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REVIEW ARTICLE

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Right ventricular dysplasia: management and treatment in light of current evidence

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare cardiovascular disease that predisposes to ventricular arrhythmias potentially leading to sudden cardiac death (SCD). ARVC varies considerably with multiple clinical presentations, ranging from no symptoms to cardiac arrhythmias to SCD. ARVC prevalence is not well known, but the estimated prevalence in the general population is 1:5000. Diagnosis of ARVC can be made by using the Revised European Society of Cardiology criteria for ARVC that includes ventricular structural and functional changes, ECG abnormalities, arrhythmias, family and genetic factors. The management of ARVC is focused on prevention of lethal events such as SCD. Implantable cardioverter defibrillator placement is the only proven mortality benefit in treatment of ARVC. Other treatment strategies include medications such as beta blockers and antiarrhythmics, radiofrequency ablation, surgery, cardiac transplantation, and lifestyle changes. All these interventions help in symptomatic treatment but none of them have proved to decrease mortality rates. ARVC is a progressive disease that leads to SCD if not treated appropriately. Management of these diseases has been a challenge for physicians. With the advent of technology and many new drugs/devices under clinical investigation, this might change in the future. However, while advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain of this unique disease. With continued research, we can expect more cost-effective and patient-friendly drug therapies and ablation techniques to be developed in the near future.

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1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as 'Arrhythmogenic right ventricular dysplasia', is a rare cardiovascular disease, often familial, that predisposes to ventricular arrhythmias (VA) potentially leading to sudden cardiac death (SCD) in young patients [1–4]. ARVC is more prevalent in young people and athletes [5–7]. ARVC was first described in the literature back in the eighteenth century by the Pope's physician that reported four generations in one family having progressive congestive heart failure with unexplained SCD [8]. This was followed by a case series by Marcus et al., which reported 24 patients with ventricular tachycardia (VT) having left bundle branch block [9]. Additionally, the electrocardiographic epsilon (σ) wave was first described by Fontaine which helped enhance recognition of potential electrocardiographic features of ARVC [10]. Epsilon wave can be seen in the ECG as a small positive deflection (blip) buried in the end of the QRS complex helping identify and diagnose patients with ARVC [10].

ARVC has multiple clinical presentations, ranging from no symptoms to abnormal cardiac arrhythmias and SCD [11]. ARVC prevalence is not well known, but the estimated prevalence in the general population is 1:5000 [12]. ARVC has been reported more commonly in young adults in their 20s, men and in northern Italy [11–14]. ARVC is responsible for 17% of SCD in general population and 22% of SCD in athletes [14–17].

ARVC is caused by fibrous-adipose tissue replacement of right ventricular muscle. This leads to regional wall motion abnormalities which progress to global regional wall motion abnormalities and right ventricular dilation which in turn causes VA, right ventricular failure, and SCD [14,18]. In recent years, several genetic mutations that lead to cardiac cell defects have been discovered and linked to ARVC such as desmoplakin, plakoglobin, and plakophilin [19]. The tissue replacement can also involve areas of the left ventricle with relative sparing of the septum [20].

2. Diagnosis of ARVC

Diagnosis of ARVC may be challenging, as no single modality is sufficiently specific to establish ARVC diagnosis. Therefore, multiple sources of diagnostic information are combined in a complex set of diagnostic criteria. ARVC should be suspected in a young patient with

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palpitations, syncope, or aborted SCD. First symptom is often SCD, which makes early detection and a family screening test the cornerstone in the diagnostic evaluation. In a study of 100 patients with ARVC, 23% of the patients had SCD as the first symptom [21]. Other common presentations were palpitations (27%) and syncope (26%) [11]. These symptoms are usually exercise-related which may lead to premature beats and abnormal arrhythmogenic circuits. In a pathological myocardial substrate, this can perpetuate the incidence of life-threatening arrhythmias. Other studies have suggested that up to 67% of individuals with ARVC present with palpitations, 32% present with syncope, 27% with atypical chest pain, 6% with right ventricular failure, and 6% may remain asymptomatic [22].

In the last few years, dependence on diagnosing a patient with ARVC has increased on imaging studies. Imaging modalities commonly used for ARVC evaluation include echocardiography, cardiovascular magnetic resonance (CMR), and right ventricular angiography. Both echocardiography and angiography have significant limitations in assessing the right ventricle due to its complex geometry. Initially, the International Task Force for the diagnosis of ARVC (setup in 1994) was based on structural, electrocardiographic, and familial features of the disease. However, in the recent years, additional ECG markers along with use of technology has been favored. Growing experience with quantification of imaging criteria for ARVC as well as the recent introduction of newer techniques like contrast-enhanced echocardiography and CMR with late enhancement and electroanatomic voltage mapping has increased the sensitivity and specificity for diagnosing ARVC. Furthermore, the genotype–phenotype association studies have highlighted the deficiencies of the criteria based on familial disease.

Clinical diagnosis of ARVC is often difficult because of the nonspecific nature of the disease and the broad spectrum of clinical variations. There is no definitive diagnostic standard. Several investigations contribute to the diagnosis of ARVC. Consensus diagnostic criteria have been developed, which include right ventricular biopsy, noninvasive electrocardiography, family history, and imaging evaluation with echocardiography, CMR, and angiography. These diagnostic criteria incorporate the advances in both technology and genetics. This article reviews the current evidence for ARVC management and treatment strategies along with prognosis.

3. Management of ARVC

3.1. Risk factors and prevention of SCD

The management of ARVC is focused on prevention of lethal events such as SCD [21,22]. High-risk groups with an increased risk of SCD should be identified. These include young patients who have had a previous syncopal episode, history of cardiac arrest or ventricular tachyarrhythmia, two or more ARVC genetic mutations, patients having ARVC with LV involvement, and patients with TMEM43 gene missense mutation [23–27].

Genetic testing maybe considered for patients with possible ARVC but not yet established diagnosis (class IIb) [28]. Furthermore, mutation-specific genetic testing is recommended for family members of ARVC patients following the identification of the causative genetic mutation (class I) and comprehensive genetic testing can be useful for patients who meet the criteria for ARVC diagnosis (class IIa) [28].

3.2. ARVC treatment

Implantable cardioverter defibrillator (ICD) placement is the only proven intervention to have been associated with mortality benefit in the treatment of ARVC. Other treatment strategies including medications such as beta blocker (BB) and antiarrhythmics, radiofrequency ablation (RFA), cardiac transplantation, and lifestyle changes all may help in ARVC manifestations, but none of them have proven mortality benefits [29–35].

4. Lifestyle modification and patient education

Educating patients with ARVC and their affected children about the cause, manifestations, progressions, and possible lethal consequences is the first and most important step in treating patients with ARVC. Strenuous exercise can induce ventricular tachyarrhythmias, manifesting at an earlier age and promoting the disease progression due to right ventricular dilation with increased risk for VT [35–37]. The risk of SCD is significantly higher among competitive athletes compared with either recreational athletes or inactive patients [37]. It is thought that exercise leads to disruption of cellular junctions by increasing myocardial stress thus accelerating disease progression [35]. Both endurance and frequent exercise increase the risk of VA in patients with ARVC [35]. Therefore, physical exercise should be minimized with an exception of low-intensity recreational sports (class IIa) [38].

Any competitive sport or activity that causes symptoms in ARVC patients should be prohibited (Class I) [38]. It is recommended that athletes with syncope be evaluated by an electrophysiologist prior to resuming competitive sports (class I) [38]. Assessment by an electrophysiologist is reasonable for athletes with syncope and high-risk markers which include electric instability, including the frequency of premature ventricular contractions and sustained ventricular arrhythmia, extent of structural disease, cardiac syncope, male sex,

and the presence of multiple mutations (class IIa) [38]. It has been also suggested that family members of ARVC patients be restricted in participation in competitive sports (class IIa) [38].

5. Beta-blockers

Increasing physical activity leads to increased heart rate, myocardial stress, and oxygen demand, predisposing patients to recurrent arrhythmias [16,35,39–41]. BBs blunt these effects; however, no current clinical trial showed definitive mortality benefit for BB in patients with ARVC. Despite the lack of evidence, decreasing the sympathetic activity might decrease SCD. BB has been used in ARVC patients with VA, supra-VT, or atrial fibrillation/flutter with high-ventricular rate (class I) [22]. BB can be useful in patients with symptomatic ARVC regardless of arrhythmias (class IIa) [22]. Most common symptoms for which BB can be helpful in ARVC patients include lightheadness, shortness of breath, and palpitations (class IIa) [22]. However, BB is not recommended for an asymptomatic healthy patient with gene carriers (Class III) [22].

6. Antiarrhythmic medications

No current clinical trial has shown definitive mortality benefit for any antiarrhythmic medication. Despite the lack of evidence for mortality benefit, eliminating or decreasing the frequency of arrhythmias in ARVC by using antiarrhythmic medications could be theoretically useful in patients with ARVC [22]. Wichter et al. conducted the first systematic study to assess the antiarrhythmic therapy in ARVC [30]. It showed that Sotalol was the most effective antiarrhythmic medication in the treatment of ARVC-associated arrhythmias compared to BB, sodium channel blockers, verapamil, amiodarone, and other combination therapies. Authors suggested that amiodarone should be avoided due its potential for toxic side effects [42].

Antiarrhythmic drugs are not recommended to be used solely as an alternative to ICD in ARVC patients. Antiarrhythmic drugs are recommended as an adjunct therapy in ARVC patients along with ICD placement (class I) [22]. Antiarrhythmic drugs should be considered in ARVC patients who are suffering from premature ventricular beats and/or nonsustained VT for symptomatic improvement (class IIa) [22]. Antiarrhythmic drugs can be considered as an adjunct therapy to RFA without ICD in selected ARVC patients with recurrent VT who are hemodynamically stable (class IIb) [22]. On the other hand, antiarrhythmic drugs or ICD placement are not recommended in asymptomatic ARVC patients with no VT or in healthy carriers (class III) [22].

7. Heart failure management in ARVC

ARVC is a progressive disease that might lead to left ventricular failure and ultimately to biventricular pump failure [18]. Thromboembolic events are one of the complications in end stage ARVC because of progressive dilatation [43]. BB, diuretics, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs) are recommended for patients with ARVC who develop symptomatic congestive heart failure (class I) [22]. For ARVC patients who develop left ventricular dysfunction, ACEI or ARBC can be considered with considerable symptomatic benefit (class IIb) [22]. Besides, animal studies showed that preload-reducing drug therapy is efficient in ARVC patients, but no clinical trials have been conducted to prove their efficiency in humans [44,45]. Therefore, preload reducing medications are not yet included in the standard treatment of ARVC patients [22].

8. Radiofrequency ablation

RFA is not a definitive therapy for patients with ARVC [31,46]. However, RFA can be considered as an adjuvant therapy to ICD placement in patients with VT or frequent ICD firing despite using BB or antiarrhythmic drugs or in patients who were not able to tolerate ARVC recommended medications (class I) [22]. Furthermore, multiple electrophysiologic mapping techniques have been used to treat VA including voltage mapping and substrate mapping [31,32,46–48].

An epicardial approach for RFA is recommended in patients who fail one or more attempts at endocardial ablation (class I) [22]. Combined endocardial–epicardial VT ablation has had significant short- and long-term success rates compared to endocardial VT ablation alone [22,49]. VT recurrence following VT ablation could be explained by the patchy nature of ARVC; hence, development of new arrhythmic foci is not infrequent [32,50,51]. Therefore, RFA is currently not recommended as stand-alone therapy or as an alternative to ICD for ARVC patients due the progressive nature of ARVC (class III) [22].

9. ICD placement

ICD placement is the only proven mortality benefit treatment for ARVC [11,23,24,27,29,52–54]. ICD placement can also be used for primary or secondary prevention [23,24,54]. Multiple observational studies have shown clinical efficacy of ICD placement for preventing SCD in patients with ARVC [11,23,54–57]. The following are the current recommendations regarding ICD implantation for patients with ARVC [22]:

9.1. Class I recommendations for ICD implantation

(1) Patients with ARVC with LV dysfunction or severe RV systolic dysfunction.
(2) Patients with ARVC who experienced at least one episode of hemodynamically unstable, sustained VT, or ventricular fibrillation (VF).

9.2. Class II recommendations for ICD implantation

(1) Class IIa: Patients with ARVC with major risk factors.
(2) Class IIa: Patients with ARVC who experienced at least one episode of hemodynamically stable, sustained VT.
(3) Class IIb: Patients with ARVC who are at low risk (including those with stable ECG findings, female sex and patients with no family history of ARVC) of SCD after discussing risks and benefits with the patient.

9.3. Class III recommendations for ICD implantation

ICD implantation is currently not recommended in healthy carriers or even in asymptomatic ARVC patients with no other risk factors.

10. Cardiac transplantation

There are no systemic evaluations to study the effectiveness of cardiac transplantation in patients with ARVC. A small prospective study conducted by Tedorfd et al. which included 18 patients showed 1-year survival rate as 94% and 6-year survival rate as 88% following cardiac transplantation [34]. However, no data regarding symptomatic benefits or mortality benefits were available. Cardiac transplantation is usually indicated as the last resort for ARVC patients with severe heart failure or recurrent episodes of VT and VF despite RFA, surgical ablation, and ICD placement [22].

10.1. Prognosis

ARVC is a progressive disease that leads to SCD if not treated appropriately. ARVC is no longer considered an isolated RV disease [18]. LV changes either macroscopic or microscopic have been found in more than 75% of 42 examined hearts in patients with ARVC [18]. These findings were more age dependent and more common in patients with longstanding clinical history of ARVC [18]. Hence, ARVC can follow multiple pathological and clinical phases [14]. The concealed phase is the silent form of ARVC with subtle RV histological and structural changes. SCD can be the first manifestation in this phase if ARVC is not recognized early on in the disease process. Furthermore, these histological changes can lead to regional wall motion abnormalities and overt electrical changes that may manifest as VT that might possibly lead to SCD. With disease progression, global regional wall motion abnormalities along with right ventricular dilatation can be expected that can lead to right ventricular failure with preserved left ventricular function. The final phase of ARVC is left ventricular involvement that leads to biventricular heart failure and end stage cardiac disease.

Regarding prognosis, Groenweng et al. did an interesting study. He looked at 439 ARVC patients and 562 of their family members with median follow-up of 7 years [58,59]. SCD rate during the follow-up period was higher (16%) among patients without ICD placement compared to ARVC with ICD placement (0.6%). The study showed low mortality rate (6%) and low cardiac transplantation need (4%) among patients with ARVC [58,59]. In addition, the study showed that family members of ARVC with gene mutations were much more likely to develop symptomatic disease and die from a cardiac cause compared to family members without gene mutations.

11. Conclusion

Keeping in mind the extent of heart disease globally, studies should be carried out extensively on the management of patients with ARVC. Management of these diseases has been a challenge for physicians. However, with the advent of technology and many new drugs/devices under clinical investigation, this might change in the future. In the past few decades, research into the management of ARVC has increased tremendously. With it, our understanding of the relevant pathophysiology and treatment options has improved as well. With our ageing population and ever increasing prevalence of ARVC, optimized treatment plans for individuals are essential. Better therapeutic strategies for ARVC should be focused on disease-specific targets that aim to control pathophysiologic remodeling. The hope in the end will be a cure or a prevention strategy that will prevent triggers, substrate, or both from occurring. Cooperation between cardiologists and primary care physicians will undoubtedly facilitate risk stratification and ensure that optimal decisions will be made to provide maximum treatment benefit to the patient, while at the same time reducing the adverse effects. However, while advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain. With continued research, we can expect more cost-effective and patient-friendly drug therapies and ablation techniques to be developed in the near future. Besides, side effects of particular management plan/strategy should be highlighted and well documented, especially in regions where these protocols are routinely followed.

Disclosure statement

No potential conflict of interest was reported by the author.

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