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From Genes to Gym: The Impact of Physical Exercise on Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary heart muscle disorder characterized by the progressive replacement of right ventricular myocardium with fibrofatty tissue. This condition predisposes individuals to arrhythmias and an elevated risk of sudden cardiac death (SCD). The etiology of ARVC is predominantly genetic, with mutations in genes encoding desmosomal proteins playing a crucial role. Physical exercise has a significant impact on the progression of ARVC, often exacerbating the disease's severity and increasing the likelihood of life-threatening arrhythmic events. Diagnosing ARVC remains challenging due to its variable clinical presentation and overlapping features with other cardiomyopathies. Advanced imaging techniques, electrocardiography, and genetic testing are essential tools in the diagnostic process. Treatment strategies for ARVC include lifestyle modifications, pharmacotherapy, implantable cardioverter-defibrillators (ICDs), and in some cases, catheter ablation or heart transplantation. Preventing disease progression and SCD involves a multidisciplinary approach, emphasizing early diagnosis, risk stratification, and tailored therapeutic interventions. This review comprehensively examines the etiology of ARVC, the detrimental effects of physical exercise on the disease, the associated SCD risk, and the challenges in diagnosis, while also discussing current treatment modalities and preventive measures to mitigate disease progression.

Materials and Methods

Review and summary of research studies available in databases on Google Scholar and PubMed. Databases such as PubMed and Google Scholar were searched using the keywords: ‘Arrhythmogenic right ventricular cardiomyopathy, ‘ARVC in athletes’, ‘Sudden cardiac death’, ‘impact of physical exercise on ARVC’.

Keywords

Arrhythmogenic right ventricular cardiomyopathy; ARVC in athletes; Sudden cardiac death; impact of physical exercise on ARVC;

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy [1-4], characterized by the replacement of cardiomyocytes with fibrous or fibro-fatty tissue [1,5-8]. This process primarily affects the right ventricle, but recent reports suggest it can sometimes involve the left ventricle of the heart [4]. The disease is marked by ventricular arrhythmias, right ventricular dysfunction, heart failure, and in extreme cases, sudden cardiac death without preceding symptoms [1-4]. ARVC accounts for up to 20% of cases of sudden cardiac death and is more prevalent among athletes [1].

The etiology of ARVC is not fully understood, but it is often caused by genetic mutations in desmosomal complex proteins [4,7]. However, in 40-50% of cases, the genetic cause of the cardiomyopathy remains unknown [6]. There is evidence that physical activity accelerates the progression of the disease and exacerbates its symptoms in patients with identified genetic mutations as well as those without detected genetic mutations [9]. Managing the risks associated with physical activity, its intensity, slowing the progression of the disease, and ensuring the patient's psychological comfort and quality of life pose challenges.

This review focuses on providing current knowledge about the etiology of ARVC, diagnostic difficulties, the impact of physical activity on the course of the disease, as well as treatment and prevention of disease progression.

Etiology

Arrhythmogenic cardiomyopathy is primarily inherited in an autosomal dominant manner. The most common mutations are located in genes encoding desmosomal proteins. Five genes are identified where mutations occur most frequently: plakoglobin (JUP), desmoglein 2 (DSG2), desmocollin 2 (DSC2), plakophilin 2 (PKP2), and desmoplakin (DSP). These genes are responsible for the disease in nearly 50% of patients [10]. Up to 16% of patients with ARVC may have mutations involving more than one gene. Such cases are associated with more severe cardiomyopathy symptoms and worse prognosis [11-14]. ARVC can also be caused by mutations in non-desmosomal genes. These include cadherin 2 (CDH2), transforming growth factor beta 2 (TGFß3), and lamin (LMNA). The variety of possible

mutations and the fact that more than one can occur simultaneously affect the disease phenotype, which in some cases may involve the left ventricle [4]. There is suspicion that the ARVC phenotype could develop in individuals without confirmed genetic mutations but who engage in intense endurance exercise. Sawant and colleagues [15] identified 43 cases of patients with developed arrhythmogenic right ventricular cardiomyopathy phenotype without detected genetic mutations. They were compared with 39 cases of ARVC with confirmed gene mutations. Patients without mutations reported five times more intense endurance exercise compared to the activity of the other group. The conducted study showed a link between physical exercise and the development of ARVC. It may also prove that the presence of mutations lowers the threshold of exercise intensity leading to the development and progression of the disease. However, it cannot be excluded that not all genetic mutations leading to ARVC have been identified, and some might have been present in cases classified in this study as the mutation-free group [16].

Diagnosis of ARVC and challenges in differentiation from the athlete's heart

The diagnosis of ARVC is based on the 2010 TFC guidelines. The diagnostic process outlined in these guidelines includes: electrocardiography, electrophysiology, genetic testing, imaging, histological heart assessment, and family history of ARVC. The diagnostic criteria are divided into major and minor categories. Diagnosis is considered definitive with the fulfillment of two major criteria or one major and two minor criteria, or four minor criteria [17]. Changes detectable in cardiac magnetic resonance imaging (CMR) and histological examination from endomyocardial biopsy (EMB) appear later than functional changes [18]. The disease can be asymptomatic for a long time, with a risk of significant ventricular arrhythmias or sudden cardiac death [19,20]. Therefore, it is very important to pay attention to information from the family history or changes noticed in ECG, which can suggest ARVC and allow for early diagnosis of the disease [17]. T-wave inversion in leads V1-V3 is often present in patients with ARVC and is considered a major diagnostic criterion. However, these same changes can also be observed in endurance athletes. A feature that may help differentiate an athlete's heart from ARVC is the presence of a J-point elevation >0.2mV preceding T-wave inversions. Studies indicate that this change occurred ten times more frequently in athletes than in patients with ARVC. The 0.2mV value may serve as a good cutoff (98% sensitivity) that can help exclude ARVC but does not allow for a definitive diagnosis [21]. Another change indicating ARVC is the presence of an epsilon wave in the ECG. However, this has limited

diagnostic utility due to the difficulty in identifying it by physicians [22]. Other ECG parameters worth noting are T-wave inversions in leads above V3, which may occur in ARVC patients but not in athletes, or the presence of PVCs, which often accompany ARVC and are rare among athletes. In ECHO imaging, due to the remodeling of the right ventricle occurring in athletes [23], isolated measurements of the right ventricle have no diagnostic value as they do not allow for the differentiation between physiological and pathological changes. According to current knowledge, quantitative measurements of the right ventricle are not useful in diagnostics because they do not allow differentiation between an athlete's heart and ARVC. Characteristic for ARVC is focal RVOT remodeling with segmental dyskinesia, while athletes exhibit generalized remodeling with functional impairment [24,25]. A more precise method of cardiac imaging is magnetic resonance imaging (MRI). It allows for better assessment of regional wall motion abnormalities (WMA), which studies suggest can help differentiate ARVC from an athlete's heart. It was found that 51% of ARVC patients had WMAs, while athletes did not [26-28]. An additional advantage of cardiac MRI is the ability to enhance tissues using gadolinium. Genetic testing is a crucial part of ARVC diagnostics. It allows for the detection of potential desmosomal mutations that may be responsible for the development of cardiomyopathy. A negative result in genetic tests does not exclude the disease 100%, as there is a possibility that not all genes causing ARVC have been identified yet [29]. In cases of diagnostic uncertainty, histological examination, which can reveal the pathological fibro-fatty tissue characteristic of ARVC, finds its utility. Due to its invasiveness, this examination is the final stage of diagnostics. For professional athletes, obtaining a definitive diagnosis is extremely important as it can impact the course of their sports career [30,31].

The Impact of Physical Exercise on Disease Progression and the Risk of Sudden Cardiac Death

Physical exercise is one of the key factors influencing disease progression and increasing the risk of sudden cardiac death in young patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Intensive physical activity can lead to the development of ARVC traits in athletes without a diagnosed genetic mutation. According to current reports, the development of ARVC and disease progression in individuals with a confirmed genetic mutation occur under the influence of endurance exercise. There has been no evidence of ARVC development or progression, in the form of right ventricular remodeling, with strength

training [32]. Other studies suggest, after multivariate analysis, that the intensity of exercise influences disease progression more significantly than the duration of exercise. Among patients with a genetic mutation and their close family members, a higher frequency of ventricular arrhythmia episodes was found in individuals engaging in higher intensity and volume physical exercise [33]. The significant impact of physical activity on phenotypic expression, disease progression, and prognosis in ARVC is also indicated by other studies, which observed accelerated disease development (by about 10 years earlier) in individuals with a confirmed genetic mutation when comparing patients engaging in endurance exercise and those leading a sedentary lifestyle [9,35]. This has also been confirmed in imaging studies, as they showed worse right and left ventricular function in athletes [34]. Among endurance athletes meeting the criteria for ARVC, only 12% were found to have a desmosomal genetic mutation. This may suggest that intensive exercise can lead to the development of the ARVC phenotype [4]. Moreover, intensive physical activity may be associated with up to a fivefold higher risk of sudden cardiac death compared to non-exercisers [36].

Treatment and Prevention of Disease Progression

Arrhythmogenic right ventricular cardiomyopathy (ARVC) and its progressive course predispose patients to life-threatening ventricular arrhythmias, progressive heart failure, and increased risk of sudden cardiac death [37]. This necessitates appropriate management, treatment, and mitigation of the aforementioned risks. A crucial role in this is played by the proper management of physical activity. Studies indicate that reducing sports activity decreases the frequency of ventricular arrhythmias and may reduce the risk of heart failure in patients with ARVC. The challenge lies in setting appropriate sports restrictions to prevent disease progression while not reducing activity to zero, thereby depriving patients of the health benefits of physical activity. According to international European guidelines, individuals with ARVC should not engage in high-intensity sports and professional athletics. Recreational activity is permissible and recommended, with regular health check-ups [38,39]. Research by Wang et al. suggests that limiting activity to <650 METs per year may be advisable, equivalent to 30-minute brisk walks daily beyond the level of everyday activity [40].

There are no definitive guidelines for the pharmacological treatment of ARVC. Data availability is limited, and there is a lack of reproducible studies evaluating the efficacy of

pharmacological treatment. Antiarrhythmic treatment consistent with the guidelines for treating ventricular arrhythmias seems to be an appropriate approach for managing ARVC. Krahn et al. recommend the use of beta-blockers in patients with ARVC and ventricular arrhythmias [41]. In cases of persistent ventricular arrhythmias, the addition of flecainide to beta-blocker therapy can be considered [42]. Studies have examined the efficacy of amiodarone and sotalol in treating ARVC, but their results have not provided conclusive answers regarding their effectiveness [43,44]. Studies are currently underway to investigate the efficacy and utility of the sacubitril/valsartan preparation, belonging to the ARNI group. Their goal is to assess its anti-remodeling and anti-fibrotic effects, which, if positive, could prevent disease progression and improve the clinical course of the disease.

ICD implantation can be a method of sudden cardiac death prevention in ARVC. ITF guidelines recommend ICD implantation for primary prevention in patients with a history of sustained VT with a rate >100 beats/min for >30 seconds or advanced dysfunction of the left or right ventricle. Indications for ICD implantation for secondary prevention include ARVC and a previous episode of cardiac arrest with resuscitation. For other patients, it is recommended to make decisions based on the estimated 5-year risk of sustained VAs, using appropriate risk calculators [41].

Ablation is also used in treating patients with ARVC, which can reduce the frequency of ventricular arrhythmias and provides an alternative for patients unwilling to undergo ICD implantation. Daimee et al. conducted a study involving 116 patients with ARVC who underwent catheter ablation, achieving a 70% five-year survival without ventricular arrhythmias [45]. The last treatment method for ARVC, indicated by severe right ventricular failure resulting from disease progression, is heart transplantation. New data shows the high effectiveness of such a procedure [46].

Summary

Arrhythmogenic right ventricular cardiomyopathy (ARVC) does not exhibit a uniform phenotypic expression. It often can be asymptomatic, posing challenges in diagnosis, which requires vigilance from clinicians. Attention to important family history details and a thorough analysis of baseline tests such as ECG are crucial, as certain changes may allow for early disease detection. Patients with ARVC and athletes' hearts share a spectrum of

electrophysiological and morphological features, which can complicate diagnosis but is necessary for further management.

The role of intense endurance physical activity in disease development is undeniable. Therefore, it is important to develop appropriate strategies that balance activity restriction to halt disease progression and reduce the frequency of ventricular arrhythmias, while maintaining the health benefits of exercise, which should not be entirely eliminated. Currently, reducing and limiting the intensity of physical exercise is the most critical step in preventing disease progression and reducing the risk of sudden cardiac death.

In the treatment of ARVC, the challenge remains in developing effective pharmacological treatments, as current research does not provide definitive data on the efficacy of drug therapy. Other treatment methods such as implantation of ICDs, ablation, or heart transplantation may be considered at an advanced stage of the disease. These approaches are invasive, carry certain risks, and their application requires careful consideration of potential benefits and risks to the patient.

Disclosure

Author's contribution

Conceptualization: Rafał Makuch and Adam Kucharski; Methodology: Alicja Wawrzyniak; Software: Alicja Chrościcka; Check: Andrzej Czajka and Kamil Gała; Formal analysis: Konrad Pilarski and Martyna Dewicka; Investigation: Paweł Lenard and Sara Michalska; Resources: Kamil Gała; Data curation: Alicja Chrościcka; Writing - rough preparation: Adam Kucharski and Rafał Makuch; Writing - review and editing: Alicja Wawrzyniak and Konrad Pilarski; Visualization: Martyna Dewicka; Supervision: Sara Michalska; Project administration: Rafał Makuch and Paweł Lenard; Receiving funding - no specific funding.

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The authors deny any conflict of interest.

REFERENCES:

1. Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. *Circulation*. 2005;112(25):3823-3832. doi:10.1161/CIRCULATIONAHA.105.542266
2. Orgeron GM, Calkins H. Advances in the Diagnosis and Management of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Curr Cardiol Rep*. 2016;18(6):53. doi:10.1007/s11886-016-0732-y
3. Coelho SA, Silva F, Silva J, António N. Athletic Training and Arrhythmogenic Right Ventricular Cardiomyopathy. *Int J Sports Med*. 2019;40(5):295-304. doi:10.1055/a-0750-5848
4. Prior D, La Gerche A. Exercise and Arrhythmogenic Right Ventricular Cardiomyopathy. *Heart Lung Circ*. 2020;29(4):547-555. doi:10.1016/j.hlc.2019.12.007
5. Francés RJ. Arrhythmogenic right ventricular dysplasia/cardiomyopathy. A review and update. *Int J Cardiol*. 2006;110(3):279-287. doi:10.1016/j.ijcard.2005.07.004
6. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical Diagnosis, Imaging, and Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018;72(7):784-804. doi:10.1016/j.jacc.2018.05.065
7. Murray B. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): a review of molecular and clinical literature. *J Genet Couns*. 2012;21(4):494-504. doi:10.1007/s10897-012-9497-7

8. Zorzi A, Cipriani A, Bariani R, Pilichou K, Corrado D, Bauce B. Role of Exercise as a Modulating Factor in Arrhythmogenic Cardiomyopathy. Curr Cardiol Rep. 2021 May 7;23(6):57. doi: 10.1007/s11886-021-01489-0. PMID: 33961139; PMCID: PMC8105216.
9. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013;62(14):1290-1297. doi:10.1016/j.jacc.2013.06.033
10. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020
11. Fressart V, Duthoit G, Donal E, et al. Desmosomal gene analysis in arrhythmogenic right ventricular dysplasia/cardiomyopathy: spectrum of mutations and clinical impact in practice. *Europace*. 2010;12(6):861-868. doi:10.1093/europace/euq104
12. Cox MG, van der Zwaag PA, van der Werf C, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study. *Circulation*. 2011;123(23):2690-2700. doi:10.1161/CIRCULATIONAHA.110.988287
13. Rigato I, Bauce B, Rampazzo A, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6(6):533-542. doi:10.1161/CIRCGENETICS.113.000288
14. Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. 2015;36(14):847-855. doi:10.1093/eurheartj/ehu509
15. Sawant AC, Bhonsale A, te Riele AS, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. *J Am Heart Assoc*. 2014;3(6):e001471. doi:10.1161/JAHA.114.001471
16. Kindermann W, Corrado D, Scharhag J. The right heart in athletes. Do we really have sufficient evidence for exercise-induced arrhythmogenic right ventricular cardiomyopathy?. *Herzschrittmacherther Elektrophysiol*. 2012;23(2):144-146. doi:10.1007/s00399-012-0207-9
17. 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, Protonotarios N,

Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010 Apr 6;121(13):1533-41. doi: 10.1161/CIRCULATIONAHA.108.840827. Epub 2010 Feb 19. PMID: 20172911; PMCID: PMC2860804.

18. Kirchhof P, Fabritz L, Zwiener M, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation*. 2006;114(17):1799-1806. doi:10.1161/CIRCULATIONAHA.106.624502
19. Delmar M, McKenna WJ. The cardiac desmosome and arrhythmogenic cardiomyopathies: from gene to disease. *Circ Res*. 2010;107(6):700-714. doi:10.1161/CIRCRESAHA.110.223412
20. Heuser A, Plovie ER, Ellinor PT, Grossmann KS, Shin JT, Wichter T, Basson CT, Lerman BB, Sasse-Klaassen S, Thierfelder L, MacRae CA, Gerull B. Mutant desmocollin-2 causes arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 2006 Dec;79(6):1081-8. doi: 10.1086/509044. Epub 2006 Oct 3. PMID: 17186466; PMCID: PMC1698714.
21. Brosnan MJ, te Riele ASJM, Bosman LP, Hoorntje ET, van den Berg MP, Hauer RNW et al. Electrocardiographic Features Differentiating Arrhythmogenic Right Ventricular Cardiomyopathy From an Athlete's Heart. JACC: Clinical Electrophysiology. 2018 Dec 1;4(12):1613-1625. doi: 10.1016/j.jacep.2018.09.008
22. Platonov PG, Calkins H, Hauer RN, et al. High interobserver variability in the assessment of epsilon waves: Implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm*. 2016;13(1):208-216. doi:10.1016/j.hrthm.2015.08.031
23. D'Andrea A, La Gerche A, Golia E, et al. Right heart structural and functional remodeling in athletes. *Echocardiography*. 2015;32 Suppl 1:S11-S22. doi:10.1111/echo.12226
24. D'Ascenzi F, Pisicchio C, Caselli S, Di Paolo FM, Spataro A, Pelliccia A. RV Remodeling in Olympic Athletes. *JACC Cardiovasc Imaging*. 2017;10(4):385-393. doi:10.1016/j.jcmg.2016.03.017
25. Bauce B, Frigo G, Benini G, et al. Differences and similarities between arrhythmogenic right ventricular cardiomyopathy and athlete's heart adaptations. *Br J Sports Med*. 2010;44(2):148-154. doi:10.1136/bjsm.2007.042853
26. Zaidi A, Sheikh N, Jongman JK, et al. Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies. *J Am Coll Cardiol*. 2015;65(25):2702-2711. doi:10.1016/j.jacc.2015.04.035

27. Luijkx T, Velthuis BK, Prakken NH, et al. Impact of revised Task Force Criteria: distinguishing the athlete's heart from ARVC/D using cardiac magnetic resonance imaging. *Eur J Prev Cardiol*. 2012;19(4):885-891. doi:10.1177/1741826711414215
28. Etoom Y, Govindapillai S, Hamilton R, et al. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. *J Am Coll Cardiol*. 2015;65(10):987-995. doi:10.1016/j.jacc.2014.12.041
29. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice [published correction appears in Eur Heart J. 2022 Nov 7;43(42):4468. doi: 10.1093/eurheartj/ehac458]. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
30. Dello Russo A, Pieroni M, Santangeli P, et al. Concealed cardiomyopathies in competitive athletes with ventricular arrhythmias and an apparently normal heart: role of cardiac electroanatomical mapping and biopsy. *Heart Rhythm*. 2011;8(12):1915-1922. doi:10.1016/j.hrthm.2011.07.021
31. Narducci ML, Pelargonio G, La Rosa G, et al. Role of extensive diagnostic workup in young athletes and nonathletes with complex ventricular arrhythmias. *Heart Rhythm*. 2020;17(2):230-237. doi:10.1016/j.hrthm.2019.08.022
32. Haykowsky MJ, Samuel TJ, Nelson MD, La Gerche A. Athlete's Heart: Is the Morganroth Hypothesis Obsolete?. *Heart Lung Circ*. 2018;27(9):1037-1041. doi:10.1016/j.hlc.2018.04.289
33. Lie ØH, Dejgaard LA, Saberniak J, et al. Harmful Effects of Exercise Intensity and Exercise Duration in Patients With Arrhythmogenic Cardiomyopathy. *JACC Clin Electrophysiol*. 2018;4(6):744-753. doi:10.1016/j.jacep.2018.01.010
34. Saberniak J, Hasselberg NE, Borgquist R, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail*. 2014;16(12):1337-1344. doi:10.1002/ejhf.181
35. Ruwald AC, Marcus F, Estes NA 3rd, et al. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2015;36(27):1735-1743. doi:10.1093/eurheartj/ehv110
36. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults?. *J Am Coll Cardiol*. 2003;42(11):1959-1963. doi:10.1016/j.jacc.2003.03.002

37. Kaddoura R, Al-Tamimi H. Physical Exercise and Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An Overview. *Heart Views*. 2022;23(4):215-220. doi:10.4103/heartviews.heartviews_70_22
38. Pelliccia A, Solberg EE, Papadakis M, et al. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2019;40(1):19-33. doi:10.1093/eurheartj/ehy730
39. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on Sports Cardiology and Exercise in Patients with Cardiovascular Disease. *Rev Esp Cardiol (Engl Ed)*. 2021;74(6):545. doi:10.1016/j.rec.2021.05.003
40. Wang W, Tichnell C, Murray BA, et al. Exercise restriction is protective for genotype-positive family members of arrhythmogenic right ventricular cardiomyopathy patients. *Europace*. 2020;22(8):1270-1278. doi:10.1093/europace/euaa105
41. Krahn AD, Wilde AAM, Calkins H, et al. Arrhythmogenic Right Ventricular Cardiomyopathy. *JACC Clin Electrophysiol*. 2022;8(4):533-553. doi:10.1016/j.jacep.2021.12.002
42. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm*. 2017;14(4):564-569. doi:10.1016/j.hrthm.2016.12.010
43. 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(1):29-37. doi:10.1161/01.cir.86.1.29
44. Marcus GM, Glidden DV, Polonsky B, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. *J Am Coll Cardiol*. 2009;54(7):609-615. doi:10.1016/j.jacc.2009.04.052
45. Daimee UA, Assis FR, Murray B, et al. Clinical outcomes of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy: Insights from the Johns Hopkins ARVC Program. *Heart Rhythm*. 2021;18(8):1369-1376. doi:10.1016/j.hrthm.2021.04.028
46. Giuliano K, Scheel P 3rd, Etchill E, et al. Heart transplantation outcomes in arrhythmogenic right ventricular cardiomyopathy: a contemporary national analysis. ESC Heart Fail. 2022;9(2):988-997. doi:10.1002/ehf2.13687