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Scarring/arrhythmogenic cardiomyopathy

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The designation of 'arrhythmogenic cardiomyopathy' reflects the evolving concept of a heart muscle disease affecting not only the right ventricle (ARVC) but also the left ventricle (LV), with phenotypic variants characterized by a biventricular (BIV) or predominant LV involvement (ALVC). Herein, we use the term 'scarring/arrhythmogenic cardiomyopathy (S/ACM)' to emphasize that the disease phenotype is distinctively characterized by loss of ventricular myocardium due to myocyte death with subsequent fibrous or fibro-fatty scar tissue replacement. The myocardial scarring predisposes to potentially lethal ventricular arrhythmias and underlies the impairment of systolic ventricular function. S/ACM is an 'umbrella term' which includes a variety of conditions, either genetic or acquired (mostly post-inflammatory), sharing the typical 'scarring' phenotypic features of the disease. Differential diagnoses include 'non-scarring' heart diseases leading to either RV dilatation from left-to-right shunt or LV dilatation/dysfunction from a dilated cardiomyopathy. The development of 2020 upgraded criteria ('Padua criteria') for diagnosis of S/ACM reflected the evolving clinical experience with the expanding spectrum of S/ACM phenotypes and the advances in cardiac magnetic resonance (CMR) imaging. The Padua criteria aimed to improve the diagnosis of S/ACM by incorporation of CMR myocardial tissue characterization findings. Risk stratification of S/ACM patients is mostly based on arrhythmic burden and ventricular dysfunction severity, although other ECG or imaging parameters may have a role. Medical therapy is crucial for treatment of ventricular arrhythmias and heart failure. Implantable cardioverter defibrillator (ICD) is the only proven life-saving treatment, despite its significant morbidity because of device-related complications and inappropriate shocks. Selection of patients who can benefit the most from ICD therapy is one of the most challenging issues in clinical practice.

Introduction

The original designation of 'arrhythmogenic right ventricular dysplasia' reflected the old misconception that the disease was the result of a congenital developmental defect of the right ventricular (RV) myocardium. The subsequent discovery that the disease is frequently genetically determined and caused by a defect of genes encoding cardiac desmosomal proteins led to the more appropriate designation of 'arrhythmogenic right ventricular cardiomyopathy' (ARVC) and its official introduction among the World Health Organization classification of cardiomyopathies (CMPs).[1]

Insights arising from post-mortem investigations, genotype–phenotype correlation studies and myocardial tissue characterization by contrast-enhanced cardiac magnetic resonance (CMR) have increased the awareness that the disease often involves the left ventricle (LV).

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Accordingly, the current designation of 'arrhythmogenic cardiomyopathy' (ACM), which better reflects the evolving concept of a heart muscle disease that affects both ventricles with biventricular and left-dominant phenotypic variants, has progressively replaced that of ARVC.[2,3]

The appropriateness of the relatively non-specific designation 'arrhythmogenic cardiomyopathy' has been rightly disputed. It has been argued that the term 'arrhythmogenic cardiomyopathy' encompasses all CMPs, as all CMPs are potentially arrhythmogenic. Historically, the adjective 'arrhythmogenic' was first introduced by Marcus and Fontaine in their original report on a series of affected patients presenting with RV tachycardia. Hence, it refers to the propensity of the disease to cause ventricular arrhythmias (VAs) in relation to the underlying myocardial scarring that acts as an arrhythmogenic substrate. Accordingly, basic scientists and clinical cardiologists over time have used the term ACM thinking about a primarily 'scarring' and secondarily 'arrhythmogenic' heart muscle disease. Four decades later, the time has come to appropriately revise the terminology in order to preserve the nosographic autonomy of the disease. In this review article, we will propose the updated designation of 'scarring/arrhythmogenic cardiomyopathy (S/ACM)' to emphasize that the disease phenotype is distinctively characterized by loss of ventricular myocardium due to myocyte death with fibrous or fibro-fatty scar tissue replacement, common to the phenotypic varieties of the disease (with involvement of RV, LV, or both) and independent from the disease aetiology, either genetic forms or phenocopies. The myocardial scarring predisposes to potentially lethal VAs and underlies the impairment of systolic ventricular function. Furthermore, we will refer to S/ACM as an 'umbrella term' which includes a variety of conditions sharing the typical 'scarring' phenotypic features of the disease: (1) genetic CMPs either desmosomal or non-desmosomal; (2) genetic neuromuscular CMPs; (3) acquired inflammatory CMPs including viral myocarditis and cardiac sarcoidosis; and (4) acquired inflammatory cardiomyopathy in the context of autoimmune multisystem diseases. Differential diagnoses include 'non-scarring' heart diseases leading to either RV dilatation from left-to-right shunt or LV dilatation/dysfunction from a dilated cardiomyopathy (DCM).

Pathogenesis and pathology

The wave-front of ventricular myocardium loss due to myocyte death with subsequent substitution by scar tissue progresses from the epicardium towards the endocardium, both in the RV and LV wall, accounting for the 'non-ischaemic' pattern of myocardial lesions (*Figure 1*).[1,4,5]

The study of transgenic mice confirmed that myocyte death is the leading factor for development of the disease phenotype.[6] Transgenic mice (Tg-NS) with cardiac overexpression of desmoglein (DSG)-2 gene mutation N271S-dsg2 reproduced the clinical features of the disease, including spontaneous VAs, cardiac dysfunction, biventricular dilation with aneurysms, and sudden death at young age. Investigation of transgenic lines with different levels of transgene expression attested to a dose-dependent dominant-negative effect of the mutation. The study results showed unequivocally that myocyte death was the key initiator of myocardial injury. Electron microscopic evaluation in 2–3-week-old Tg-NS/H mice showed disruption of the sarcolemma, disgregation of myofilaments, and other cytoplasmic elements and mitochondrial swelling, all ultrastructural features consistent with cardiomyocyte necrosis. Cell death subsequently triggered an inflammatory response, followed later by injury repair with fibrous tissue replacement. Rather than being a continuous process, disease progression might occur during periodic bursts ('hot phases') in an otherwise stable disease. These disease exacerbations can be clinically silent in most patients but sometimes can be characterized by the appearance of chest pain and life-threatening arrhythmias. Environmental factors such as physical exercise or inflammation might facilitate disease progression by worsening cell adhesion disruption. According to the widely accepted 'defective desmosome' hypothesis, genetically determined disruption of desmosomal integrity is the key factor leading to the development of S/ACM. It is believed that the lack of the protein or the incorporation of defective proteins into cardiac desmosomes may provoke detachment of myocytes at the intercalated discs, particularly under mechanical stress conditions. As a consequence, there is progressive myocyte degeneration and death with subsequent repair by scar tissue.[7] In this regard, sports has been implicated as a principal environmental factor promoting development of phenotypic expression, acceleration of disease progression, and worsening of arrhytmogenic substrate and triggering life-threatening VAs leading to sudden cardiac death (SCD).[1,2,8] There is compelling evidence that inflammation contributes to the development of the myocardium lesion. Inflammatory infiltrates (predominantly T-lymphocytes) have been consistently observed in association with dying myocytes on histologic examination of both post-mortem or endomyocardial biopsies myocardial samples of S/ACM patients, suggesting that the pathologic process of myocyte death is likely to be myocarditis mediated.[9] In addition, acute episodes of chest pain, ECG changes, troponin release, and evidence of myocardial oedema on CMR, clinically resembling acute myocarditis ('hot-phase'), may occur as either initial presentation or pathologic progression of the myocardial disease, mostly in patients with desmoplakin (DSP) gene defects.[10]

Phenotypic classification

The classification of S/ACM includes the following phenotypic variants:[11] (i) the classic ARVC phenotype (also referred to as 'dominant-right' S/ACM), characterized by RV involvement with no detectable LV abnormalities; (ii) the biventricular phenotype (BIV), characterized by the involvement of both RV and LV; and (iii) the arrhythmogenic left ventricular cardiomyopathy (ALVC) phenotype (also referred to as 'dominant-left' S/ACM), characterized by LV involvement with no detectable RV abnormalities.

Upgraded diagnostic criteria (the 'Padua criteria')

In 2019, an international expert report critically reviewed the 2010 Task Force (TF) criteria for the diagnosis of ARVC with the aim to identify areas of potential improvement.[12] The 2010 TF guidelines exclusively targeted the original RV phenotype and did not include findings by
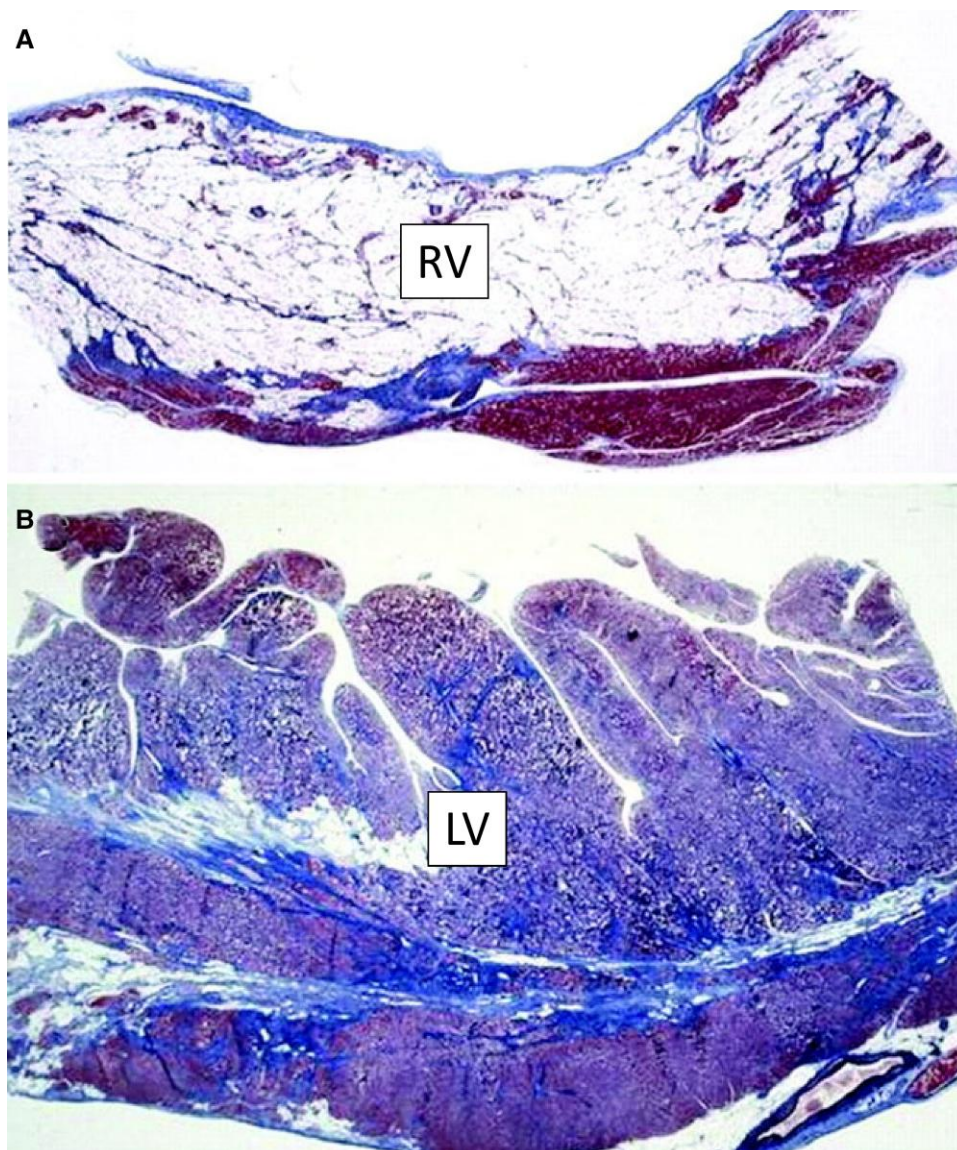
Figure 1 Histopathologic features of biventricular scarring/arrhythmogenic cardiomyopathy (S/ACM). The figure shows that S/ACM is a distinctive and unique cardiomyopathy with a variety of phenotypes, whose myocardial scarring represents the hallmark myocardial lesion which affects both the right and left ventricle. Post-mortem histologic features of the heart of a SCD victim with a genetic defect of desmoplakin: (*A*) panoramic histologic section of the RV free wall showing almost transmural fibrofatty myocardial scarring (Heidenhain trichrome); (*B*) panoramic histologic section of the LV lateral wall showing subepicardial and mid-mural fibrofatty scarring with prevalent fibrous tissue replacement (Heidenhain trichrome). *Adapted from Ref.# 13.*

gadolinium-enhanced CMR for detection of myocardial scar, which are necessary for an accurate characterization of the LV phenotype.[13] In 2020, an international consensus document provided upgraded criteria (the 'Padua criteria') for the diagnosis of the entire phenotypic spectrum of the disease, with the introduction of specific diagnostic criteria for the LV phenotype.[11,14] The Padua criteria represent a modern approach to diagnosis of S/ACM based on the research achievements and the clinical and imaging progress over 30 years at the Medical School of the University of Padua. The Padua criteria were reviewed and shared by several international experts, resulting in an international consensus document.[11] According to the Padua criteria, the diagnosis of BIV and ALVC variants of S/ACM is based on the same multiparametric approach recommended by

the 2010 TF criteria for ARVC, with six categories of criteria which encompass morpho-functional ventricular abnormalities, structural myocardial tissue alterations, ECG changes of ventricular depolarization and repolarization, VAs, and familial and genetic findings (*Table 1*).[11,14]

While based on the 2010 TF criteria myocardial tissue characterization relied exclusively on the histopathological study of endomyocardial biopsy samples, the Padua criteria recommend that structural myocardial abnormalities are investigated by the CMR using the late-gadolinium enhancement (LGE) technique, which allows the identification of LV myocardium replacement by scar tissue. The superiority of the Padua criteria scoring system for phenotypic diagnosis of left-sided S/ACM has been clinically validated.[14]

Table 1. 'Padua criteria' for diagnosis of arrhythmogenic cardiomyopathy

Category	Right ventricle	Left ventricle

I. Morpho-functional ventricular abnormalities	*Major*
	• Regional RV akinesia, dyskinesia, or bulging *plus* one of the following:
	   - Global RV dilatation (increase of RV EDV according to the imaging test specific nomograms for age and sex)
	   - Global RV systolic dysfunction (reduction of RV EF according to the imaging test specific nomograms for age and sex)
	Minor
	• Regional RV akinesia, dyskinesia, or aneurysm of RV free wall
		Minor
		• Global LV systolic dysfunction (depression of LV EF or reduction of echocardiographic global longitudinal strain) with or without LV dilatation (increase of LV EDV according to the imaging test specific nomograms for age, sex, and BSA)
		Minor
		• Regional LV hypokinesia or akinesia of LV free wall, septum, or both

II. Structural myocardial abnormalities	*Major* • Transmural LGE (stria pattern) of $\geq$1 RV region(s) (inlet, outlet, and apex in two orthogonal views) *Major* • Fibrous replacement of the myocardium in $\geq$1 sample, with or without fatty tissue	*Major* • LV LGE (stria pattern) of $\geq$1 Bull's Eye segment(s) (in two orthogonal views) of the free wall (subepicardial or midmyocardial), septum, or both (excluding septal junctional LGE)
III. Repolarization abnormalities	*Major* • Inverted T waves in right precordial leads (V$_1$, V$_2$, and V$_3$) or beyond in individuals with complete pubertal development (in the absence of complete RBBB) *Minor* • Inverted T waves in leads V$_1$ and V$_2$ in individuals with completed pubertal development (in the absence of complete RBBB) • Inverted T waves in V$_1$, V$_2$, V$_3$, and V$_4$ in individuals with completed pubertal development in the presence of complete RBBB	*Minor* • Inverted T waves in left precordial leads (V4–V6) (in the absence of complete LBBB)
IV. Depolarization abnormalities	*Minor* • Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V$_1$ to V$_3$) • Terminal activation duration of QRS $\geq$55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V$_1$, V$_2$, or V$_3$ (in the absence of complete RBBB)	*Minor* • Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
V. Ventricular arrhythmias	*Major* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained, or sustained ventricular tachycardia of LBBB morphology *Minor* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained, or sustained ventricular tachycardia of LBBB morphology with inferior axis ('RVOT pattern')	*Minor* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained, or sustained ventricular tachycardia with a RBBB morphology (excluding the 'fascicular pattern')
VI. Family history/genetics	*Major* • ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic or likely pathogenetic ACM mutation in the patient under evaluation *Minor* • History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative • ACM confirmed pathologically or by diagnostic criteria in second-degree relative	

ACM, arrhythmogenic cardiomyopathy; BSA, body surface area; EDV, end-diastolic volume; EF, ejection fraction; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle; RVOT, right ventricular outflow tract.

Characterization of the disease phenotype and aetiology

The diagnosis of S/ACM according to the Padua criteria is a three-step process which also includes phenotype characterization and aetiologic classification.

The first step is the application of the multiparametric approach to evaluate whether a sufficient number of major/minor diagnostic criteria for RV and LV disease are fulfilled. It is noteworthy than only one criterion either major or minor for each category can be considered. According to the Padua criteria, the diagnosis of each phenotypic variant of S/ACM requires that at least one criterion from category I (i.e. morpho-functional ventricular abnormalities) or category II (i.e. structural myocardial abnormalities), either major or minor, is met. The reason is that S/ACM is not a channelopathy, but a cardiomyopathy with distinctive structural ventricular abnormalities, which are an integral part of the phenotype. Pathogenic gene variants, ECG abnormalities or arrhythmias alone in the presence of a normal heart (i.e. in the absence of morpho-functional and structural criteria) can be observed in individuals, mostly family members, with 'preclinical' or 'clinically concealed' disease. These recognized early stages are characterized by an incomplete development of the disease phenotype because of the lack of structural abnormalities (overt myocardial scarring) and/or morpho-functional alterations (regional or global systolic dysfunction), which are a prerequisite for clinical diagnosis of S/ACM.

The second step is to characterize the S/ACM phenotype (i.e. ARVC, BIC, or ALVC) according to the combination of diagnostic criteria. If morpho-functional and/or structural criteria (either major or minor) are met only for the RV the patient is diagnosed with classic ARVC phenotype, provided that a sufficient number of additional RV diagnostic criteria are fulfilled. If morpho-functional and/or structural criteria are met for both ventricles, the patient is diagnosed with biventricular S/ACM that can be considered definite, borderline, or possible according to the number of additional criteria that are fulfilled from either the LV or RV categories. For the diagnosis of ALVC, the presence of structural LV criterion (i.e. non-ischaemic LV LGE) is mandatory.[15]

The third step is the aetiologic classification of the disease phenotype, whether genetically determined or acquired. By analogy with current classification of other CMPs such as hypertrophic (HCM) and DCM, it has been proposed a disease classification which includes under the umbrella term 'scarring/arrhythmogenic cardiomyopathy' a spectrum of conditions of different aetiologies whose common denominator is the prominent ventricular myocardial scarring and the scar-related VAs.[12] The variety of conditions which share the structural phenotypic features of S/ACM include inherited forms either desmosomal or non-desmosomal gene related; CMPs in the context of genetic neuromuscular diseases; and acquired inflammatory conditions (phenocopies) such as viral myocarditis, sarcoidosis, or autoimmune systemic disorders. A common denominator to all these aetiologic variants of S/ACM is the distinctively higher risk of SCD, because the pathogenesis of life-threatening VAs goes beyond the severity of systolic ventricular dysfunction, being strongly related to the large amount of myocardial scar which is an independent arrhythmogenic risk factor.

The identification of the specific cause of S/ACM is crucial because the clinical outcome, disease progression, and the risk of SCD vary depending on disease aetiology.

Isolated LV LGE with subepicardial–midmyocardial distribution may be the consequence of a previous viral myocarditis (post-inflammatory S/ACM). The post-inflammatory scar is hard to distinguish from that of genetic S/ACM (*Figure 2*) and may induce ECG changes, such as low-amplitude QRS complexes in limb leads, T-wave inversion, VAs with a right bundle branch block morphology, and reduction of LV systolic function, all features consistent with the ALVC phenotype.[15] Post-inflammatory ALVC has been reported to act as a myocardial substrate for life-threatening VAs and cardiac arrest, mostly in young people and athletes. A previous study reported that during a mean 3-year follow-up, 22% of athletes with a myocarditis-like LV scar and scar-related VAs experienced major arrhythmic events including SCD, compared with none of the control athletes with VAs in the absence of LV scar. An important clinical implication of detection of a LV scar is that it cannot be dismissed as a benign sign of a healed remote inflammatory process but deserves proper clinical attention. Affected patients should be evaluated for a family history of cardiomyopathy, clinical history of acute myocarditis, presence of symptoms, and the arrhythmogenicity of the myocardial fibrosis; molecular genetic testing searching for S/ACM pathogenic gene variants is required for an appropriate aetiologic characterization.

Cardiac sarcoidosis is another phenocopy that may share all the ALVC phenotypic features with myocardial scarring, ventricular dilatation/dysfunction, life-threatening VAs, and heart failure. A distinctive feature of the sarcoid variant of ALVC is the presence of atrioventricular (AV) conduction abnormalities such as bundle branch block and AV block as a consequence of the predilection of granulomatous infiltration for the basal interventricular septum. Although definitive diagnosis of sarcoidosis is made by demonstration of granulomatous infiltration on endomyocardial or extracardiac biopsy, non-invasive imaging modalities such as CMR and positron emission tomography are increasingly used in the clinical setting. Suggestive of cardiac sarcoidosis are findings of LGE localized in the basal septum and regional fluorodeoxyglucose uptake which indicates active inflammatory lesions.[12]

Differential diagnosis

Differential diagnoses include 'non-scarring' heart diseases leading to either RV dilatation from left-to-right shunt or LV dilatation/dysfunction from DCM. This latter is the most common condition requiring a differential diagnosis with left-sided variants of S/ACM due to overlapping phenotypic features.[16] In case of biventricular ACM, the fulfilment of morpho-functional/structural criteria for the RV phenotype ensures that the concomitant left-sided abnormalities are disease-specific. Instead, in patients without clinically detectable RV morpho-functional and structural abnormalities, the differential diagnosis between ALVC and DCM relies on myocardial tissue characterization by gadolinium-enhanced CMR. Indeed, the main discriminant features include the extent and regional distribution of myocardial fibrosis as evidenced by LGE and the relation between the amount of LGE and LV systolic
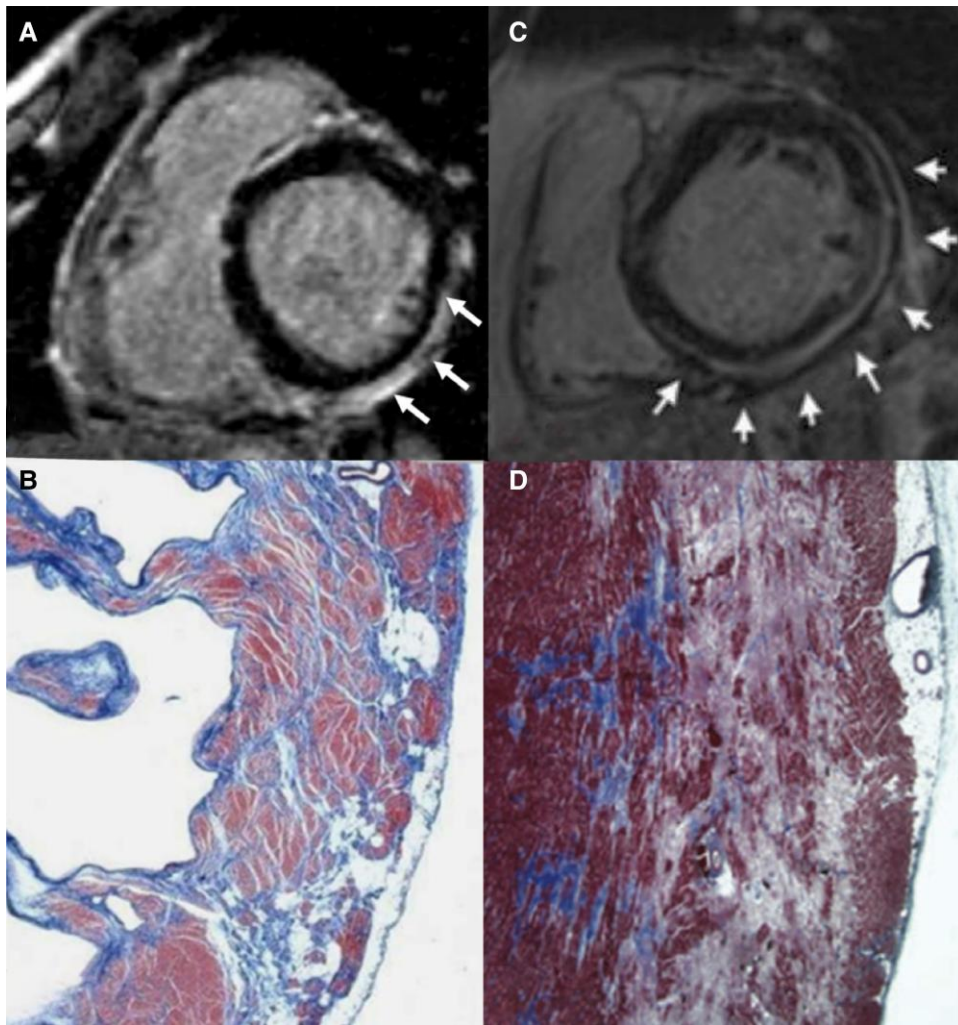
Figure 2 Cardiac magnetic resonance features and histopathological findings in post-myocarditis (left panels) and genetic (right panels) ALVC. Post-myocarditis ALVC: post-contrast T1 inversion recovery sequence in short-axis view showing subepicardial LGE of the inferolateral LV wall (arrows) (*A*); corresponding panoramic histopathological view of the inferolateral LV wall showing extensive fibrofatty scar tissue replacement in the subepicardial layer of the myocardium (*B*). DSP-gene related ALVC: post-contrast T1 inversion recovery sequence in short-axis view showing subepicardial LGE of the inferolateral LV wall (arrows) (*C*). Panoramic histopathological view showing fibrofatty myocardial replacement of the outer layer of the inferolateral LV wall (*D*). ALVC, arrhythmogenic left ventricular cardiomyopathy; LGE, late-gadolinium enhancement; LV, left ventricle. *Adapted from Ref.#* 12.

dysfunction (*Figure 3*). The amount of LV LGE/myocardial scar is significantly greater in patients with ALVC than in patients with DCM and directly impacts the severity of LV systolic dysfunction. On the contrary, LV LGE in DCM represents an epiphenomenon which is unrelated to the reduction of the LV systolic function.[16]

Implications for a revision of cardiomyopathy classification

CMPs are classically defined as myocardial disease characterized by structural and functional abnormality of the heart muscle in the absence of coronary artery disease or ventricular overload induced by hypertension, valvular disease, and congenital heart disease sufficient to cause the phenotype. CMPs have been traditionally classified as hypertrophic, restrictive, dilated, and arrhythmogenic right ventricular cardiomyopathy on the basis of their distinctive clinical, arrhythmic, echocardiographic, and

haemodynamic features. The introduction of contrast-enhanced CMR for clinical imaging of CMPs has provided important new insights into our understanding of pathobiological differences between heart muscle disorders. The presence, distribution, and amount of LGE/myocardial scar differs according to the different nature of CMPs. In HCM and DCM, the presence of scar tissue is not the primary cause of the myocardial dysfunction but appears as an epiphenomenon: HCM is primarily caused by genetically defective sarcomeric proteins leading to disproportionate LV hypertrophy and DCM is primarily caused by a contractile dysfunction of myocytes, either genetic or acquired, leading to ventricular systolic dysfunction and dilatation.

With regard to DCM, which often enters in the differential diagnosis with S/ACM, experimental studies of genetically determined disease identified several mechanisms potentially involved in the generation of the impaired myocyte contractility. These include disruption of energy
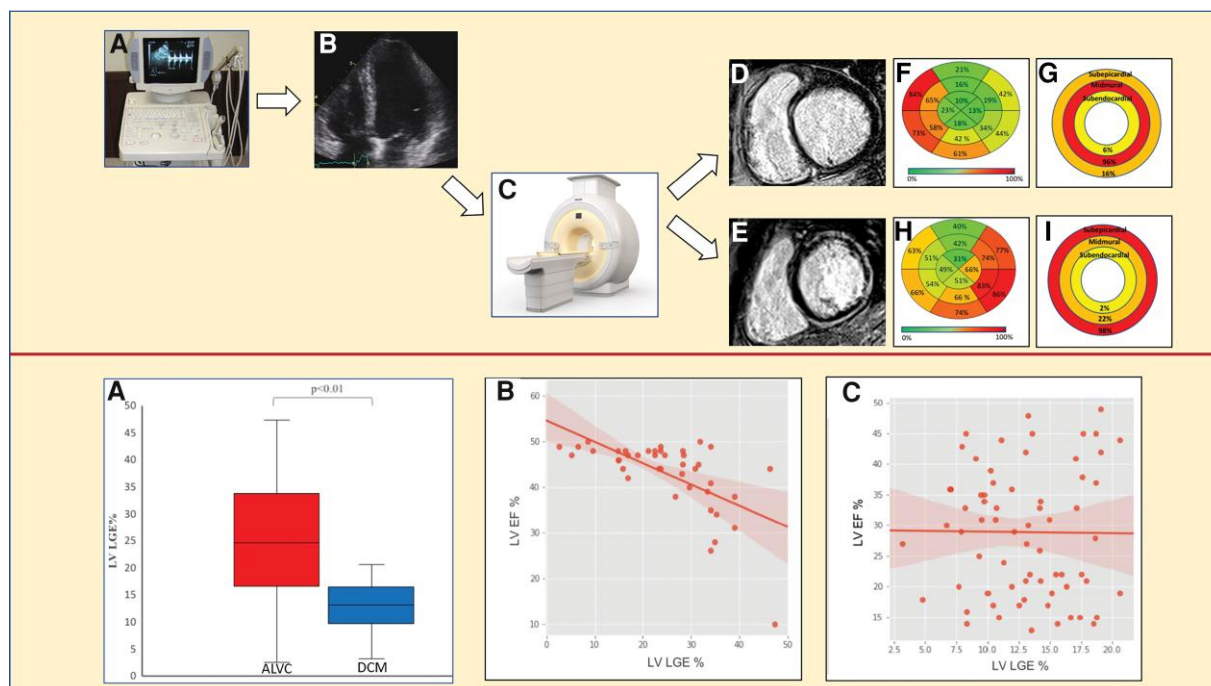
Figure 3 Differential diagnosis between ALVC and DCM based on myocardial tissue characterization by cardiac magnetic resonance. (Top panels) CMR scan of hearts with an echocardiographic diagnosis of DCM (*A–C*) allows to differentiate true DCM with no or patchy myocardial LGE unrelated to ventricular dilatation/dysfunction ('non-scarring' myocardial disease) (*D*), from ALVC with large amount of subepicardial/midmyocardial LGE directly impacting the LV remodelling ('scarring' myocardial disease) (*E*). Tissue characterization findings by CMR allows to identify, localize and quantify the myocardial LGE/scar tissue. While LGE is detected in <50% of DCM cases, 100% of patients with ALVC show the presence of LV LGE. The distribution of LGE differs between the two conditions, predominantly affecting the subepicardial inferolateral regions in ALVC (*F, G*) vs. mid-mural septal segments in DCM (*H, I*). (Bottom panels) Box plot showing the significantly greater amount of LGE in ALVC vs. DCM (*A*). A linear correlation between LVEF reduction and extent of LV LGE (expressed as percentage of LV mass) is observed in ALVC patients (*B*), but no in DCM patients (*C*). *Adapted from Ref.# [16].*

production and consumption, abnormal nuclear integrity, transcriptional dysregulation, altered metabolic profiles, altered protein degradation, and calcium homoeostasis and abnormal calcium handling, leading to a final outcome of altered force generation and transmission.[17] When present (<50% of cases), patchy myocardial fibrosis occurs in DCM as a consequence of the primary myocardial dysfunction/ventricular remodelling, due to a focal process of myocyte death and repair underlined secondarily induced by mechanical, ischaemic, or metabolic myocardial injuries. Most important, the phenotype and the severity of ventricular remodelling of DCM is unrelated to the presence and amount of myocardial scar ('non-scarring' cardiomyopathy).

On the contrary, the phenotype of S/ACM essentially consists of genetically determined or post-inflammatory (or both) myocardial scarring of the RV, LV, or both ventricles, due to myocyte necrosis followed by repairing myocardial fibrous or fibro-fatty scar tissue. Ventricular dilatation and systolic dysfunction in S/ACM are primarily caused by the amount of loss of myocardium and replacement fibrosis ('scarring' cardiomyopathy).

On the basis of the advances into our understanding of genetic and pathobiological background, imaging features and clinical outcome of CMPs, to classify as DCM any LV myocardial abnormality presenting with dilatation or systolic dysfunction appears inappropriate. According to the 2016 revised definition, DCM is classified as 'dilated' (D) and 'non-dilation' (ND) or hypokinetic (H) and non-hypokinetic (NH); it has also been introduced a new DCM variant, named 'hypokinetic, non-dilated cardiomyopathy (HNDC)', which is considered as part of the clinical spectrum of DCM.[18] This approach to classification of DCM is based on morpho-functional features of the ventricular remodelling as evidenced by echocardiography, without taking into account new and crucial information coming from myocardial tissue characterization by gadolinium-enhanced CMR. Putting in separate baskets a cardiomyopathy based on whether the heart is dilated or non-dilated, while ignoring the importance of new CMR imaging findings, reflects a step-back into our pathobiological perspective of heart muscle diseases (*Figures 3* and *4*). CMR scan demonstrates that most HNDCs are characterized by an extensive, non-transmural scarring of the LV which scarcely affects the global LV systolic function and induces only mild LV dilatation. This phenotype fits better with that of left-sided S/ACM, suggesting that a sizeable proportion of HNDCs should be re-classified as BIV or ALVC.[15]

Risk stratification

Prognosis of S/ACM depends on the severity of VAs and ventricular systolic dysfunction.[1,19] Patients who have experienced sustained ventricular tachycardia (VT) or fibrillation (VF) have a high rate of recurrences. Unexplained syncope, non-sustained VT, and moderate-to-severe dilation/dysfunction of RV, LV, or both have been reported as major predictors of malignant arrhythmic events. A number of minor
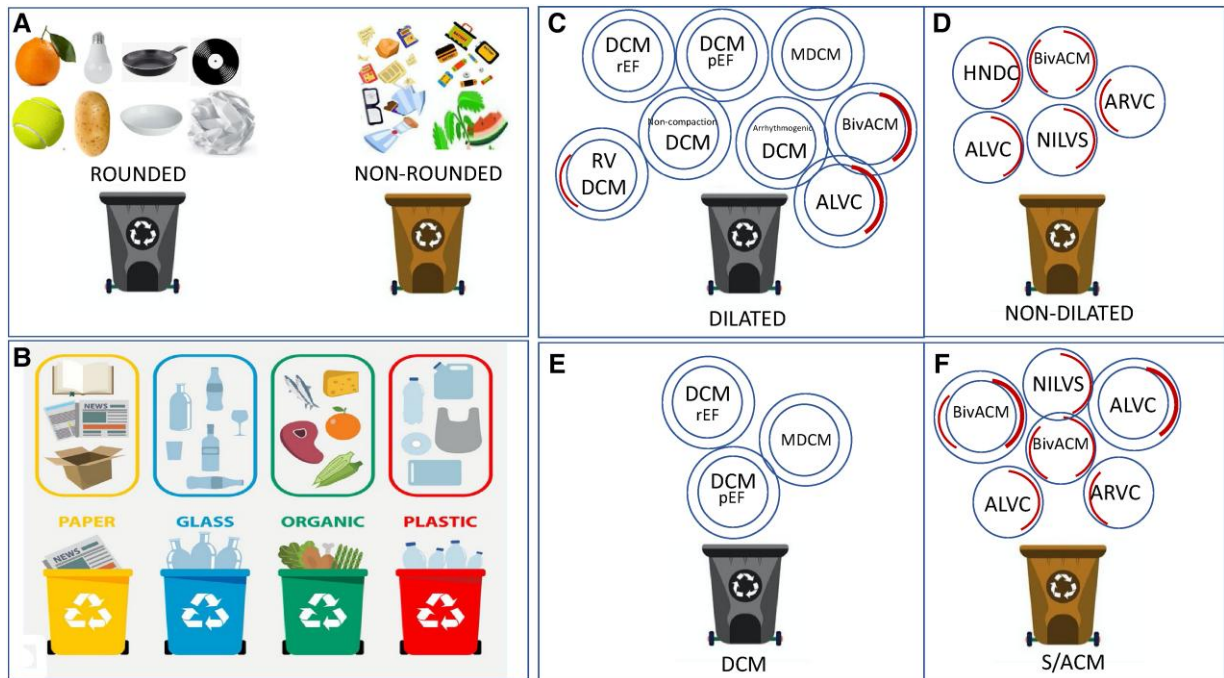
Figure 4 Metaphorical analogy between waste selection and cardiomyopathy classification. The figure depicts a wrong approach to perform the separate collection of rubbish, based on the external look of different items and leading to put in the same basket any rounded waste such as tennis balls, oranges, crystal balls, and paper balls (*A*), without considering their intrinsic nature of plastic, organic, glass, and paper, which would lead to the correct waste selection (*B*). By analogy, future upgrading of cardiomyopathy classification should not be based on the echocardiographic findings on whether the ventricle is dilated or not, that represents a secondary and non disease-specific ventricular remodeling (*C*); rather it should rely on the intrinsic and distinctive biological, pathological, and functional properties of the heart muscle disorder. Specifically, S/ACM has to be distinguished from DCM, which is a non-scarring myocardial disease (see text for further details). Note that, LV non-compaction is not a cardiomyopathy but a congenital heart disease. HNDC most often coincides with ALVC. ARVC, arrhythmogenic right ventricular cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; BIV, biventricular arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; DCMrEF, dilated cardiomyopathy with reduced ejection fraction; DCMpEF, dilated cardiomyopathy with preserved ejection fraction (isolated LV dilatation); HNDC, hypokinetic non-dilated cardiomyopathy; MDCM; mildly dilated cardiomyopathy; NILVS, non-ischaemic left ventricular scar; S/ACM, scarring/arrhythmogenic cardiomyopathy.

clinical predictors of arrhythmic outcome have been identified. The 'three categories' arrhythmic risk stratification of S/ACM is summarized in *Figure 5A*.

A gene-specific risk stratification of S/ACM is still a matter of debate. Among carriers of desmosomal gene defects, available data indicate that multiple desmosomal gene mutations are likely to have a more severe phenotypic expression and an increased lifetime risk of malignant arrhythmias and SCD. Single truncating mutations in the DSP gene have also been associated with a worse arrhythmic prognosis. With regard to non-desmosomal gene defects, the TMEM43 p.S358L founder mutation, identified almost exclusively in Newfoundland, is almost fully penetrant and highly lethal among male carriers so to be considered by itself an indication to prophylactic ICD. Other non-desmosomal gene defects mostly responsible for biventricular or left-dominant S/ACM, which include mutations of the genes encoding filamin C, lamin A/C, desmin, RNA binding motif protein, and phospholamban, have been associated with a distinctively higher risk of SCD.

Novel biomarkers are currently emerging as useful tools for risk prediction in patients with of the original ARVC disease variant. Testosterone, plasma bridging integrator 1, soluble ST2, miRNAs, and anti-DSG2 antibodies have been reported to correlate with disease severity and arrhythmias incidence.[12]

The specific risk of SCD in patients with ALVC remains to be established. Emerging risk predictors include moderate LV systolic dysfunction (ejection fraction <45%), the amount of myocardial fibrosis, and a series of scar-related electrical features such as T-wave inversion in the lateral leads, low QRS voltages, and frequent/complex VAs.

A calculator to predict the arrhythmic outcome of the classic ARVC phenotype has been proposed. It incorporates a number of disease-related features into a logistic regression equation aimed to provide estimates of the 5- and 10-year risk. However, this prediction model suffers from biases due to the inhomogeneous study population, comprising both patients with and those without an implantable defibrillator (ICD) and the combined end-point used for the assessment of the arrhythmic outcome, which includes appropriate ICD intervention for VT/VF. Appropriate ICD intervention is a poor surrogate of arrhythmic cardiac arrest: indeed, most VT episodes treated by ICD are expected to be self-terminating and even short episodes of fast (>180/min) VT haemodynamically could be well-tolerated, because the LV systolic function in most ARVC patients is preserved or only slightly depressed. Since appropriate ICD interventions accounted for more than 70% of the study outcomes, the model likely overestimated the true risk of SCD and benefit of an ICD. Of note, as only one fourth of the total study population
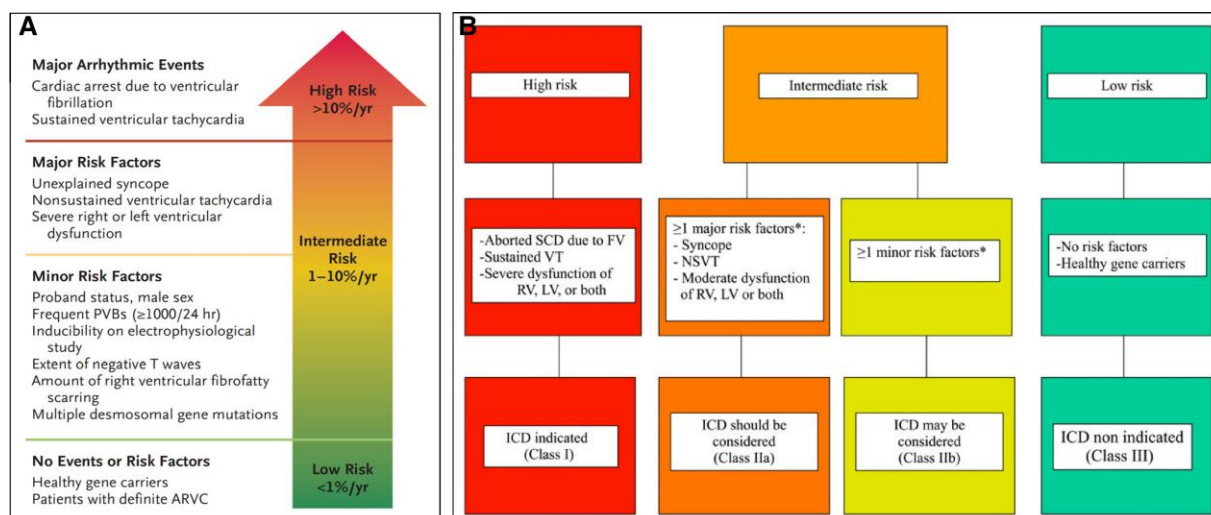
Figure 5 Risk stratification and indication to ICD implantation. (*A*) Proposed scheme for prognostic stratification of patients with ACM. The 'three risk categories' have been defined on the basis of the estimated probability of a major arrhythmic event (i.e. sudden cardiac death, cardiac arrest due to ventricular fibrillation, sustained ventricular tachycardia, or an event requiring defibrillator intervention) during follow-up, in relation to previous arrhythmic events or risk factors. An estimated annual risk of more than 10% defines the high-risk group, a risk between 1% and 10% the intermediate risk group, and a risk below 1% the low-risk group. (*B*) The 2015 Task Force consensus recommendations for ICD implantation in patients with S/ACM based on the 'three risk categories' (see text for details). *Adapted from Ref.# 1,19.*

had an ICD, 60% of the study patients (without an ICD) were prevented from experiencing an appropriate ICD intervention. A more specific calculator for prediction of life-threatening VAs (i.e. fast VT, VF, or sudden cardiac arrest), using the same study design and database, has also been proposed. Surprisingly, traditionally recognized and clinically validated major risk factors such as a history of non-sustained VT, syncope and the severity of ventricular systolic dysfunction did not predict the occurrence of life-threatening VAs. Conversely, malignant arrhythmic events were associated with younger age, male sex, the burden of ectopic ventricular beats, and the extent of T-wave inversion in the inferior and precordial leads, which are common disease features. Because both available calculators for risk assessment of either VT or VF are based on outcome data that are inhomogeneous and unbalanced in favour of ICD recipients, they are potentially misleading with overestimation of the arrhythmic risk, which translates into overtreatment with ICD of asymptomatic S/ACM patients. Before these calculators can be recommended for clinical use, rigorous validation studies are needed to assess their superiority in the prediction of SCD (rather than appropriate ICD discharges) in comparison with the traditional 'single risk factor' approach.[20]

Clinical therapy

The aims of clinical management of S/ACM include (1) the reduction of the risk of SCD; (2) the prevention of disease progression; and (3) the treatment of heart failure which can occur over time as a consequence of the worsening of systolic dysfunction of the RV, LV, or both.[19] Restriction from intense sports activity is regarded as an important preventive tool for both healthy mutation carriers and clinically affected persons in order to protect them from the risk of exercise-related malignant arrhythmic events and disease development or progression.

β-blockers are essential drugs to be offered in all clinically affected individuals, for both prevention of arrhythmias and reduction of ventricular wall stress. Antiarrhythmic drug therapy offers the potential to ameliorate symptoms in S/ACM patients with VAs, although there is no proof that it confers protection against SCD. Catheter ablation has emerged as a valuable treatment in patients with sustained monomorphic VT, when antiarrhythmic drug therapy is either ineffective or non-tolerated. Although feasibility and long-term efficacy of epicardial VT catheter ablation for patients in whom one or more endocardial procedures have been unsuccessful has been shown, it remains a 'symptomatic' therapy in S/ACM patients and should not be looked upon as an alternative to ICD therapy, which is the only treatment of proven efficacy to prevent SCD by interrupting potentially lethal VAs. Data from observational studies have consistently shown that ICD therapy is effective and safe. The 2015 TF consensus guidelines on treatment of S/ACM provided recommendations for ICD implantation based on the 'three categories' arrhythmic risk stratification (*Figure 5B*).[19] The aim was not only to optimize the prevention of SCD but also to avoid overtreatment of patients at low risk. According to the 2015 TF consensus document, ICD therapy is recommended for secondary prevention in patients who survived an episode of spontaneous VF or sustained VT (high risk category), because of the high recurrence rate of lethal arrhythmic events. The indication of ICD implantation for primary prevention in patients without prior spontaneous life-threatening VAs is still debated because the prediction of arrhythmic cardiac arrest based on clinical risk factors may not be sufficiently accurate to justify a device implant (intermediate risk category). The implantation of an ICD is considered reasonable in patients with major risk factors (intermediate-high risk category). An ICD may be also indicated in selected patients with minor risk factors (intermediate-low risk category). In these patients, the

decision to implant an ICD should be made on individual basis, by assessing the overall clinical profile, the age, the strength of the risk factor(s) identified, the level of SCD risk that is acceptable to the patient, and, most important, the potential high risk of serious complications over time.[20] Implantation of an ICD is not generally indicated in asymptomatic patients with no risk factors and healthy mutation carriers who have a low risk of malignant VAs. The performance of the 2015 TF consensus algorithm to guide ICD implantation in patients with S/ACM was validated by clinical studies which demonstrated that the algorithm accurately differentiated survival from any sustained VT or VF among the different ICD class indications. Moreover, the comparison of the clinical performance of current algorithms for ICD implantation confirmed that the 2015 Task Force Consensus provide the highest ICD protection rates and remain the best-performing algorithm to indicate an ICD in S/ACM, if one considers a threshold of >6% 5-year risk (similar to the threshold for HCM patients) of fast VT. Traditional transvenous ICD therapy in young patients with S/ACM may lead to considerable morbidity, because many patients experience ICD-related adverse events and inappropriate interventions over time. The lead system constitutes the most common malfunction and, consequently, is the most vulnerable part of the ICD system. Lead failure/fracture requiring lead extraction is the most frequent and potentially life-threatening adverse event, which increases with the age of the lead, and thus young patients with a long-life prediction are the most vulnerable. The recent availability of subcutaneous, leadless ICD (S-ICD) that maintains protection from SCD while minimizing the risks of intravascular lead failure or infection has offered an alternative to the transvenous ICD in young patients with CMPs. The S-ICD is not without its risks and shortcomings that include potential oversensing of electrical signals and inability to provide anti-bradycardia, anti-tachycardia, or cardiac resynchronization pacing. Available strategies that may increase S-ICD eligibility and reduce inappropriate shocks include proper pre-implantation ECG testing, new implantation techniques, device programming (single-zone vs. dual-zone programming), and software upgrading including the 'SMART Pass', which is a recently introduced filter that should reduce oversensing. The main objective of ICD therapy is the prevention of SCD (not the interruption of VT) without exposing the patient to potentially lethal complications. Accordingly, in the absence of indication to ventricular pacing all efforts should be made to implant a life-saving device which reduces the risk of electrode and device-related side-effects, including intravascular lead failure or infection requiring surgical intervention, which significantly impact the quality of life of young patients and may increase morbidity and mortality because of their many decades of life expectancy.[20] For patients who developed heart failure, standard pharmacological treatment with angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists and diuretics is indicated. The use of sacubitril/valsartan and SGLT2 inhibitors to improve cardiovascular outcomes, including hospitalization and death for heart failure require validation in patients with S/ACM. Selected S/ACM patients with untreatable heart failure or uncontrollable ventricular tachyarrhythmias may require heart transplantation.

Conclusion

S/ACM is a distinctive cardiomyopathy characterized by post-necrotic myocardial scarring which represents its hallmark myocardial lesion, common to all the phenotypic disease variants (ARVC, BIV, and ALVC) and acting as a substrate of life-threatening arrhythmias. The 2020 upgraded diagnostic criteria ('Padua criteria') are heavily dependent on CMR, which has become mandatory to characterize the S/ACM phenotype and to exclude other diagnoses. Preliminary data confirm that the clinical use of the Padua criteria substantially impacts the diagnostic accuracy and permits a comprehensive identification of the phenotypic variety of S/ACM, mostly by virtue of demonstration of RV and LV LGE/myocardial scarring by CMR.

ICD remains the only proven life-saving treatment, despite its significant morbidity due to device-related complications that can be overcome by available S-ICD. Risk stratification of S/ACM patients is mostly based on arrhythmic burden and ventricular dysfunction severity, although other ECG or imaging parameters may have a role.

Future directions of research include comprehensive understanding of the pathogenesis, increased awareness of clinical manifestations and outcome, as well as more accurate risk stratification and effective therapy for left-sided disease variants.

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