Perspective Görüş

A comprehensive strategy for managing arrhythmogenic right ventricular cardiomyopathy

Aritmojenik sağ ventrküler kardiyomiyopatinin kapsamlı bir tedavi stratejisi

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Arrhythmogenic right ventricular cardiomyopathy (ARVC, also called dysplasia) is a rare, but severe cardiovascular disease that predisposes patients to ventricular arrhythmias, heart failure, and increased risk of sudden cardiac death (SCD). With an estimated prevalence in the range of 1:5000 to 1:2000 in the general population, ARVC is one of the leading causes of SCD in young people and in athletes.[1–3] It is unlikely to be monogenic in origin; there are more than 13 reported variants that may be disease modifiers of ARVC in the databases.[4]

The current goals in the management of ARVC are early diagnosis, risk stratification for SCD, minimizing ventricular arrhythmias, and delaying progression. Though it is an inherited cardiovascular disease with progressive myocardial degeneration and fibrosis accompanied by inflammation in the sub- and mid-myocardium,[5,6] ARVC is not easy to diagnose early. In children, ARVC may present with severe ventricular arrhythmias, syncope, and cardiac arrest.[7] Even an electrical storm might be an initial presentation of ARVC.[8]

The clinical diagnosis of ARVC is still challenging due to the lack of a definitive diagnostic test. Although there are electrocardiographic (ECG), histopathological, and imaging features, the classic, early clinical manifestations of ARVC are relatively rare, and some patients only have palpitations, fatigue, syncope, and SCD as the first manifestations of ARVC.[6,9,10] Moreover, there are some asymptomatic genetic carriers with no significant structural abnormalities at an early stage; therefore, it is difficult to quantify the progression of the disease through ECG changes alone.[11] Some clinical tests, such as ECG,[12] exercise treadmill testing, and plasma biomarker levels, e.g., bridging integrator 1 or sex hormones, can be useful in the diagnosis of ARVC.[13] Suspected ARVC patients should go through a risk assessment and follow-up process for better management and prevention of complications.[14]

Abbreviations:

ARVC	*Arrhythmogenic right ventricular cardiomyopathy*
CMR	*Cardiac magnetic resonance*
CRISPR	*Clustered regularly interspaced short palindromic repeats*
DSG2	*Desmoglein-2*
DSP	*Desmoplakin*
ECG	*Electrocardiogram*
ES	*Exome sequencing*
FDG-PET	*F-fluorodeoxyglucose positron emission tomography*
ICD	*Implantable cardioverter defibrillator*
iRT-ABCDEF	*Intervention in RT-ABCDEF*
PKP2	*Plakophilin-2*
SCD	*Sudden cardiac death*
SEEDi	*Sleep-emotion-exercise-diet intervention*
TMEM43	*Transmembrane protein 43*

There are several ECG features of ARVC. A very low 12-lead QRS voltage is characteristic of patients with ARVC with heart failure severe enough to warrant orthotopic heart transplantation,[15] and thus may serve as a clue to the diagnosis. Atrial arrhythmias are also common in patients with ARVC and they are as-

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sociated with increased atrial size and right ventricular dysfunction.[16] Bradyarrhythmias are commonly seen in ARVC and intraventricular conductional block is the most common type.[17] Premature ventricular contraction and low QRS voltages are more prevalent among ARVC patients. A QRS duration ratio of V2: V5 >1.2, prolonged terminal S wave activation duration in V2 of >55 milliseconds, or anterior, inferior, or lateral T-wave inversion may be seen. The J-point preceded anterior T-wave inversion <0.1 mV in 98% of patients with ARVC in 1 study.[18] Region-specific ECG depolarization, such as QRS fragmentation, is frequently observed in patients with ARVC and reflects delayed conduction due to right ventricular fibrosis.[19] However, there are often no demonstrable ECG phenotypes in electronic health records.[20]

Conventional immunohistochemical analysis of endomyocardial biopsy samples is highly sensitive and specific for ARVC.[21] As an important differential diagnostic method,[22] endomyocardial biopsy is still suitable for children with ARVC. However, it is invasive and not easily accepted by patients.

There is increasing need for the development of new, objective, non-invasive imaging techniques for diagnosis; for example, emerging imaging techniques, such as echocardiogram/magnetic resonance imaging strain measurements or computed tomography scanning, and high-throughput sequencing. It has been reported that only the American Society of Echocardiography criteria were able to differentiate ARVC from a control population.[23] Cardiac magnetic resonance (CMR) imaging also plays an important role in the clinical diagnosis of ARVC. CMR evidence of left ventricular involvement is a strong, independent predictor of cardiac events in patients with a definite, borderline, or possible ARVC diagnosis.[24] An abnormal CMR has a very high negative predictive value for hard cardiac events. CMR-based regional strain, late gadolinium enhancement, and electroanatomic mapping may enhance the diagnostic accuracy of CMR in ARVC without the need for invasive procedures.[25]

F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a validated technique for detecting myocardial inflammation. Some patients with ARVC demonstrate evidence of myocardial inflammation on FDG-PET,[26] suggesting that myocarditis may play a role in the ARVC pathogenesis.

However, because there is no "gold standard" to reach the diagnosis of ARVC, multiple categories of routine diagnostic information should be combined with ECG changes, arrhythmias, tissue characterization, family history, and imaging technologies, such as contrast-enhanced cardiac magnetic resonance imaging. Electrical instability linked to SCD often presents before structural abnormalities, and therefore early accurate diagnosis is of utmost importance, and there is a need for genetic analysis and testing.

Genetic basis of ARVC and responsible genes

Genetic testing using next-generation semiconductor sequencing is essential in family screening and may be helpful in risk assessment. It can provide a precise clinical diagnosis and guidance for medical care for some ARVC individuals. As an inherited cardiomyopathy, a genetic abnormality is the most probable cause of ARVC, and it has ever been termed a "disease of the desmosome" because ARVC in 60% of patients is currently caused by mutations in pathogenic desmosomal variants.

The desmosomal proteins plakophilin-2 (PKP2), desmoplakin (DSP), and desmoglein-2 (DSG2) are the most commonly seen mutations. Mutated desmosomal proteins cause the detachment of cardiac myocytes through the loss of cellular adhesions and also affect signaling pathways, leading to cell death and substitution by fibrofatty adipocytic tissue.[27] A DSP mutation has frequently been associated with SCD and biventricular arrhythmogenic cardiomyopathy.[28,29]

However, the mechanisms of PKP2 and DSG2 genetic variations are not precisely the same in all populations.[30] The molecular pathomechanisms of DSG2 mutations causing ARVC are still unknown.[31] Whole exome sequencing (ES) of DNA from peripheral blood has shown that DSG2 p.F531C was the main cause of ARVC.[32] A recent study found that anti-DSG2 antibodies are a sensitive and specific biomarker for ARVC and may represent a new therapeutic target.[33]

As we know, mutations in desmosomal proteins are not the sole cause of ARVC, since mutations in non-desmosomal genes have also been implicated in its pathogenesis. In fact, since the discovery of 6 gene loci and mutations in ARVC patients in the early 21st century,[34,35] in particular deletion of the plakoglobin gene, more than 13 genetic variants or mutations have

been found to be associated with ARVC.[36–39]

There may also be an identifiable mutation of pathogenic sarcomere variants (actin alpha cardiac muscle 1, myosin-binding protein C 3, myosin heavy chain 7, myosin light chain 2, myosin light chain 3, troponin C type 1, troponin I type 3, cardiac troponin T2, tropomyosin 1, sodium voltage-gated channel alpha subunit 5, and phospholamban).[40] Transmembrane protein 43 (TMEM43) gene mutations typically cause aggressive ARVC. ARVC type 5 is the most aggressive subtype and is caused by a p.S358L mutation in TMEM43.[41] TMEM43-S358L may lead to sustained cardiomyocyte death and fibrofatty replacement, and it is more likely to have a biventricular arrhythmogenic substrate and more inducible ventricular tachycardia.[42] A new study found that down-regulation of the canonical Wnt/β-catenin pathway signaling might be considered a common key event in the pathogenesis of ARVC.[43] Titin missense variants have also been commonly identified in arrhythmogenic cardiomyopathy.[44] Furthermore, tight junction protein 1 gene variants have been identified in patients with ARVC.[45] Naxos disease is an unusual cause.[46,47]

Since only 50% to 70% of confirmed cases are currently attributed to genetics,[20] there may be some unidentified genes that play a key role. The currently known gene mutations to be involved are summarized in Table 1. It will be interesting and important to search for a new variant to control ARVC and its risk factors in the future, but whether false positives exist is uncertain.

In the era of precision medicine, ES is very important and beneficial as a criterion for screening and diagnosis of ARVC. ARVC-related mutations can be easily controlled through powerful laboratory tools, such as new technologies including gene or biological structure editing, and "molecular scissors" applied to the clustered regularly interspaced short palindromic repeats (CRISPR), a new type of base editing.[65] CRISPR-Cas9-mediated gene editing could be used to effectively knock out ARVC-related genes.

Since the novel RT-ABCDE strategy (E means examination, D means disease and risk factors control, C means changing unhealthy lifestyle and cutting genetic or spreading pathways, B means bio-hazard control, A means antagonistic treatment, and RT means reversible, right, and routine treatment) was developed to treat human disease in 2008,[66] it was further developed into intervention of RT-ABCDEF (iRT-ABCDEF), with the inclusion of F for follow-up. Now iRT-ABCDEF programs have been successfully used for the control and prevention of major non-communicable diseases, such as cancer,[67] chronic heart failure,[68] and acute myocardial infarction.[69] The combination of iRT-ABCDEF and ES may help us to control ARVC more effectively in the era of precision medicine (Fig. 1). Obviously, in the management of ARVC, long-term follow-up and systemic examination is very important for early diagnosis.

As we know, some lifestyle factors, such as en-

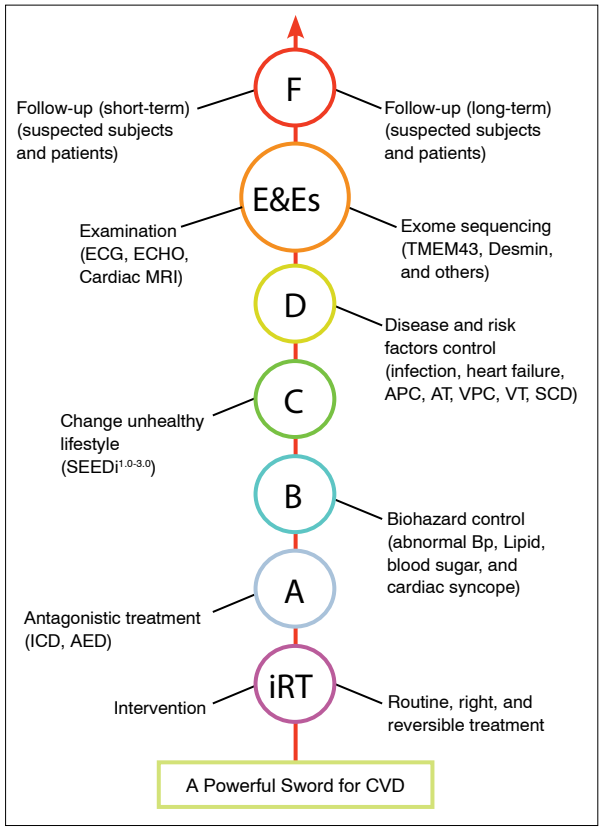

Figure 1. A combination of iRT-ABCDEF and ES for ARVC. A: Antagonistic treatment; AED: Automated external defibrillator; APC: Atrial premature contraction; AT: Atrial tachycardia; B: Bio-hazard control; Bp: Blood pressure; C: Changing unhealthy lifestyle and cutting genetic or spreading pathways; CVD: Cardiovascular disease; D: Disease and risk factor control; E: Examination; ECG: Electrocardiogram; ECHO: Echocardiography; ES: Exome sequencing; F: Follow-up; I: Intervention; ICD: Implantable cardioverter defibrillator; RT: Reversible, right, and routine treatment; SCD: Sudden cardiac death; SEEDi; Sleep-emotion-exercise-diet intervention; TMEM43: Transmembrane protein 43; VPC: Ventricular premature contraction; VT: Ventricular tachycardia.

Table 1. ARVC-related genetic variants or mutations and published articles

No.	ARVC-related genes	Frequency	Authors	Published articles
1	Plakoglobin (JUP)	Common	McKoy G, et al.[48]	Lancet 2000;355:2119-24.
			Franz WM, et al.[35]	Lancet 2001;358:1627-37.
			Protonotarios N, et al.[49]	JACC 2001;38:1477-84.
			Kirchhof P, et al.[50]	Circulation 2006;114:1799-806.
			Antoniades L, et al.[51]	Eur Heart J 2006;27:2208-16.
			Xu T, et al.[52]	JACC 2010;55:587-97.
2	Desmoplakin (DSP)	Common	Franz WM, et al.[35]	Lancet 2001;358:1627-37.
			Norman M, et al.[53]	Circulation 2005;112:636-42.
			Bauce B, et al.[54]	Eur Heart J 2005;26:1666-75.
			Xu T, et al.[52]	JACC 2010;55:587-97.
			Kapplinger JD, et al.[55]	JACC 2011;57:2317-27.
			Gomes J, et al.[56]	Eur Heart J 2012;33:1942-53.
3	Ryanodine receptor (RYR2)	Rare	Franz WM, et al.[35]	Lancet 2001;358:1627-37.
4	Desmoglein-2 (DSG2)	Common	Pilichou K, et al.[57]	Circulation 2006;113:1171-9.
			Syrris P, et al.[58]	Eur Heart J 2007;28(5):581-8.
			Xu T, et al.[52]	JACC 2010;55:587-97.
			Kapplinger JD, et al.[55]	JACC 2011;57:2317-27.
			Dieding M, et al.[31]	Scientific Reports 2017;7(1):13791.
	DSG2 p.F531C	Common	Lin Y, et al.[32]	J Electrocardiol 2018;51:837-43.
5	Plakophilin-2 (PKP2)	Common	Syrris P, et al.[59]	Circulation 2006;113:356-64.
			van Tintelen JP, et al.[60]	Circulation 2006;113:1650-8.
			Antoniades L, et al.[51]	Eur Heart J 2006;27:2208-16.
			Xu T, et al.[52]	JACC 2010;55:587-97.
			Kapplinger JD, et al.[55]	JACC 2011;57:2317-27.
			Cruz FM, et al.[61]	JACC 2015;65:1438-50.
6	Desmocollin-2 (DSC2)	Common	Xu T, et al.[52]	JACC 2010;55:587-97.
			Kapplinger JD, et al.[55]	JACC 2011;57:2317-27.
7	Plakophilin-4 (PKP4)	Rare	Xu T, et al.[52]	JACC 2010;55:587-97.
8	Titin (TTN)	Rare	Taylor M, et al.[62]	Circulation 2011;124:876-85.
			Chen K, et al.[44]	Clin Cardiol 2018;41:615-22.
9	Transmembrane protein 43 (TMEM43)	Common	Kapplinger JD, et al.[55]	JACC 2011;57:2317-27.
			Haywood AF, et al.[63]	Eur Heart J. 2013;34:1002-11.
	TMEM43-p.R312W		Milting H, et al.[38]	Eur Heart J. 2015;36:872-81.
	TMEM43-p.S358L		Padrón-Barthe L, et al.[41]	Circulation 2019;140:1188-204.
10	Lamin A/C gene (LMNA)	Rare	Quarta G, et al.[64]	Eur Heart J 2012;33:1128-36.
11	Catenin alpha 3 (CTNNA3)	Rare	van Hengel J, et al.[36]	Eur Heart J. 2013;34:201-10.
12	Others	Rare		
	Sarcomere variants (ACTC1, TPM1, SCN5A)		Murray B, et al.[40]	J Cardiovasc Electrophysiol 2018;29:1004-9.
	TJP1		De Bortoli M, et al.[45]	Circ Genom Precis Med 2018;11:e002123.

Notes: The most common mutations resulting in ARVC are seen in genes DSC2, DSG2, DSP, JUP, PKP2, and TMEM43. Less commonly encountered genes are CTNNA3, LMNA, RYR2, Transforming growth factor beta-3 (TGFB3), and TTN. Desmosomal genes are JUP, DSP, PKP2, DSG2, DSC2, and LMNA. ACTC1: Actin alpha cardiac muscle 1; ARVC: Arrhythmogenic right ventricular cardiomyopathy; SCN5A: Sodium voltage-gated channel alpha subunit 5; TPM1: Tropomyosin 1; TJP1: Tight junction protein 1.

vironment and exercise, may affect the outcome and prognosis of ARVC. To change unhealthy lifestyles, it is advisable to follow the "sleep-emotion-exercise-diet" intervention (SEEDi$^{1.0\text{-}3.0}$) strategy.[70] A healthy lifestyle has a role in the prevention of ARVC-related SCD, which not only reduces risk factors, but also reduces genetic variation. ES is of great significance for ARVC screening and early diagnosis. Risk stratification has been conducted according to the results of major risk factors, such as electrical instability, cardiogenic syncope, or SCD events, as well as multiple mutations, such as TMEM43[71] and others. This helps to control the risk of ARVC in registered and suspected subjects and improve the clinical management of ARVC.

Early screening and diagnosis of ARVC using iRT-ABCDEF with ES for comprehensive management of ARVC patients according to risk stratification and long-term follow-up is of great significance for control and prevention of ARVC-related SCD. Implantable cardioverter defibrillator therapy, automated external defibrillators in public places, and SEEDi$^{1.0\text{-}3.0}$ technologies are very helpful in reducing SCD and other unexpected events in ARVC patients. Of course, prevention of SCD with a device is crucial in the management of these patients.

When combined with ES, iRT-ABCDEF (Fig. 1) is not only suitable for the management of ARVC, but also for the management of arrhythmia associated with left ventricular cardiomyopathy caused by a PKP2 variant and other conditions. Although the right ventricle is most affected, left ventricular involvement has been increasingly recognized. At present, there is still a lack of data on long-term follow-up outcomes and prognosis of left ventricular cardiomyopathy and ARVC. Therefore, it is very helpful to use the combination of iRT-ABCDEF and ES in the clinical management of arrhythmogenic cardiomyopathy, and to use a model developed for the individualized prediction of incident ventricular arrhythmia/SCD events in ARVC patients.[72]

Summary

This article provides a brief definition of ARVC and describes its importance in clinical practice, diagnostic methods currently used in clinical medicine and their limitations, the genetic basis and analysis of ARVC, the responsible genes, and the iRT-ABCDEF concept and its application combined with ES in the management of ARVC. In conclusion, as a novel, personalized, and comprehensive strategy, the combination of iRT-ABCDEF and ES is a better method for management of ARVC in the new era of precision medicine, and will help to find new ARVC-related genetic variants or mutations in the future.

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REFERENCES

1. Oomen AWGJ, Semsarian C, Puranik R, Sy RW. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy: Progress and Pitfalls. Heart Lung Circ 2018;27:1310–7. [CrossRef]
2. Calkins H, Corrado D, Marcus F. Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation 2017;136:2068–82. [CrossRef]
3. Bermúdez-Jiménez FJ, Carriel V, Brodehl A, Alaminos M, Campos A, Schirmer I, et al. Novel Desmin Mutation p.Glu401Asp Impairs Filament Formation, Disrupts Cell Membrane Integrity, and Causes Severe Arrhythmogenic Left Ventricular Cardiomyopathy/Dysplasia. Circulation 2018;137:1595–610. [CrossRef]
4. Ye JZ, Delmar M, Lundby A, Olesen MS. Reevaluation of genetic variants previously associated with arrhythmogenic right ventricular cardiomyopathy integrating population-based cohorts and proteomics data. Clin Genet 2019;96:506–14. [CrossRef]
5. Raju H, Alberg C, Sagoo GS, Burton H, Behr ER. Inherited cardiomyopathies. BMJ 2011;343:d6966. [CrossRef]
6. Corrado D, Link MS, Calkins H. Arrhythmogenic Right Ventricular Cardiomyopathy. N Engl J Med 2017;376:61–72.
7. Sevinç Şengül F, Tunca Şahin G, Özgür S, Kafalı HC, Akıncı O, Güzeltaş A, et al. Clinical features and arrhythmic complications of patients with pediatric-onset arrhythmogenic right ventricular dysplasia. Anatol J Cardiol 2019;22:60–7. [CrossRef]
8. Gülgün M, Fidancı MK, Genç AF. Electrical storm might be the initial presentation of arrhythmogenic right ventricular cardiomyopathy. Anatol J Cardiol 2016;16:218–9. [CrossRef]
9. Soni R, Oade Y. Arrhythmogenic right ventricular cardiomyopathy. BMJ Case Rep 2011;pii:bcr0520114242. [CrossRef]
10. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P, et al. Sudden Cardiac Arrest during Participation in Competitive Sports. N Engl J Med 2017;377:1943–53. [CrossRef]
11. Mast TP, James CA, Calkins H, Teske AJ, Tichnell C, Murray B, et al. Evaluation of Structural Progression in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. JAMA Cardiol 2017;2:293–302. [CrossRef]
12. Calore C, Zorzi A, Sheikh N, Nese A, Facci M, Malhotra A, et al. Electrocardiographic anterior T-wave inversion in athletes of

different ethnicities: differential diagnosis between athlete's heart and cardiomyopathy. Eur Heart J 2016;37:2515–27. [CrossRef]

13. Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, et al. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. Eur Heart J 2017;38:1498–508. [CrossRef]
14. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, et al. EORP Cardiomyopathy Registry Investigators. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J 2018;39:1784–93. [CrossRef]
15. Roberts WC, Kondapalli N, Hall SA. Usefulness of Total 12-Lead QRS Voltage for Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy in Patients With Heart Failure Severe Enough to Warrant Orthotopic Heart Transplantation and Morphologic Illustration of Its Cardiac Diversity. Am J Cardiol 2018;122:1051–61. [CrossRef]
16. Cardona-Guarache R, Åström-Aneq M, Oesterle A, Asirvatham R, Svetlichnaya J, Marcus GM, et al. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy: Prevalence, echocardiographic predictors, and treatment. J Cardiovasc Electrophysiol 2019;30:1801–10.
17. Liang E, Wu L, Fan S, Li X, Hu F, Zheng L, et al. Bradyarrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy. Am J Cardiol 2019;123:1690–5. [CrossRef]
18. Finocchiaro G, Papadakis M, Dhutia H, Zaidi A, Malhotra A, Fabi E, et al. Electrocardiographic differentiation between 'benign T-wave inversion' and arrhythmogenic right ventricular cardiomyopathy. Europace 2019;21:332–8. [CrossRef]
19. Tschabrunn CM, Haqqani HM, Santangeli P, Zado ES, Marchlinski FE. 12-Lead Electrocardiogram to Localize Region of Abnormal Electroanatomic Substrate in Arrhythmogenic Right Ventricular Cardiomyopathy. JACC Clin Electrophysiol 2017;3:654–65. [CrossRef]
20. Haggerty CM, James CA, Calkins H, Tichnell C, Leader JB, Hartzel DN, et al. Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing. Genet Med 2017;19:1245–52. [CrossRef]
21. Asimaki A, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, et al. A New Diagnostic Test for Arrhythmogenic Right Ventricular Cardiomyopathy. N Engl J Med 2009;360:1075–84. [CrossRef]
22. Wang M, Chen K, Chen X, Chen L, Song J, Hu S. Endomyocardial biopsy in differential diagnosis between arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy: an in vitro simulated study. Cardiovasc Pathol 2018;34:15–21. [CrossRef]
23. Boczar KE, Alqarawi W, Green MS, Redpath C, Burwash IG, Dwivedi G. The echocardiographic assessment of the right ventricle in patients with arrhythmogenic right ventricularcardiomyopathy/dysplasia compared with athletes and matched controls. Echocardiography 2019;36:666–70. [CrossRef]
24. Aquaro GD, Pingitore A, Di Bella G, Piaggi P, Gaeta R, Grigoratos C, et al. Prognostic Role of Cardiac Magnetic Resonance in Arrhythmogenic Right Ventricular Cardiomyopathy. Am J Cardiol 2018;122:1745–53. [CrossRef]
25. Zghaib T, Ghasabeh MA, Assis FR, Chrispin J, Keramati A, Misra S, et al. Regional Strain by Cardiac Magnetic Resonance Imaging Improves Detection of Right Ventricular Scar Compared With Late Gadolinium Enhancement on a Multimodality Scar Evaluation in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Cardiovasc Imaging 2018;11:e007546. [CrossRef]
26. Protonotarios A, Wicks E, Ashworth M, Stephenson E, Guttmann O, Savvatis K, et al. Prevalence of F-fluorodeoxyglucose positron emission tomography abnormalities in patients with arrhythmogenic rightventricular cardiomyopathy. Int J Cardiol 2019;284:99–104. [CrossRef]
27. Vimalanathan AK, Ehler E, Gehmlich K. Genetics of and pathogenic mechanisms in arrhythmogenic right ventricular cardiomyopathy. Biophys Rev 2018;10:973–82. [CrossRef]
28. Singh SM, Casey SA, Berg AA, Abdelhadi RH, Katsiyiannis WT, Bennett MK, et al. Autosomal-dominant biventricular arrhythmogenic cardiomyopathy in a large family with a novel in-frame DSP nonsense mutation. Am J Med Genet A 2018;176:1622–6. [CrossRef]
29. Blusztein DI, Zentner D, Thompson T, Jayadeva P, Liang D, Wang R, et al. Arrhythmogenic Right Ventricular Cardiomyopathy: A Review of Living and Deceased Probands. Heart Lung Circ 2019;28:1034–41. [CrossRef]
30. Bidina L, Kupics K, Sokolova E, Pavlovics M, Dobele Z, Caunite L, et al. PKP2 and DSG2 genetic variations in Latvian arrhythmogenic right ventricular dysplasia/cardiomyopathy registry patients. Anatol J Cardiol 2018;20:296–302.
31. Dieding M, Debus JD, Kerkhoff R, Gaertner-Rommel A, Walhorn V, Milting H, et al. Arrhythmogenic cardiomyopathy related DSG2 mutations affect desmosomal cadherin binding kinetics. Sci Rep 2017;7:13791. [CrossRef]
32. Lin Y, Huang J, Zhao T, He S, Huang Z, Chen X, et al. Compound and heterozygous mutations of DSG2 identified by Whole Exome Sequencing in arrhythmogenic right ventricularcardiomyopathy/dysplasia with ventricular tachycardia. J Electrocardiol 2018;51:837–43. [CrossRef]
33. Chatterjee D, Fatah M, Akdis D, Spears DA, Koopmann TT, Mittal K, et al. An autoantibody identifies arrhythmogenic right ventricular cardiomyopathy and participates in its pathogenesis. Eur Heart J 2018;39:3932–44. [CrossRef]
34. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000;355:2119–24. [CrossRef]

35. Franz WM, Müller OJ, Katus HA. Cardiomyopathies: from genetics to the prospect of treatment. Lancet 2001;358:1627–37. [CrossRef]
36. van Hengel J, Calore M, Bauce B, Dazzo E, Mazzotti E, De Bortoli M, et al. Mutations in the area composita protein αT-catenin are associated with arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2013;34:201–10. [CrossRef]
37. Haywood AF, Merner ND, Hodgkinson KA, Houston J, Syrris P, Booth V, et al. Recurrent missense mutations in TMEM43 (ARVD5) due to founder effects cause arrhythmogenic cardiomyopathies in the UK and Canada. Eur Heart J 2013;34:1002–11. [CrossRef]
38. Milting H, Klauke B, Christensen AH, Müsebeck J, Walhorn V, Grannemann S, et al. The TMEM43 Newfoundland mutation p.S358L causing ARVC-5 was imported from Europe and increases the stiffness of the cell nucleus. Eur Heart J 2015;36:872–81. [CrossRef]
39. Cruz FM, Sanz-Rosa D, Roche-Molina M, García-Prieto J, García-Ruiz JM, Pizarro G, et al. Exercise triggers ARVC phenotype in mice expressing a disease-causing mutated version of human plakophilin-2. J Am Coll Cardiol 2015;65:1438–50.
40. Murray B, Hoorntje ET, Te Riele ASJM, Tichnell C, van der Heijden JF, Tandri H, et al. Identification of sarcomeric variants in probands with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). J Cardiovasc Electrophysiol 2018;29:1004–9. [CrossRef]
41. Padrón-Barthe L, Villalba-Orero M, Gómez-Salinero JM, Domínguez F, Román M, Larrasa-Alonso J, et al. Severe Cardiac Dysfunction and Death Caused by Arrhythmogenic Right Ventricular Cardiomyopathy Type 5 Are Improved by Inhibition of Glycogen Synthase Kinase-3β. Circulation 2019;140:1188–204. [CrossRef]
42. AbdelWahab A, Gardner M, Parkash R, Gray C, Sapp J. Ventricular tachycardia ablation in arrhythmogenic right ventricular cardiomyopathy patients with TMEM43 gene mutations. J Cardiovasc Electrophysiol 2018;29:90–7. [CrossRef]
43. Calore M, Lorenzon A, Vitiello L, Poloni G, Khan MAF, Beffagna G, et al. A novel murine model for arrhythmogenic cardiomyopathy points to a pathogenic role of Wnt signalling and miRNA dysregulation. Cardiovasc Res 2019;115:739–51.
44. Chen K, Song J, Wang Z, Rao M, Chen L, Hu S. Absence of a primary role for TTN missense variants in arrhythmogenic cardiomyopathy: From a clinical and pathological perspective. Clin Cardiol 2018;41:615–22. [CrossRef]
45. De Bortoli M, Postma AV, Poloni G, Calore M, Minervini G, Mazzotti E, et al. Whole-Exome Sequencing Identifies Pathogenic Variants in TJP1 Gene Associated With Arrhythmogenic Cardiomyopathy. Circ Genom Precis Med 2018;11:e002123. [CrossRef]
46. Astarcıoğlu MA, Yaymacı M, Şen T, Kilit C, Amasyalı B. Arrhythmogenic right ventricular cardiomyopathy in monozygotic twin sisters, and persistent left superior vena cava in one complicating implantation of ICD. Turk Kardiyol Dern Ars 2015;43:644–7. [CrossRef]
47. Kaya H, Oylumlu M, Ertaş F, Cetinçakmak MG. Naxos disease: an unusual cause ofcardiomyopathy. Turk Kardiyol Dern Ars 2013;41:265. [CrossRef]
48. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet (London, England) 2000;355:2119–24. [CrossRef]
49. Protonotarios N, Tsatsopoulou A, Anastasakis A, Sevdalis E, McKoy G, Stratos K, et al. Genotype-phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. J Am Coll Cardiol 2001;38:1477–84. [CrossRef]
50. Kirchhof P, Fabritz L, Zwiener M, Witt H, Schäfers M, Zellerhoff S, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation 2006;114:1799–806. [CrossRef]
51. Antoniades L, Tsatsopoulou A, Anastasakis A, Syrris P, Asimaki A, Panagiotakos D, et al. Arrhythmogenic right ventricular cardiomyopathy caused by deletions in plakophilin-2 and plakoglobin (Naxos disease) in families from Greece and Cyprus: genotype-phenotype relations, diagnostic features and prognosis. Eur Heart J 2006;27:2208–16. [CrossRef]
52. Xu T, Yang Z, Vatta M, Rampazzo A, Beffagna G, Pilichou K, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2010;55:587–97. [CrossRef]
53. Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P,et al. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 2005;112:636–42. [CrossRef]
54. Bauce B, Basso C, Rampazzo A, Beffagna G, Daliento L, Frigo G, et al. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. Eur Heart J 2005;26:1666–75.
55. Kapplinger JD, Landstrom AP, Salisbury BA, Callis TE, Pollevick GD, Tester DJ, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol 2011;57:2317–27. [CrossRef]
56. Gomes J, Finlay M, Ahmed AK, Ciaccio EJ, Asimaki A, Saffitz JE, et al. Electrophysiological abnormalities precede overt structural changes in arrhythmogenic right ventricular cardiomyopathy due to mutations in desmoplakin-A combined murine and human study. Eur Heart J 2012;33:1942–53.
57. Pilichou K, Nava A, Basso C, Beffagna G, Bauce B, Lorenzon A, et al. Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. Circulation 2006;113:1171–9. [CrossRef]
58. Syrris P, Ward D, Asimaki A, Evans A, Sen-Chowdhry S, Hughes SE, et al. Desmoglein-2 mutations in arrhythmogenic

right ventricular cardiomyopathy: a genotype-phenotype characterization of familial disease. Eur Heart J 2007;28:581–8.

59. Syrris P, Ward D, Asimaki A, Sen-Chowdhry S, Ebrahim HY, Evans A, et al. Clinical expression of plakophilin-2 mutations in familial arrhythmogenic right ventricular cardiomyopathy. Circulation 2006;113:356–64. [CrossRef]
60. van Tintelen JP, Entius MM, Bhuiyan ZA, Jongbloed R, Wiesfeld AC, Wilde AA, et al. Plakophilin-2 mutations are the major determinant of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2006;113:1650–8. [CrossRef]
61. Cruz FM, Sanz-Rosa D, Roche-Molina M, García-Prieto J, García-Ruiz JM, Pizarro G, et al. Exercise triggers ARVC phenotype in mice expressing a disease-causing mutated version of human plakophilin-2. J Am Coll Cardiol 2015;65:1438–50.
62. Taylor M, Graw S, Sinagra G, Barnes C, Slavov D, Brun F, et al. Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. Circulation 2011;124:876–85. [CrossRef]
63. Haywood AF, Merner ND, Hodgkinson KA, Houston J, Syrris P, Booth V, et al. Recurrent missense mutations in TMEM43 (ARVD5) due to founder effects cause arrhythmogenic cardiomyopathies in the UK and Canada. Eur Heart J 2013;34:1002–11. [CrossRef]
64. Quarta G, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J, et al. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2012;33:1128–36. [CrossRef]
65. Stokstad E, Pennisi E, Kaiser J, Cohen J, Couzin-Frankel J, Voosen P, et al. The runners up. Science 2017;358:1522–7.
66. Hu CS. RT-ABCDE strategy for management and prevention of human diseases. Chin J Integr Med 2008;14:147–50. [CrossRef]
67. Hu CS. Intervention of RT-ABCDEF for cancer. Croat Med J 2019 28;60:55–7. [CrossRef]
68. Hu CS, Wu QH, Hu DY, Tkebuchava T. Treatment of chronic heart failure in the 21st century: A new era of biomedical engineering has come. Chronic Dis Transl Med 2018;5:75–88.
69. Hu C, Tkebuchava T, Hu D. Managing acute myocardial infarction in China. Eur Heart J 2019;40:1179–81. [CrossRef]
70. Hu CS, Tkebuchava T. SEEDi1.0-3.0 strategies for major noncommunicable diseases in China. J Integr Med 2017;15:265–9. [CrossRef]
71. Calkins H, Corrado D, Marcus F. Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation 2017;136):2068–82. [CrossRef]
72. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2019;40:1850–8. [CrossRef]