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Review

Current and state of the art on the electrophysiologic characteristics and catheter ablation of arrhythmogenic right ventricular dysplasia/cardiomyopathy

Fa-Po Chung (MD)[a,b], Yenn-Jiang Lin (MD)[a,b], Shih-Lin Chang (MD)[a,b], Li-Wei Lo (MD)[a,b], Yu-Feng Hu (MD)[a,b], Ta-Chuan Tuan (MD)[a,b], Tze-Fan Chao (MD)[a,b], Jo-Nan Liao (MD)[a], Chuen-Wang Chiou (MD)[a,b], Shih-Ann Chen (MD)[a,b,*]

[a] Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited genetic disease caused by defective desmosomal proteins, and it has typical histopathological features characterized by predominantly progressive fibro-fatty infiltration of the right ventricle. Clinical presentations of ARVD/C vary from syncope, progressive heart failure (HF), ventricular tachyarrhythmias, and sudden cardiac death (SCD). The 2010 modified Task Force criteria were established to facilitate the recognition and diagnosis of ARVD/C. An implantable cardiac defibrillator (ICD) remains to be the cornerstone in prevention of SCD in patients fulfilling the diagnosis of definite ARVD/C, especially among ARVD/C patients with syncope, hemodynamically unstable ventricular tachycardia (VT), ventricular fibrillation, and aborted SCD. Further risk stratification is clinically valuable in the management of patients with borderline or possible ARVD/C and mutation carriers of family members. However, given the entity of heterogeneous penetrance and non-uniform phenotypes, the standardization of clinical practice guidelines for at-risk individuals will be the next frontier to breakthrough.

Antiarrhythmic drugs are prescribed frequently to patients experiencing frequent ventricular tachyarrhythmias and/or appropriate ICD shocks. Amiodarone is the recommended drug of choice. Radiofrequency catheter ablation (RFCA) has been demonstrated to effectively eliminate the drug-refractory VT in patients with ARVD/C. However, the efficacy and clinical prognosis of RFCA via endocardial approach alone was disappointing prior to the era of epicardial approach. In recent years, it has been proven that the integration of endocardial and epicardial ablation by targeting the critical isthmus or eliminating abnormal electrograms within the diseased substrates could yield higher acute success and lower recurrence of ventricular tachyarrhythmias during long-term follow-up. Heart transplantation is the final option for patients with extensive disease, biventricular HF with uncontrollable hemodynamic compromise, and refractory ventricular tachyarrhythmias despite aggressive medical and ablation therapies.

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* Corresponding author at: Division of Cardiology, Taipei Veterans General Hospital, 201 Section 2, Shih-Pai Road, Taipei, Taiwan. Tel.: +886 2 2875 7156; fax: +886 2 2873 5656.
E-mail address: linyennjiang@gmail.com (S.-A. Chen).

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Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy, which was first described in 1965 [1]. ARVD/C predominantly affects the right ventricle (RV) with fibrofatty replacement pathologically. The left ventricle (LV) involvement, typically the posterior lateral wall, accounts for an estimated 10% of patients, and presents usually as one of the late manifestations [2,3]. Mutations of seven dominant genes in the desmosome result in defective cell-to-cell binding and contribute to the pathogenesis of ARVD/C.

The presentations of ARVD/C are diverse, ranging from syncope, heart failure (HF), and sudden cardiac death (SCD). The clinical courses have been categorized into four phases: concealed phase, overt electrical disorder, RV failure, and bi-ventricular failure [3]. Overlapping of each phase may occur. Given the diversity of disease course, the 2010 modified Task Force (TF) criteria were proposed to facilitate the diagnosis [4]. Nevertheless, risk stratification for individuals with ARVD/C and at-risk subjects is of clinical significance. In this review, we summarize current diagnostic guidelines, risk stratification schemes, and the management of ARVD/C.

Diagnosis of ARVD/C: from past to present

McKenna et al. [5] initially proposed international TF criteria for the diagnosis of ARVD/C in 1994, and Marcus et al. [4] revised them (Fig. 1) through the incorporation of new knowledge and technology to improve the diagnostic sensitivity and yet to maintain diagnostic specificity. Quantitative parameters, particularly imaging studies, were used. Individuals are categorized into definite, borderline, or possible diagnosis of ARVD/C after detailed investigation of structural, histological, electrocardiographic, arrhythmogenic, family history, and genetic features of the disease. The modification of the TF criteria maintains the major and minor criteria for each aspect to facilitate clinical diagnosis of ARVD/C in early stage and first-degree relatives with incomplete expression of the disease [6].

Based on the revised TF criteria, series of evaluations consisting of non-invasive studies of electrocardiography (ECG), signal averaged ECG, echocardiogram and/or magnetic resonance imaging (MRI), Holter monitoring, genetic analysis, and invasive studies of RV angiography, RV endomyocardial biopsy (EMB), are recommended for individuals at-risk to establish the diagnosis. Importantly, although 12-lead ECG (Fig. 2) is considered as an initial screening tool, 12% of patients with ARVD/C may have normal ECG [7], emphasizing the need for comprehensive clinical evaluations.

Structural abnormalities in ARVD/C can be evaluated by echocardiogram, MRI noninvasively, or RV angiography invasively. Incorporation of quantitative parameters by echocardiography or MRI yields high specificity (90–98% for major criteria) [4]. However, the application of revised TF criteria significantly reduced the incidence of structural abnormalities fulfilling any diagnostic criteria than the original criteria [8]. On the other hand, despite the development of computerized analysis in quantifying RV abnormalities by angiography [9,10], the presence of RV akinesia, dyskinesia, or aneurysm remains one of the major criteria. RV angiography may depict sacculation, segmental contraction impairment, and variable trabecular patterns in patients with ARVD/C [11], and therefore, remains the gold standard for structural assessment in some laboratories.

Distinguishing ARVD/C from other mimicking diagnoses, such as idiopathic RV outflow tract tachycardia (RVOT VT), myocarditis, sarcoidosis, or endomyocardial fibrosis, is warranted. Assessment of transmural fibrofatty infiltration by means of EMB may provide valuable histopathological features despite potential risk of free wall perforation and possibility of false negative results owing to the nature of segmental involvement. Guiding EMB based on the low voltage area identifiable on electroanatomic mapping (EAM) may yield higher diagnostic sensitivity [12].

Of note, electrophysiological studies by programmed stimulation (PVS) not only have a pivotal role in evaluating the vulnerability of ventricular tachyarrhythmias, but provide clues for the diagnosis of ARVD/C. Denis et al. [13] demonstrated that either the presence of polymorphic premature ventricular contractions (PVCs) with $\geq$1 couplet or sustained or nonsustained VT with left bundle branch block (LBBB) after excluding RVOT VT by high dose isoproterenol (45 μg/min) infusion could help in making the diagnosis of ARVD/C in the early stage of disease yielding a sensitivity of 91.4% and a specificity of 88.9%.

Risk stratification and disease progression of ARVD/C

Risk stratification in patients with ARVD/C

Several factors have been proposed [2,14–16] for stratifying the risk of mortality and/or ventricular tachyarrhythmias in ARVD/C. Corrado et al. [17] established an arrhythmic risk stratification pyramid, which categorized patients with ARVD/C into highest, intermediate, and lowest risk groups according to the variables shown in Fig. 3A to facilitate early recognition of individuals who would be benefit from an implantable cardioverter-defibrillator (ICD) implantation. Because of a high annual arrhythmic risk up to 8–10%, an ICD implantation is mandatory for those with aborted SCD, hemodynamically unstable sustained VT, or syncope.

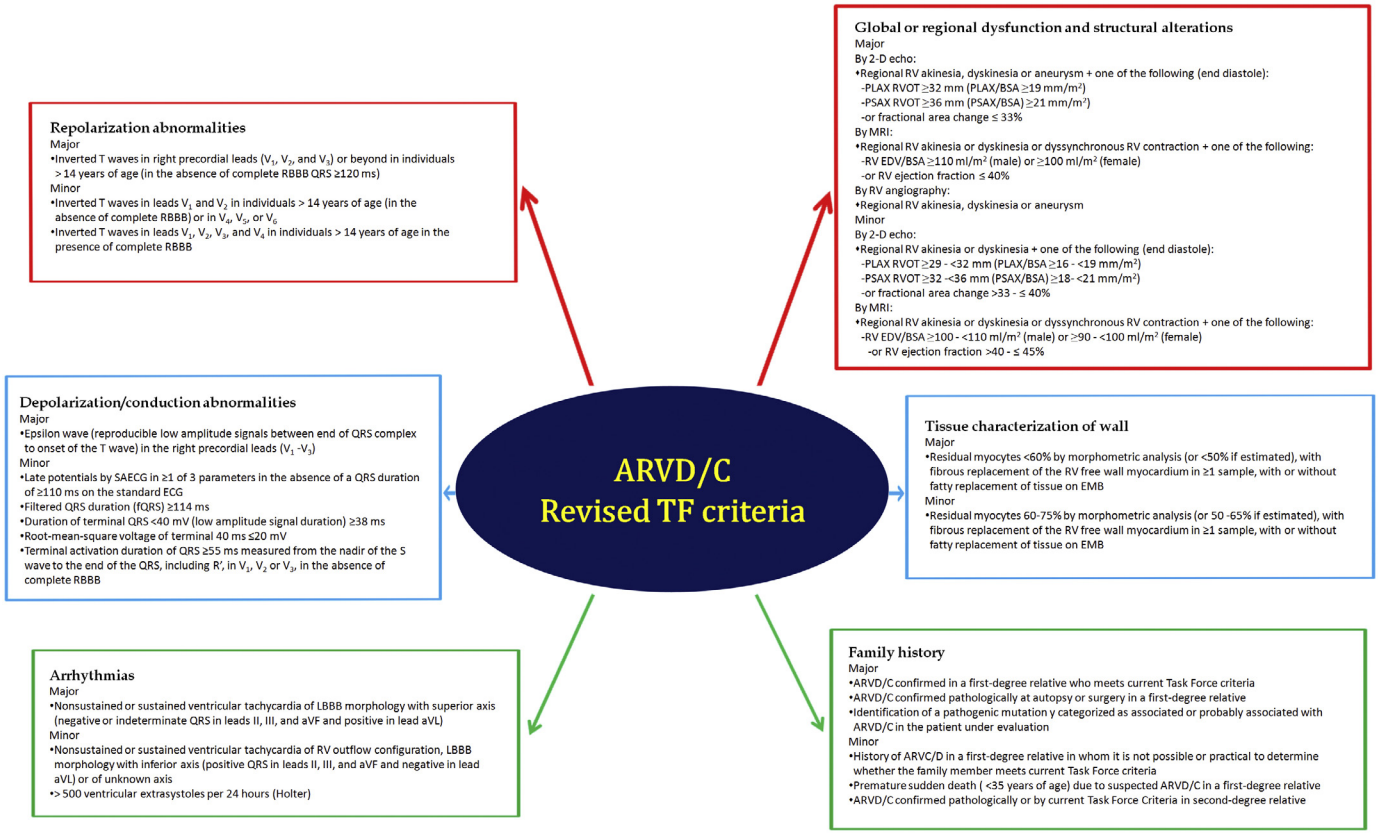

Fig. 1. Current Task Force criteria for the diagnosis of ARVD/C proposed in 2010. Comprehensive evaluations were composed of structural alteration and dysfunction, tissue characteristics from endomyocardial biopsy, family history, electrocardiographic manifestations of depolarization abnormalities, repolarization abnormalities, and arrhythmia features. Modified from Marcus et al. [4]. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; BSA, body surface area; EDV, end diastolic volume; EMB, endomyocardial biopsy; LBBB, left bundle branch block; PLAX, parasternal long axis; PSAX, parasternal short axis; RBBB, right bundle branch block; RV, right ventricular; RVOT, right ventricular outflow tract; SAECG, signal-averaged electrocardiogram.

Likewise, Bhonsale et al. [18] evaluated the arrhythmic risk among patients with ARVD/C-associated desmosomal mutations, and similarly classified subjects into high-, intermediate-, and low-risk groups based on the integrated assessments of the proband's status, ECG features, family history, and the density of PVCs from Holter monitoring to assist risk stratification during pedigree evaluation (Fig. 3B).

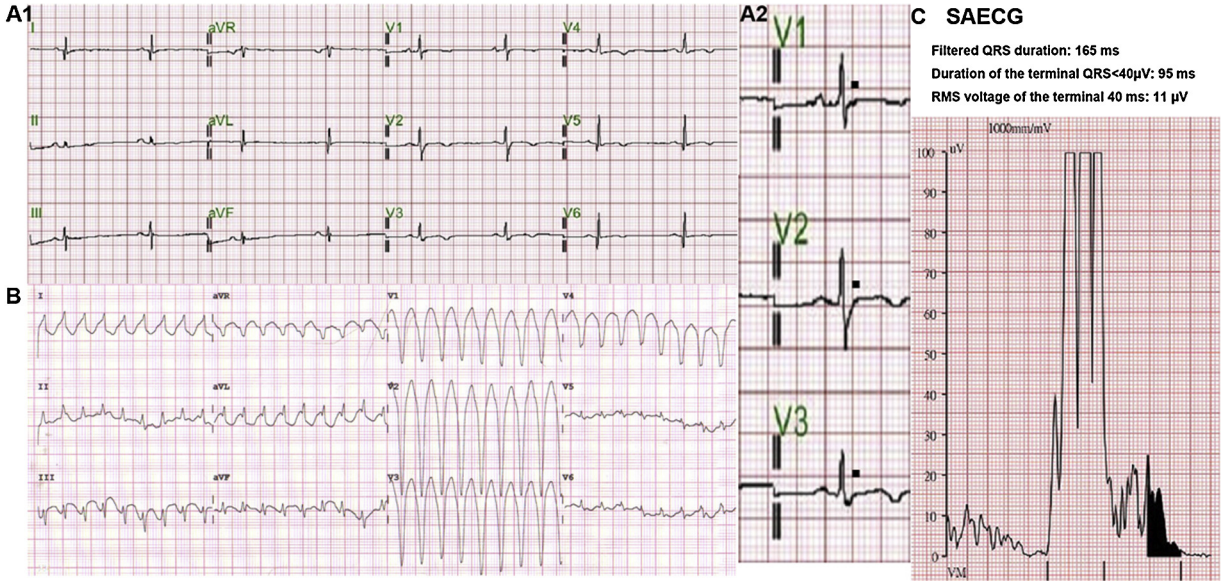

Fig. 2. A 35-year-old man presented with syncope and aborted sudden cardiac death. A standard electrocardiogram (A1) showed low amplitude signals at the end of QRS complex (epsilon wave) in V_{1-3} (A2) and diffuse T wave inversion in V_{1-6}. The morphology of clinical ventricular tachycardia (B) was characterized by left bundle branch block morphology and superior axis (indeterminate QRS in lead II, III, and aVF and positive in lead aVL) with a tachycardia cycle length of 286 ms. Signal-averaged electrocardiogram (SAECG) (C) also depicted 3+ according to Task Force criteria.

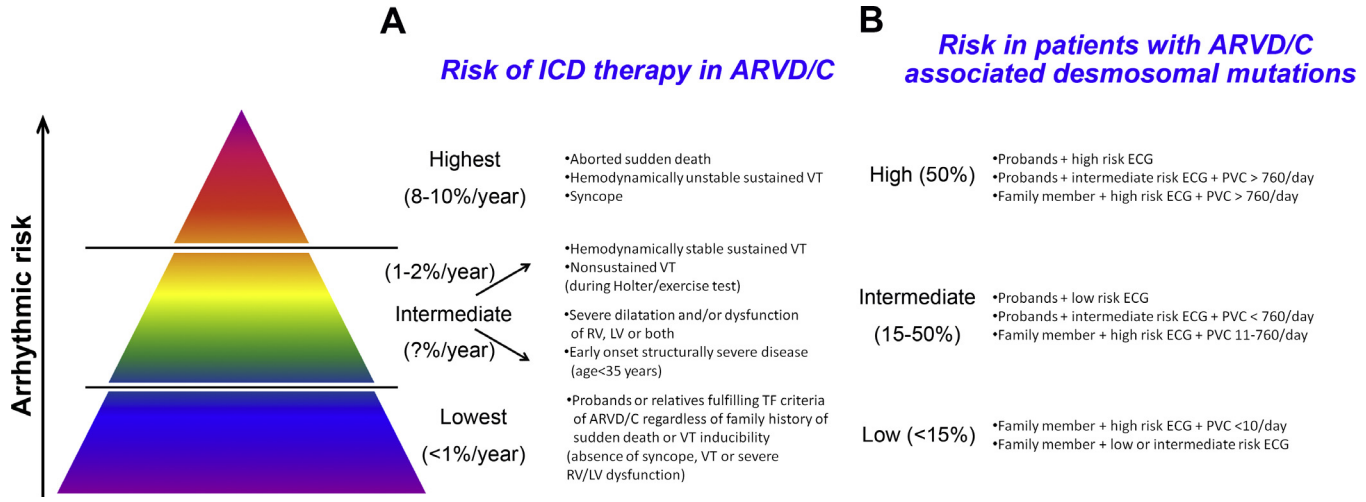

Fig. 3. Schemes of arrhythmic risk stratification in patients with ARVD/C undergoing ICD therapies (A) and individuals with ARVD/C-associated desmosomal mutations (B). Subjects were categorized to high, intermediate, and low risk accordingly. Modified from Corrado et al. [17] and Bhonsale et al. [18]. PVC burden was obtained by a Holter monitoring. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LV, left ventricle; PVC, premature ventricular complex; RV, right ventricle; TF, task force; VT, ventricular tachycardia.

Factors influence disease progression and the arrhythmic episodes

Notwithstanding the progressive nature of ARVD/C, incomplete genetic penetrance and variable manifestations suggested that the clinical phenotype might be influenced by certain factors. Endurance training can induce RV enlargement and/or ventricular tachyarrhythmias in heterozygous plakoglobin-deficient mice experimentally and desmosomal mutation carriers clinically, implying the contribution of non-genetic factors on clinical manifestations in ARVD/C [19,20].

Additionally, Chung et al. [21] found that the accumulation of ventricular arrhythmia and SCD episodes in patients with ARVD/C was independently associated with certain meteorological factors during the summer season, reflecting the role of environmental factors on triggering arrhythmic events. These findings bring insight into the education and risk modification in patients with ARVD/C and their relatives.

Management and catheter ablation in ARVD/C

The aim of management of patients with ARVD/C is to prevent the occurrence of ventricular tachyarrhythmias and SCD, and it has been traditionally achievable by the incorporation of antiarrhythmic drugs (AADs), ICD, and radiofrequency catheter ablation. Rarely, heart transplantation is required for patients with severe diffuse biventricular failure or catastrophic ventricular tachyarrhythmias refractory to other treatments. Education on the risk of SCD and serial evaluations for affected individuals and the relatives are of clinical importance.

ICD implantation

A previous study investigated the natural history of ARVD/C with an annual mortality rate of 2.3% [2]. Hodgkinson et al. studied 11 families with ARVD5 (TMEM43 mutation) in a long-term follow-up, and found a 28% reduction in five-year mortality in males with an ICD [22], which was similar to the cumulative frequency of ICD intervention for fatal ventricular tachyarrhythmias (VT > 240 beats/min). Bhonsale et al. reported an average incidence of ICD therapies for VF/VFL (ventricular fibrillation/ventricular flutter) of 4%/year in 84 patients with definite or probable ARVD/C [16], and higher incidence of ICD interventions in probands than in family members (13% vs. 3.4%/year). Regarding the risk of SCD, individuals with ARVD/C should receive an ICD implantation as a Class I indication based on current guidelines, particularly for those with sustained VT/VF who have received optimal medical therapy [23].

However, it is unknown whether and when the family members should receive an ICD implantation for primary prevention. In face of the evidence that electrical abnormalities usually precede detectable structural changes in almost one-third of at-risk relatives during follow-up [24], annual or more frequent electrocardiographic screening is essential for at-risk family members of patients with ARVD/C. An ICD implantation may be considered for family members with SCD, or undiagnosed syncope when ventricular tachyarrhythmias cannot be excluded as cause of syncope after optimal medical therapy (Class II indication) [23].

Antiarrhythmic medication

Although ICD implantation is the dominant approach in prevention of SCD in patients with ARVD/C, empirical AADs should be considered for patients with a propensity to the occurrences of VT/VF. Until now, there has been no prospective study elucidating and comparing the efficacy of individual AADs in patients with ARVD/C.

Nevertheless, Wichter et al. demonstrated sotalol was effective in suppression of inducible VT/VF by PVS, whereas Class I AADs appeared to be ineffective in prevention of either inducible or non-inducible ventricular tachyarrhythmias in ARVD/C [25]. On the contrary, in an observation study from North American ARVC Registry, Marcus et al. found that only amiodarone significantly reduced the risk of clinically relevant ventricular arrhythmias, while sotalol increased the risk of ventricular tachyarrhythmias and beta-blockers did not influence the risk [26]. In this regard, amiodarone remains as the most effective empirical AAD to prevent ventricular arrhythmias and ICD shocks in patients with ARVD/C.

Catheter ablation of ventricular tachyarrhythmias in ARVD/C

Catheter ablation of VT by entrainment mapping has been used to treat patients with ARVD/C for several years, and the characteristics of scar-related reentrant VT in ARVD/C are similar to those in ischemic VT [27]. Despite the advance in techniques in catheter ablation of VT in patients with ARVD/C, acute success

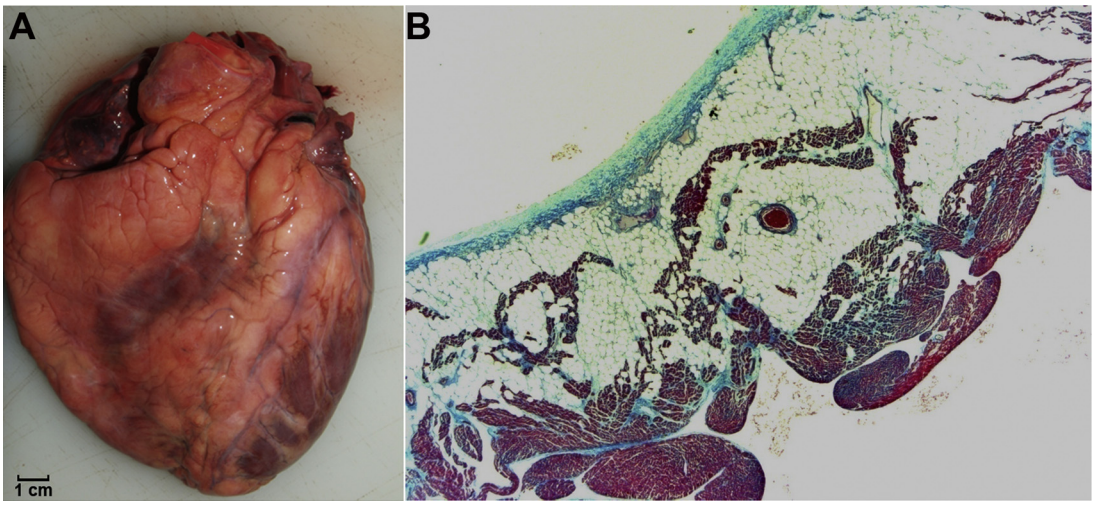

Fig. 4. An autopsied heart from 33-year-old male with arrhythmogenic right ventricular dysplasia/cardiomyopathy presenting as sudden death. (A) Extensive fatty infiltration of arrhythmogenic triangle (right ventricular outflow tract, inflow tract, and apex) with right ventricular dilatation. (B) Histopathological examination demonstrated fibrofatty infiltrations extending from epicardium to endocardium, accompanied with localized inflammatory changes.
Photos courtesy of the Taiwan National Forensic Department.

rates and clinical outcome are not consistent, ranging from 50 to 90% [28]. Previously, catheter ablation was reserved only for patients experiencing drug-refractory ventricular tachyarrhythmias and recurrent ICD shocks due to its limited effectiveness. Improved understanding of the arrhythmogenic substrates and the application of epicardial approach in recent years improved the success rate of eliminating VT in ARVD/C.

Pathogenesis of arrhythmogenic substrates and VT isthmuses

Owing to the fibrofatty replacement of epicardium gradually toward the endocardium at the RV inflow tract, outflow tract, apex, and posterior lateral wall of LV, ventricular arrhythmias, including PVCs, nonsustained to sustained VT, or VF, originate from the corresponding locations (Fig. 4) [4]. The process of fibrofatty infiltration is usually accompanied by inflammation initially and the creation of slow conducting channels as the inhomogeneous fibrosis forms subsequently. Both mechanisms provide the basis of arrhythmogenic substrates for discontinuous electrical propagation and explain the cause of ventricular arrhythmogenesis. Moreover, the different extent of fibrofatty infiltration involving epicardium more than endocardium results in longer and delayed epicardial activation sequence and contributes to layered activation of epicardial scar in ARVD/C rather than transmural activation of RV. This mechanism explains

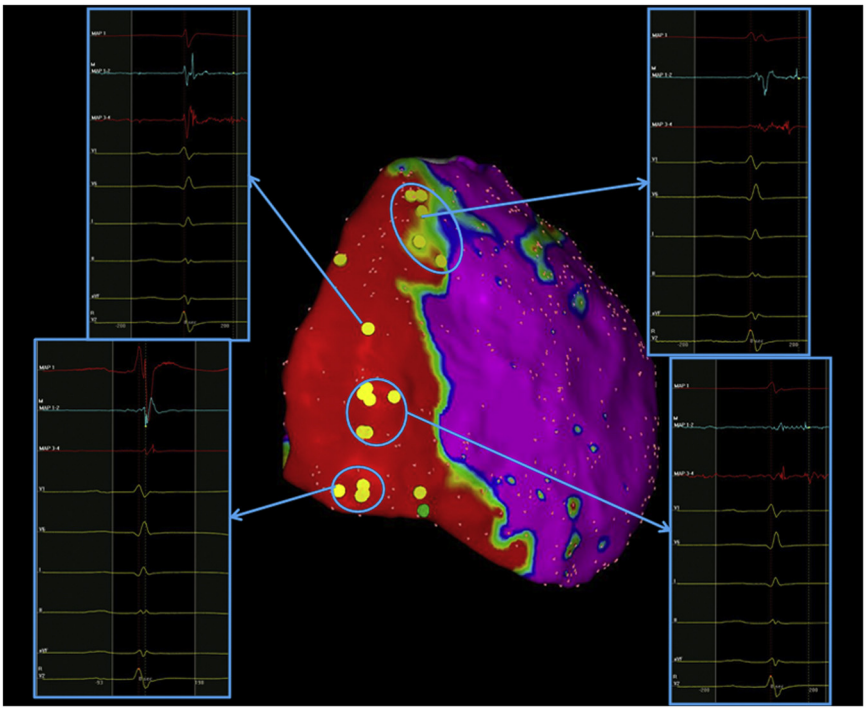

Fig. 5. Epicardial bipolar voltage mapping and the distribution of abnormal electrograms, consisting of isolated and fractionated late potentials. Widespread epicardial scar was extended from right ventricular outflow tract to anterior right ventricular free wall, whereas the abnormal electrograms were distributed within several localized area (yellow tags). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the arrhythmogenicity of epicardial VT circuits dominantly in ARVD/C [29].

It was noted that electrical and structural manifestations may evolve as the disease progresses, as a consequence of the degenerative nature of ARVD/C. However, in a majority of patients with ARVD/C undergoing repeat ablation procedures utilizing detailed EAM, the endocardial substrates showed absence of or limited macroscopic scar progression [30].

Substrate mapping of endocardium and epicardium

The application of 3-dimensional (3D) navigation systems on the VT ablation of ARVD/C has been proven to be a more reliable method. The 3D mapping system helps in realizing the underlying substrates and results in better prognosis free from VT recurrences. Detailed assessment of the endocardial and epicardial substrates during sinus rhythm by 3D color-coded voltage mapping, particularly over the area adjacent to the tricuspid valve region and the RV outflow tract, has provided important insight to identify the circuits of reentrant VTs within the scar and further ablation strategies. During sinus rhythm mapping, a cutoff value of bipolar voltage between 0.5 and 1.5 mV has been traditionally set up to define the endocardial substrates [31], whereas the voltage threshold of 1.0 mV is used for the setting of epicardial bipolar voltage mapping [32]. Typically, the distribution of epicardial scar is more extensive than scar identified endocardially. It is notably crucial to recognize and acquire the location of fractionated signals and/or isolated late potentials by EAM, which frequently are potentially responsible for the VT isthmus (Fig. 5). Finally, pacing

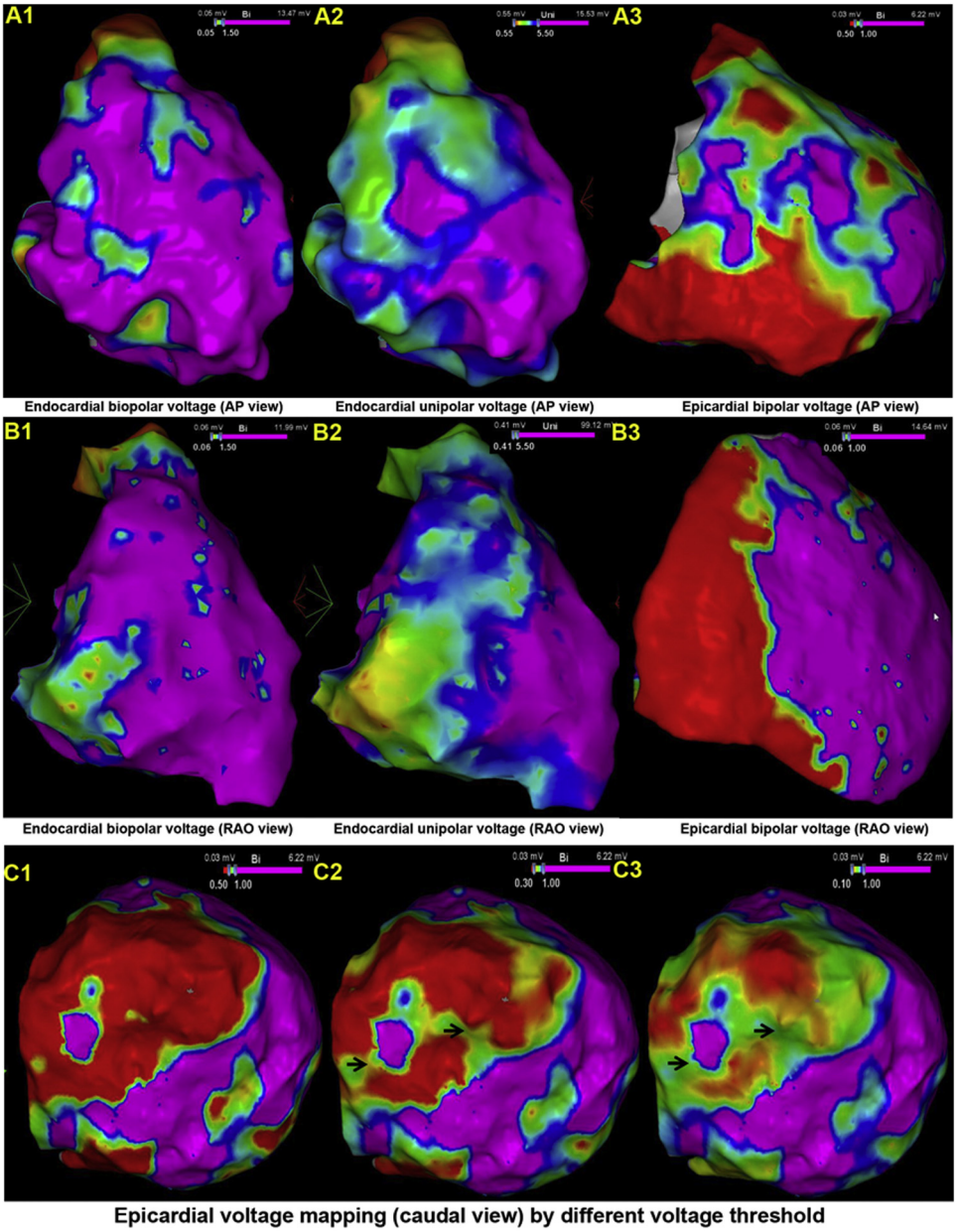

Fig. 6. A1–3 and B1–3 represent voltage mapping of 2 patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) regarding endocardial bipolar, endocardial unipolar, and epicardial bipolar voltage mapping, respectively. Endocardial voltage mapping (A1 and B1) demonstrated limited and segmental abnormal substrates, which was significantly smaller than the abnormal area identified by endocardial unipolar voltage mapping (A2 and B2) at a cut-off value of 5.5 mV, and the latter was compatible with the abnormal substrates recognized epicardially (<1 mV) (A3 and B3). (C) Epicardial voltage mapping (caudal view) by adjusting the voltage threshold (From C1–3; lower limit: 0.5–0.3–0.1 mV) in patients with ARVD/C provided information in identification of potential ventricular tachycardia isthmus. After adjusting the voltage threshold, two potential isthmuses were demonstrated at inferior basal right ventricle adjacent to the tricuspid annulus and inferior mid right ventricle (indicated by black arrows in C2 and C3). Both of these two isthmuses were responsible for the clinically-documented ventricular tachycardias.

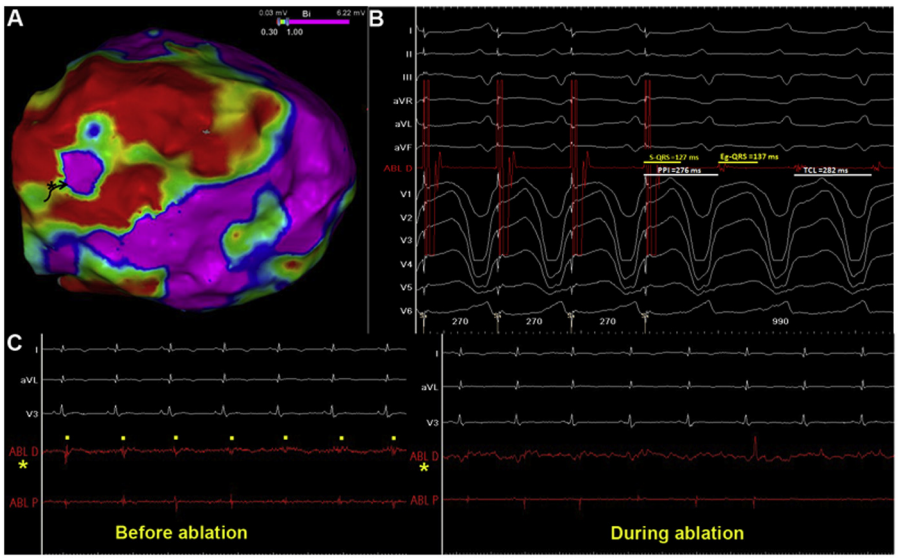

Fig. 7. (A) Epicardial voltage mapping after adjusting the voltage thresholds showed 2 potentials isthmuses as shown in Fig. 6C. The potential exit of ventricular tachycardia (VT) circuit was distal to the isthmus (black arrow; see the following description). Concealed entrainment of clinical VT (B) at inferior basal right ventricle adjacent to inflow tract (star) was achieved with a stimulus to QRS of 127 ms (local electrograms to QRS: 137 ms) and post-pacing interval of 276 ms (tachycardia cycle length: 282 ms). Local electrograms were also characterized by fractionated electrical activities, preceding QRS by 137 ms, which was compatible with the center of VT isthmus (S-QRS/TCL: 45%). Best pacemapping site was located distal to the potential isthmus, supporting the activation of VT from basal to the apical direction. (C) Left panel shows that local electrograms during sinus rhythm figuring as late potentials (yellow dots) at the point (star) with concealed entrainment (the same point as B). The late potentials of the last two beats was attenuated and eliminated during ablation (right panel) (both electrograms recorded by proximal and distal ablation catheter). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

maneuver can be used to facilitate recognition of delayed components of electrograms through different direction of wavelet propagation [33].

Noteworthy is that the endocardial voltage mapping of RV not only illustrates the substrates characteristics, but helps in evaluation of the extent of epicardial abnormalities. First, evaluation of the abnormal area by using the endocardial unipolar voltage mapping with a cutoff value of 5.5 mV, and the abnormal area is correlated to the epicardial scar in ARVD/C (Fig. 6A and B) [34]. A different cut-off value of 4.4 mV of RV endocardial unipolar voltage has been proposed by site-by site correlation [35]. Another method is to analyze the RV endocardial unipolar peak-negative voltage using a cut-off value of 1.66 mV to predict epicardial dense scar (<0.5 mV) [36].

Mapping of VT and ablation

The VTs in ARVD/C are either monomorphic or multi-monomorphic, depending on the isthmuses within the abnormal substrates. The induction of VT in patients with ARVD/C could be achieved by PVS with isoproterenol. Once the VT is induced, the morphology should be compared to clinically-documented VT, if available, and/or the ICD electrograms recorded [37].

For patients with hemodynamically stable sustained VT, both activation and entrainment mapping can be applied to facilitate the localization of tachycardia circuits (Fig. 7A and B). The activation mapping is performed by the acquisition of the earliest electrograms preceding QRS by at least more than 30 ms, typically characterized by fractionated or splitting mid-diastolic potentials along the VT isthmus. Entrainment criteria by measuring the differences between stimulus to QRS interval and the local electrograms to VT, as well as the post-pacing interval and the tachycardia cycle length could be applied to confirm the exit, center, and proximal part of protected isthmus [31]. Of interest, the endocardial EAM of VT could represent a focal activation pattern with radial spreading, and usually, concealed entrainment could be achieved at the earliest activation site, consistent with exit sites of a reentrant circuit [38]. Even though the application of pacemapping in scar-related VT is less accurate, pacing surrounding the dense scar bordering can facilitate the identification of the exit site of VT. Linear ablation lesions extending from the exit site into the identified isthmus guided by EAM can effectively terminate the tachycardia. An epicardial approach should be performed if endocardial ablation fails.

Nevertheless, nonmappable VTs are frequently encountered in ARVD/C, mostly owing to hemodynamically unstable condition, multiple reentrant circuit, and nonsustained VT. Substrate modification according to the incorporation of above methods is usually the strategy of choice to achieve procedural success. The potential channels and VT isthmuses can be visualized through the adjustment of voltage limit to assess the widespread scar area (Fig. 6C) [39], and catheter ablation can be simply performed by blocking the existence of possible channels between different voltage areas within the scar in combination with eliminating the fractionated signals endocardially and epicardially.

Given the likelihood of major complications caused by percutaneous pericardial puncture, an endocardial approach remains the initial step, although epicardial circuits are frequently present in ARVD/C. Additionally, the presence of epicardial fat can result in voltage mapping resembling dense scar tissues, and also impede the penetration of energy to the protected isthmus [40]. Furthermore, a recent study showed that endocardial ablation was able to eliminate the epicardial local abnormal ventricular activities (LAVA) in 73% of patients with ARVD/C, implying the endocardial RFCA is feasible to be used as initial strategy so as to reduce the need and risk of epicardial ablation [41].

To date, the most common energy source applied for VT ablation is radiofrequency. A 4-mm irrigated-tip catheter is widely accepted to be more effective to create deeper lesions for intramural or epicardial circuits. In our laboratory, power delivery is usually initiated at 30 W for endocardial site and 20 W for epicardium. The energy is titrated up to a maximum of 40 W for endocardium and 35 W for epicardium while targeting an impedance drop of 10 Ω by maintaining for a minimum of 120 s to site of termination in stable VT or the disappearance of abnormal potentials at each point for substrate modification (Fig. 7C).

Table 1
Clinical outcome of VT ablation in ARVD/C.

Author	Number of patients	Mapping strategies	Sites of targets	Acute results	Follow-up duration	Short-term free from VA (≤1 year)	Long-term free from VA
Dalal et al. [42]	24	Conventional or 3D mapping	Endocardial	46% for all inducible VT; 31% for clinical VT; 23% procedural failure	32 ± 36 months	50% (5 months)	25% (14 months)
Verma et al. [43]	22	3D mapping	Endocardial	82%	37 months (median)	77% (1 year)	53% (5 years)
Garcia et al. [44]	13	3D mapping	Endocardial + epicardial	92% (for all targeted VT)	18 ± 13 months	–	77%
Philips et al. [45]	87	Conventional or 3D mapping	Endocardial + epicardial	Complete success 47%; partial success 38%; procedural failure 15%	88.3 ± 66.1 months	1 year: 47% (endocardial: 45%; epicardial 64%)	5 years: 21%; 10 years: 15% (5 year-endocardial 19%; 5 year-epicardial 45%)
Bai et al. [46]	49[a]	Conventional or 3D mapping	Endocardial + epicardial	Polymorphic VT/VF: 1 from group 1 and 2 from group 2	At least 3 years[b]	300 days follow-up (group 1: 88.5%; group 2: 100%)	3 year follow-up (group 1: 52.2%; group 2 84.6%)

ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] Group 1: endocardial alone = 23; group 2: endo + epicardial = 26.
[b] Group 1: 1224 ± 310 days; group 2: 1175 ± 112 days.

Outcome of ablation of ventricular tachyarrhythmias in ARVD/C

Reviewing the literature [42–46] (Table 1), the outcome of ablation in ARVD/C has been studied with heterogeneous results, which were mostly explained by limited case numbers, the different ablation strategies, distinct disease stages, and variable follow-up duration. Generally, in the era of endocardial ablation, the long-term efficacy in prevention of VT recurrence could be achieved in only 25–53% of cases [40,43]. Advances in the understanding of underlying pathophysiology have brought forward ablation to the epicardial era [44]. Recent studies demonstrated a significant benefit of freedom from ventricular tachyarrhythmias or ICD therapy by 45–84.6% with the combination of endocardial and epicardial ablation [45,46]. Even though there has been great improvement in catheter ablation techniques and outcomes, a clinical hurdle remains in the realm of treating patients after failed epicardial ablation and patients with rapid disease progression. These challenges remain to be addressed by future breakthroughs.

Heart transplantation

Heart transplantation in ARVD/C is reserved seldom for patients with extensive HF or drug-refractory ventricular tachyarrhythmias unresponsive to other invasive interventions. Tedford et al. reported 18 patients with ARVD/C from over 1000 subjects in a registry undergoing cardiac transplantation, including 13 for HF and 5 for refractory VT [47]. Whether the advances in the understanding of pathophysiological characteristics and techniques in catheter ablation in the recent few years would attenuate the entity of disease progression and incidence of cardiac transplantation needs complementary studies.

Furthermore, load-reducing therapy with diuretics and nitrates could prevent the development of ARVD/C in heterozygous plakoglobin-deficient mice receiving endurance training [19,48]. The clinical implication of load-reducing therapy on preventing the development and progression in different stages of ARVD/C requires prospective investigation.

Conclusions

In summary, ARVD/C is an inherited progressive disease. Early investigation and risk stratification is essential for successful management. An accurate diagnosis is based on detailed evaluation of cardiac imaging, ECG, histopathology, family history, electrophysiological study, and genetic screening. Therapeutic options involving ICD, antiarrhythmic drugs, catheter ablation, and rarely heart transplantation are the current mainstay of treatments in prevention of SCD and ventricular tachyarrhythmias. With understanding of the underlying substrate properties, and improvement of navigation system, mapping, and epicardial ablation techniques, the prognosis of VT ablation in ARVD/C has improved tremendously.

Conflict of interest

None.

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Disclosures

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References

[1] Dalla Volta S, Fameli O, Maschio G. [The clinical and hemodynamic syndrome of auricularisation of the right ventricle. (Apropos of 4 personal cases)]. Arch Mal Coeur Vaiss 1965;58:1129–43.
[2] Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2004;110:1879–84.
[3] Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, Roguin A, Tichnell C, James C, Russell SD, Judge DP, Abraham T, Spevak PJ, Bluemke DA, Calkins H. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation 2005;112:3823–32.
[4] Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J 2010;31:806–14.

[5] McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994;71:215–8.
[6] Hamid MS, Norman M, Quraishi A, Firoozi S, Thaman R, Gimeno JR, Sachdev B, Rowland E, Elliott PM, McKenna WJ. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol 2002;40:1445–50.
[7] te Riele AS, James CA, Bhonsale A, Groeneweg JA, Camm CF, Murray B, Tichnell C, van der Heijden JF, Dooijes D, Judge DP, Hauer RN, Tandri H, Calkins H. Malignant arrhythmogenic right ventricular dysplasia/cardiomyopathy with a normal 12-lead electrocardiogram: a rare but underrecognized clinical entity. Heart Rhythm 2013;10:1484–91.
[8] Liu T, Pursnani A, Sharma UC, Vorasettakarnkij Y, Verdini D, Deeprasertkul P, Lee AM, Lumish H, Sidhu MS, Medina H, Danik S, Abbara S, Holmvang G, Hoffmann U, Ghoshhajra BB. Effect of the 2010 task force criteria on reclassification of cardiovascular magnetic resonance criteria for arrhythmogenic right ventricular cardiomyopathy. J Cardiovasc Magn Reson 2014;16:47.
[9] Indik JH, Wichter T, Gear K, Dallas WJ, Marcus FI. Quantitative assessment of angiographic right ventricular wall motion in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). J Cardiovasc Electrophysiol 2008;19:39–45.
[10] Wellnhofer E, Ewert P, Hug J, Hui W, Kretschmar O, Chavengsuk D, Kühne T, Abdul-Khaliq H, Nagel E, Lange PE, Fleck E. Evaluation of new software for angiographic determination of right ventricular volumes. Int J Cardiovasc Imaging 2005;21:575–85.
[11] Daliento L, Rizzoli G, Thiene G, Nava A, Rinuncini M, Chioin R, Dalla Volta S. Diagnostic accuracy of right ventriculography in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 1990;66:741–5.
[12] Avella A, d'Amati G, Pappalardo A, Re F, Silenzi PF, Laurenzi F, DE Girolamo P, Pelargonio G, Dello Russo A, Baratta P, Messina G, Zecchi P, Zachara E, Tondo C. Diagnostic value of endomyocardial biopsy guided by electroanatomic voltage mapping in arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Cardiovasc Electrophysiol 2008;19:1127–34.
[13] Denis A, Sacher F, Derval N, Lim HS, Cochet H, Shah AJ, Daly M, Pillois X, Ramoul K, Komatsu Y, Zemmoura A, Amraoui S, Ritter P, Ploux S, Bordachar P, et al. Diagnostic value of isoproterenol testing in arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2014;7:590–7.
[14] Saguner AM, Ganahl S, Baldinger SH, Kraus A, Medeiros-Domingo A, Nordbeck S, Saguner AR, Mueller-Burri AS, Haegeli LM, Wolber T, Steffel J, Krasniqi N, Delacrétaz E, Lüscher TF, Held L, et al. Usefulness of electrocardiographic parameters for risk prediction in arrhythmogenic right ventricular dysplasia. Am J Cardiol 2014;113:1728–34.
[15] Peters S, Reil GH. Risk factors of cardiac arrest in arrhythmogenic right ventricular dysplasia. Eur Heart J 1995;16:77–80.
[16] Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B, Dalal D, Tedford R, Russell SD, Abraham T, Tandri H, Judge DP, Calkins H. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. J Am Coll Cardiol 2011;58:1485–96.
[17] Corrado D, Basso C, Pilichou K, Thiene G. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart 2011;97:530–9.
[18] Bhonsale A, James CA, Tichnell C, Murray B, Madhavan S, Philips B, Russell SD, Abraham T, Tandri H, Judge DP, Calkins H. Risk stratification in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. Circ Arrhythm Electrophysiol 2013;6:569–78.
[19] Fabritz L, Hoogendijk MG, Scicluna BP, van Amersfoorth SC, Fortmueller L, Wolf S, Laakmann S, Kreienkamp N, Piccini I, Breithardt G, Noppinger PR, Witt H, Ebnet K, Wichter T, Levkau B, et al. Load-reducing therapy prevents development of arrhythmogenic right ventricular cardiomyopathy in plakoglobin-deficient mice. J Am Coll Cardiol 2011;57:740–50.
[20] James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.
[21] Chung FP, Li HR, Chong E, Pan CH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chao TF, Liao JN, Lin WY, Shaw KP, Chen SA. Seasonal variation in the frequency of sudden cardiac death and ventricular tachyarrhythmia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: the effect of meteorological factors. Heart Rhythm 2013;10:1859–66.
[22] Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, Thierfelder L, Stuckless SN, Dicks EL, McKenna WJ, Connors SP. The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol 2005;45:400–8.
[23] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death – executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Eur Heart J 2006;27:2099–140.
[24] te Riele AS, James CA, Rastegar N, Bhonsale A, Murray B, Tichnell C, Judge DP, Bluemke DA, Zimmerman SL, Kamel IR, Calkins H, Tandri H. Yield of serial evaluation in at-risk family members of patients with ARVD/C. J Am Coll Cardiol 2014;64:293–301.
[25] Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. Circulation 1992;86:29–37.
[26] Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, Estes 3rd NA, Marcus F, Scheinman MM, Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol 2009;54:609–15.
[27] 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.
[28] Arbelo E, Josephson ME. Ablation of ventricular arrhythmias in arrhythmogenic right ventricular dysplasia. J Cardiovasc Electrophysiol 2010;21:473–86.
[29] Haqqani HM, Tschabrunn CM, Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered activation of epicardial scar in arrhythmogenic right ventricular dysplasia: possible substrate for confined epicardial circuits. Circ Arrhythm Electrophysiol 2012;5:796–803.
[30] Riley MP, Zado E, Bala R, Callans DJ, Cooper J, Dixit S, Garcia F, Gerstenfeld EP, Hutchinson MD, Lin D, Patel V, Verdino R, Marchlinski FE. 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.
[31] Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation 2000;101:1288–96.
[32] Cano O, Hutchinson M, Lin D, Garcia F, Zado E, Bala R, Riley M, Cooper J, Dixit S, Gerstenfeld E, Callans D, Marchlinski FE. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. J Am Coll Cardiol 2009;54:799–808.
[33] Nogami A, Sugiyasu A, Tada H, Kurosaki K, Sakamaki M, Kowase S, Oginosawa Y, Kubota S, Usui T, Naito S. Changes in the isolated delayed component as an endpoint of catheter ablation in arrhythmogenic right ventricular cardiomyopathy: predictor for long-term success. J Cardiovasc Electrophysiol 2008;19:681–8.
[34] Polin GM, Haqqani H, Tzou W, Hutchinson MD, Garcia FC, Callans DJ, Zado ES, Marchlinski FE. Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm 2011;8:76–83.
[35] Tokuda M, Tedrow UB, Inada K, Reichlin T, Michaud GF, John RM, Epstein LM, Stevenson WG. Direct comparison of adjacent endocardial and epicardial electrograms: implications for substrate mapping. J Am Heart Assoc 2013;2:e000215.
[36] Chi PC, Lin YJ, Chang SL, Lo LW, Hu YF, Chao TF, Chung FP, Liao J, Tuan TC, Kuo JY, Huang JL, Chen SA. Unipolar peak-negative voltage as an endocardial electrographic characteristic to predict overlying abnormal epicardial substrates in patients with right epicardial ventricular tachycardia. J Cardiovasc Electrophysiol 2014;25:1343–9.
[37] Tschabrunn CM, Anter E, Marchlinski FE. Identifying non-inducible ventricular tachycardia origin utilizing defibrillator electrograms. J Interv Card Electrophysiol 2013;36:243–6.
[38] Reithmann C, Hahnefeld A, Remp T, Dorwarth U, Dugas M, Steinbeck G, Hoffmann E. Electroanatomic mapping of endocardial right ventricular activation as a guide for catheter ablation in patients with arrhythmogenic right ventricular dysplasia. Pacing Clin Electrophysiol 2003;26:1308–16.
[39] Arenal A, del Castillo S, Gonzalez-Torrecilla E, Atienza F, Ortiz M, Jimenez J, Puchol A, García J, Almendral J. Tachycardia-related channel in the scar tissue in patients with sustained monomorphic ventricular tachycardias: influence of the voltage scar definition. Circulation 2004;110:2568–74.
[40] Desjardins B, Morady F, Bogun F. Effect of epicardial fat on electroanatomical mapping and epicardial catheter ablation. J Am Coll Cardiol 2010;56:1320–7.
[41] Komatsu Y, Daly M, Sacher F, Cochet H, Denis A, Derval N, Jesel L, Zellerhoff S, Lim HS, Jadidi A, Nault I, Shah A, Roten L, Pascale P, Scherr D, et al. Endocardial ablation to eliminate epicardial arrhythmia substrate in scar-related ventricular tachycardia. J Am Coll Cardiol 2014;63:1416–26.
[42] Dalal D, Jain R, Tandri H, Dong J, Eid SM, Prakasa K, Tichnell C, James C, Abraham T, Russell SD, Sinha S, Judge DP, Bluemke DA, Marine JE, Calkins H. 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.
[43] Verma A, Kilicaslan F, Schweikert RA, Tomassoni G, Rossillo A, Marrouche NF, Ozduran V, Wazni OM, Elayi SC, Saenz LC, Minor S, Cummings JE, Burkhardt JD, Hao S, Beheiry S, 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.

[44] 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.
[45] Philips B, Madhavan S, James C, Tichnell C, Murray B, Dalal D, Bhonsale A, Nazarian S, Judge DP, Russell SD, Abraham T, Calkins H, Tandri H. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol 2012;5:499–505.
[46] Bai R, Di Biase L, Shivkumar K, Mohanty P, Tung R, Santangeli P, Saenz LC, Vacca M, Verma A, Khaykin Y, Mohanty S, Burkhardt JD, Hongo R, Beheiry S, Dello Russo A, 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.
[47] Tedford RJ, James C, Judge DP, Tichnell C, Murray B, Bhonsale A, Philips B, Abraham T, Dalal D, Halushka MK, Tandri H, Calkins H, Russell SD. Cardiac transplantation in arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2012;59:289–90.
[48] Fabritz L, Fortmüller L, Yu TY, Paul M, Kirchhof P. Can preload-reducing therapy prevent disease progression in arrhythmogenic right ventricular cardiomyopathy? Experimental evidence and concept for a clinical trial. Prog Biophys Mol Biol 2012;110:340–6.