowly progressive. Hard endpoints such as mortality are difficult to achieve in uncommon disorders with long natural histories. Therefore, it is of utmost importance to define subsets of patients with a sufficiently high likelihood of meeting clinically meaningful surrogate endpoints within the duration of a trial, for example progression of structural or electrical characteristics. The endpoint for trials targeting cardiac arrhythmias might include time to the first episode of sustained ventricular tachycardia/fibrillation or premature ventricular complex frequency, as these appear to predict the risk of sustained ventricular arrhythmias. Trials targeting heart failure endpoints are challenging due to slow and variable disease progression.[68,69] Serial evaluation of structural myocardial abnormalities is difficult due to the limitations of conventional echocardiography in assessing the right ventricle and because the presence of an implantable cardioverter-defibrillator in many patients precludes serial magnetic resonance imaging. For these reasons, it is likely that trials in this area will require other biomarkers of ventricular impairment and remodelling such as natriuretic peptides and circulating markers of fibrosis.

Specific interventions that have potential to reduce life-threatening ventricular arrhythmias include pharmacologic agents such as beta-blockers, class 1 and 3 anti-arrhythmic agents such as flecainide, sotalol, tikosyn and amiodarone, endocardial and/or epicardial catheter ablation, and sympathetic denervation. As vigorous exercise seems to be factor for disease progression in ARVC and possibly in other forms of AC such as laminopathy,[70–73] clinical trials to determine whether exercise restriction can prevent development of ARVC are warranted.

Pharmacologic agents that could directly target the underlying disease mechanism in the various forms of AC are under investigation. For example, a small molecule inhibitor of GSK3β, a major regulator of Wnt/β-catenin signalling identified in an unbiased chemical screen in a zebrafish model of ARVC,[74] has been shown to dramatically reduce arrhythmias, myocardial damage and exercise-induced injury in mouse models of ARVC.[74,75] However, effective drug therapy will require chronic administration, and long-term use of Wnt agonists may have unacceptable off-target effects, including increased risk of developing cancer. Thus, a potential future strategy to develop a truly mechanism-based drug therapy will be to identify pathways and targets downstream of GSK3β that are driving the cardiomyopathic disease phenotype.

In animal studies, loss of functional lamin proteins produces strong cellular stress signals that activate the p38 mitogen-activated protein kinase (MAPK) pathway which in turn causes decreased contractility, cardiomyocyte apoptosis, cardiomyocyte hypertrophy, and

increased brain natriuretic peptide expression.[76] ARRY-797 is an oral administered selective p38 MAPK inhibitor that reverses cardiac dysfunction in an animal model of *LMNA* and studies are now underway in patients with dilated cardiomyopathy caused by *LMNA* mutations (ClinicalTrials.gov Identifier:).

Conclusions

Since the first detailed clinical description of ARVC, dramatic advances have been made regarding its pathogenesis, diagnosis and management. This progress was made possible by the development of single centre registries working alone or in partnership and also by the efforts of dedicated basic research laboratories. With the recognition of AC as a broad spectrum of disease, the need for national and international collaborative efforts is even greater. We hope this document will contribute to this endeavour.

Funding

This project was an independent initiative supported by the Fondazione Internazionale Menarini, which had no part in designing or approving the agenda. St. Bartholomew's Hospital, the Amsterdam UMC and the Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua-Azienda Ospedaliera are members of ERN GUARD-HEART (European Reference Network for Rare and Complex Diseases of the Heart; http://guardheart.ern-net.eu), which endorsed the meeting.

Conflict of interest: H.C. reports grants and personal fees from Boston Scientifiic, and personal fees from Medtronic, St Jude Medical, during the conduct of the study. D.P.J. reports grants from Menarini Foundation, during the conduct of the study; personal fees from Alnylam, GlaxoSmithKline, Pfizer, outside the submitted work. H.T. reports personal fees from Abbott, Cooltech, outside the submitted work. All other authors have nothing to disclose.

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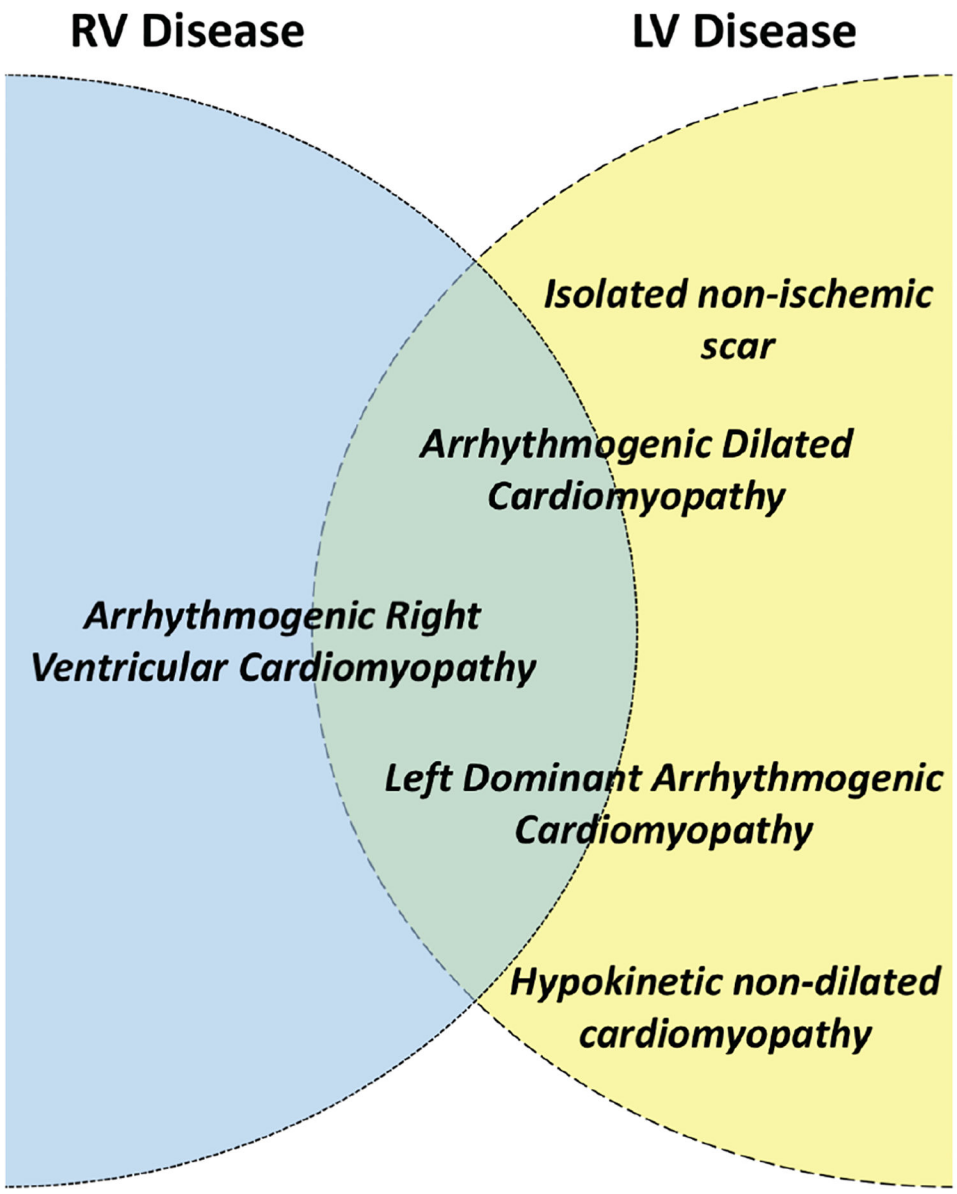

Figure 1.

Ideogram showing current terms that describe different arrhythmogenic cardiomyopathy phenotypes and their possible relationship to left (LV) and right ventricular (RV) disease. By definition, arrhythmogenic RV cardiomyopathy affects predominantly the right ventricle but biventricular forms are frequently seen. Arrhythmogenic dilated cardiomyopathy and left-dominant arrhythmogenic cardiomyopathy describe overlapping entities that mostly affect the left ventricle but RV involvement is also observed. Isolated non-ischaemic scar and hypokinetic non-dilated cardiomyopathy mostly refer to predominantly LV scarring identified using cardiac magnetic resonance imaging.[1–3]

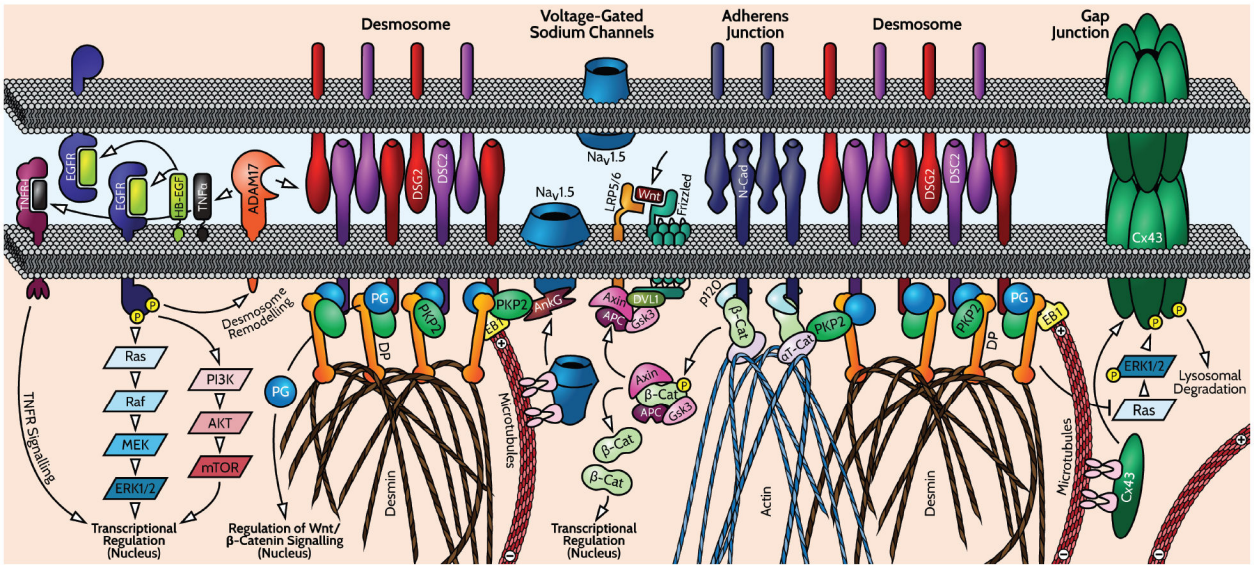

Figure 2.

This schematic shows the complex integration of mechanical and electrochemical signalling at cardiac intercalated discs and highlights the proposed remodelling of desmosomes, gap junctions and ion channels in arrhythmogenic cardiomyopathy. Desmosomes, which are a primary target for arrhythmogenic cardiomyopathy-causing mutations, are distributed in close proximity with adherens junctions, gap junctions (made of connexins) and sodium channels. Both desmosomes and adherens junctions have at their central adhesive core members of the cadherin family of calcium-dependent adhesion molecules [desmoglein 2 (DSG2) and desmocollin 2 (DSC2) in desmosomes, and N-cadherin (N-Cad) in adherens junctions]. Linking these molecules to the desmin intermediate filament and actin cytoskeletons, respectively, are a complex of armadillo and cytoskeletal linker proteins consisting of plakophilin 2 (PKP2), plakoglobin (PG) and the intermediate filament anchoring protein desmoplakin (DP) in desmosomes; and beta-catenin (β-Cat), p120 catenin and the actin binding protein alpha T-catenin (αT-Cat) in adherens junctions. In the heart, alpha-T catenin can interlink with PKP2, providing a structural link between desmosome and adherens junctions that results in inter-mixing and stabilizes the cortical cytoskeleton. Mixed junctions appearing in vertebrates are called the ‘area composita’. Examples of functional interactions at the intercalated discs relevant to arrhythmogenic cardiomyopathy are shown. These include DP-dependent trafficking and stabilization of connexin-43 (Cx43) and associated gap junction communication through(ia) EB1-dependent microtubule stabilization at junctions, and (ii) DP-dependent regulation of Erk1/2-dependent turnover of Cx43 through dampening Ras. In addition, distribution and function of the voltage-gated sodium channel (VGSC) Na$_V$1.5 depends on PKP2 and its associated adaptor protein ankyrin G (AnkG). Conflicting data associate perturbation of Wnt/β-Cat signalling through alterations in PG, β-Cat distribution and Hippo signalling (blocks Wnt), with adipogenic vs. fibrotic cell fate during arrhythmogenic cardiomyopathy development. Desmosomes can themselves be regulated by a combination of the ectodomain sheddase ADAM17 and epidermal growth factor receptor (EGFR) signalling [which is itself regulated via the release of EGFR ligands, such as EGF-like growth factor (HB-EGF) in cardiac muscle, by

ADAM17], which cooperate to regulate cleavage of DSG2. This serves to remodel desmosomes and coordinates this remodelling with gene expression changes associated with arrhythmogenic cardiomyopathy. PI3K, phosphoinositide 3-kinase; TNFα, tumour necrosis factor alpha; TNFR, tumour necrosis factor receptor.

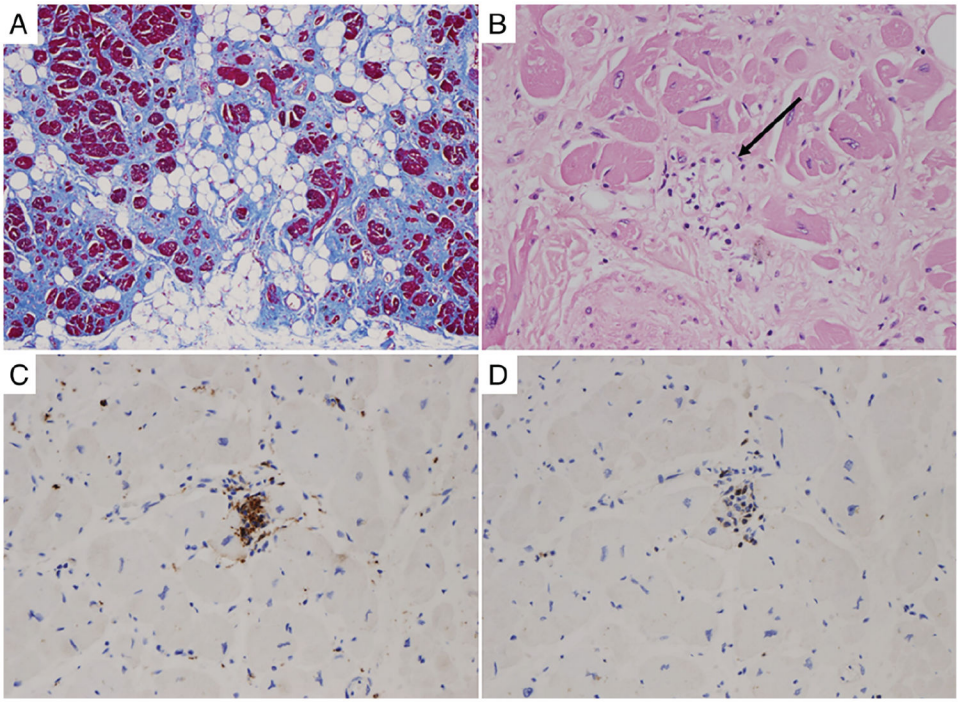

Figure 3.

Myocardial histology from a 31-year-old male competitive athlete who died suddenly as first manifestation of arrhythmogenic cardiomyopathy. Autopsy revealed biventricular arrhythmogenic cardiomyopathy and evidence of myocardial inflammation: (*A*) subepicardial fibrofatty replacement of the left ventricular free wall (Trichrome stain); (*B*) abnormal cardiomyocytes with dysmorphic nuclei, replacement fibrosis and inflammatory infiltrates with myocytolysis (arrow); (*C*) immunotyping for macrophages (CD68 antibody); (*D*) immunotyping for T lymphocytes (CD3 antibody).

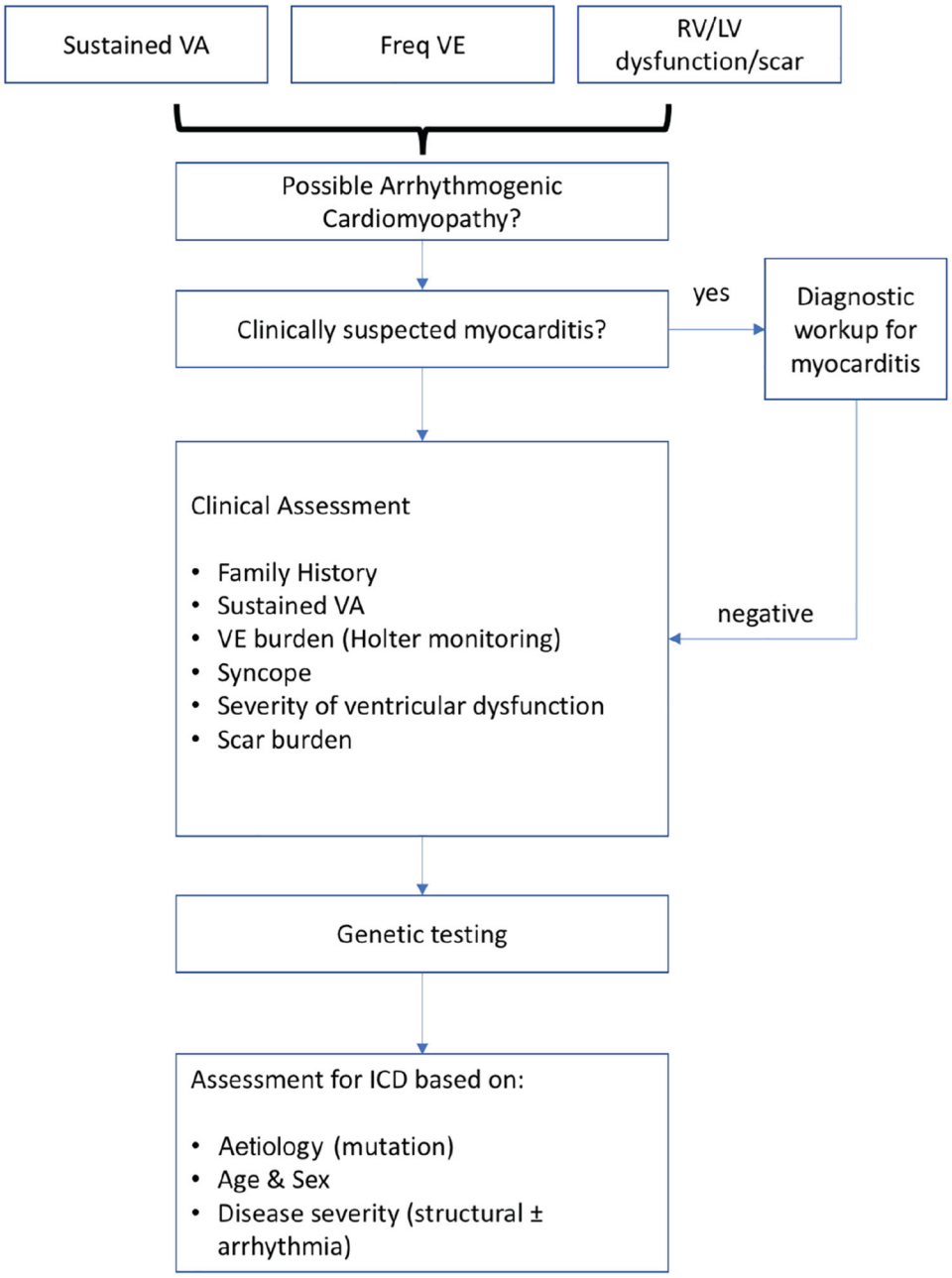

Figure 4.

Suggested flow chart for the general management of ventricular arrhythmia in arrhythmogenic cardiomyopathies. The pathways for management are critically dependent on aetiology as well as the clinical profile of individual patients. ICD, implantable cardioverter-defibrillator; LV, left ventricular; RV, right ventricular; VA, ventricular arrhythmia; VE, ventricular ectopy.

Table 1

Research priorities in arrhythmogenic cardiomyopathy

Definitions Genetic architecture	• Consensus on disease nomenclature and definition in AC. • More precise definition of clinical phenotypes encompassed by the label AC. • Studies of population incidence and prevalence of genetic mutations and phenotypes including the influence of ethnicity. • Better definitions of pathogenicity for specific genes with emphasis on final common pathways. • Genome wide association studies and extensive phenotype-genotype correlation studies of families with known pathogenic mutations to explore insights into phenotypic variation. • Investigation of non-coding and epigenetic regulation of genes and post-translational modification of proteins associated with AC.
Role of the desmosome	• Studies of extracardiac disease, as in the skin, to better define underlying disease mechanisms.
Role of inflammation	• Investigation of the characteristics of the AC inflammasome in animal models and in man. • Determination of the role of myocarditis on disease presentation and prognosis.
Sudden cardiac death prediction	• Risk prediction algorithms that quantify risk using easily measurable and repeatable clinical variables for specific forms ofAC. • Evaluation of circulating biomarkers to aid quantification of risk and predict hot phases. • Optimisation of patient selection for S-ICD vs. transvenous ICD to minimize inappropriate ICD therapies and device complications. • Systematic follow-up of clinically affected mutation carriers to better understand the evolution of the arrhythmic substrate.
Prospect clinical trials	• Trials of classical neurohormonal antagonists (BB, ACEi, ARB, ARNI, MRA) with the goal of repurposing them for AC. • Disease-specific pathogenic pathways should be evaluated as potential therapeutic targets. • Use of the skin and hair as a test bed for drug development. • Establish endpoints for clinical trials including surrogates that might hasten drug approval.

AC, arrhythmogenic cardiomyopathy; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; S-ICD, subcutaneous implantable cardioverter-defibrillator.

Table 2

Observed phenotypes associated with mutations in arrhythmogenic cardiomyopathy-related genes

Gene	Predominant RV disease	Biventricular disease	Predominant LV disease	Other characteristics	Ref.
JUP	+	+	−	Cardiocutaneous syndrome	4
DSP	−	+	+	Cardiocutaneous syndrome	25
PKP2	+	+	−		6,26
DSG2	+	+	+		8,26
DSC2	+	+	−		9,26
TGFB3	+	Unknown	Unknown		27
TMEM43	+	+	−		28
TTN	+	+	+		19,29
DES	−	+	+		10
Lamin A/C	−	+	+	Conduction disease	11
PLN	−	+	+		16,26
CTNNA3	+	+	−		14
CDH2	+	+	−		13
SCN5A	−	+	+	Electrical > structural disease	1 2,29
FLNC	−	+	+		15
RBM20	Unknown	Unknown	+		30
BAG3	Unknown	Unknown	+		31

A literature review identified the spectrum of phenotypes in relation to ventricular disease in patients with carrying mutations in AC-related genes. Presence of disease is marked with '+' and absence with '−'.

BAG3, Bcl2-associated athanogene 3; CDH2, cadherin 2; CTTNA3, catenin alpha 3; DES, desmin; DSC2, desmocolin 2; DSG2, desmoglein 2; DSP, desmoplakin; FLNC, filamin C; JUP, plakoglobin; LV, left ventricular; PKP2, plakophillin 2; PLN, phospholamban; RBM20, RNA binding motif protein 20; RV, right ventricular; SCN5A, sodium voltage-gated channel alpha subunit 5; TGFB3, transforming growth factor beta 3; TMEM43, transmembrane protein 43; TTN, titin.