Review

Arrhythmogenic right ventricular cardiomyopathy. Prevention of sudden death in athletes

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Summary

Introduction: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease characterized by progressive replacement of myocardial tissue and patched by fibrofatty tissue, which can cause ventricular arrhythmias and sudden cardiac death (SCD), even as a first manifestation. The manifestations of the disease are favoured by physical exercise, so it is one of the main causes of SCD in athletes under 35 years old.

Material and method: A systematic review in different scientific databases related to ARVC has been made. The initial research on 938 publications was eventually reduced to 36, after applying the different criteria of inclusion and exclusion.

Results: In our environment, medical history, physical examination and electrocardiogram (ECG) are the main tools used in the screening of SCD from 12 years of age (basic cardiovascular evaluation). However, in professional or high risk athletes, echocardiography and maximal exercise test are added to the initial screening (advanced cardiovascular assessment). Still, the gold standard test for the diagnosis of ARVC is cardiac magnetic resonance (RMC). The genetic test plays an important role in the study of suspected patients as well as in the evaluation of the relatives of patients who have already been diagnosed. ARVC treatment involves the use of antiarrhythmic drugs, implantation of an implantable cardioverter defibrillator (DAI) based on the risk of SCD and restriction of physical activity.

Discussion: The lack of standardized studies on large populations of athletes and the absence of sudden death registries difficult to obtain solid evidence in the interpretation of the results of the reviewed articles.

Conclusions: The preparticipative screening of all athletes should include medical history, complete physical examination and 12-lead ECG; considering running an echocardiography being highly recommended.

Prevención de la muerte súbita por miocardiopatía arritmogénica del ventrículo derecho en deportistas

Resumen

Introducción: La miocardiopatía arritmogénica del ventrículo derecho (ARVC) es una enfermedad hereditaria caracterizada por la sustitución progresiva y parcheada del tejido miocárdico por tejido fibroadiposo, lo cual puede originar arritmias ventriculares y muerte súbita (SCD), incluso como primera manifestación. Las manifestaciones de la enfermedad se ven favorecidas por el ejercicio físico, siendo una de las principales causas de SCD en deportistas menores de 35 años.

Material y método: Se ha realizado una revisión sistemática en las diferentes bases de datos científicas relacionada con la ARVC. La búsqueda inicial de 938 artículos se redujo finalmente a 36, tras aplicar los diferentes criterios de inclusión y exclusión.

Resultados: En nuestro medio, la historia clínica, la exploración física y el electrocardiograma (ECG) son las principales herramientas usadas en la prevención de la SCD a partir de los 12 años de edad (evaluación cardiovascular básica). En deportistas profesionales o con alto riesgo, se añade ecocardiografía y prueba de esfuerzo máxima (evaluación cardiovascular avanzada). Aun así, la prueba de elección para el diagnóstico de ARVC es la resonancia magnética cardiaca (RMC). El test genético juega un papel importante tanto en el estudio de pacientes sospechosos como en la evaluación de los familiares de pacientes ya diagnosticados. El tratamiento de la ARVC consiste en el uso de fármacos antiarrítmicos, la implantación de un desfibrilador automático implantable (DAI) en función del riesgo de SCD y la restricción de la actividad física.

Discusión: La falta de estudios estandarizados de grandes poblaciones de deportistas y la ausencia de registros de muerte súbita dificultan la obtención de una evidencia sólida en la interpretación de los resultados de los artículos revisados.

Conclusiones: El screening preparticipativo a todos los deportistas debería incluir: historia clínica, exploración física completa y ECG de 12 derivaciones; considerándose altamente recomendable la realización de una ecocardiografía.

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary illness characterised by the progressive loss of myocytes in the right ventricle (RV), causing a segmental or diffuse thinning of the wall[1]. The left ventricle (LV) may also be affected, with bi-ventricular progression being the most common form of the illness[2]. In Spain and Europe[3], ARVC is one of the main causes of SCD in athletes under the age of 35 years, though there is a lack of large-scale studies of incidence rates (Figure 1).

ARVC tends to arise clinically between the third and fifth decade of life, with ventricular arrhythmias that may cause sudden cardiac death (SCD)[4]. Clinical manifestations and the progression of the illness are very variable. In the initial phase, the structural changes may be absent or subtly confined to localised areas of the RV, with the most common being: the front part of the infundibulum, the apex and the infero-basal tricuspid area of the RV, which make up the so-called *triangle of dysplasia*, considered to be the identification mark of ARVC. With the onset of the illness, both ventricles may be affected with cavity dilation and even aneurysms.

In ARVC, a defect occurs in the cellular adhesion proteins such as plakoglobin, plakophilin-2, desmoplakin, desmocollin-2 and desmoglein, and in others responsible for cell stability[3]. This protein alteration causes alterations of the structure and function of the myocardial wall with the replacement of fibrofatty tissue, as shown by Saberniak *et al*[5].

In accordance with the *American Heart Association* (AHA), the diagnosis is made based on the presence of greater and lesser criteria reviewed in the *Task Force Criteria*[6] (Table 1). The criteria are based on findings in six different diagnostic categories: Basal ECG, signal-averaged EGC and Holter; endomyocardial biopsy; family history; and advanced cardiac image tests. Depending on the points scored, the patients are classified into possible, borderline or definite ARVC.

Intense physical exercise may trigger arrhythmic episodes and sudden death, as the first sign of the illness in athletes that have diagnosed ARVC or not. The mechanical stress to which the heart is subjected produces an increase of sympathetic stimulation, which can explain the ventricular arrhythmias that appear in the illness. Furthermore, it has been shown that stress maintained over time causes greater ventricular dysfunction in athletes suffering from ARVC than in non-athletes.

Despite the incidence rate of the illness being low, it is still one of the most frequent causes of SCD in young athletes, on the other hand it has a major social impact as the episodes occur in apparently healthy people, on occasions well-known people, that die unexpectedly whilst performing sport.

It is also worth highlighting its broad clinical spectrum and its difficult diagnosis, for which it is not clear which protocol should be applied routinely for its diagnosis in athletes, thus preventing the SCD. There are authors that defend the need for a greater number of initial studies to rule it out, whilst others give greater importance to the cost-effectiveness

Figure 1. Changes in the incidence and aetiology of the SCD depending on age[25].
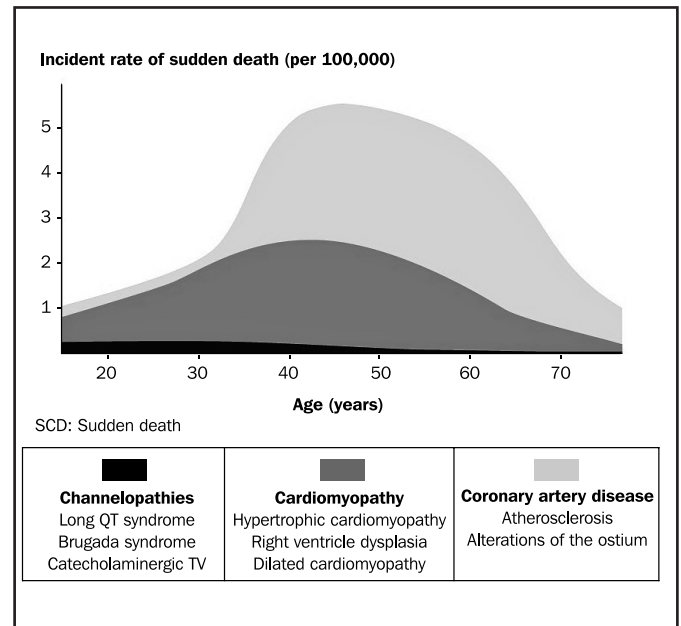
relationship. In this review the diagnostic methods and treatment of ARVC described in the current bibliography are analysed, with the aim of clarifying a suitable protocol for the screening of ARVC and finding ways of preventing SDC in athletes with this pathology.

Material and method

Design

A systematic review was performed of ARVC-related articles from scientific societies, as well as clinical practice guides and systematic reviews.

Search strategy and exclusion criteria

Firstly, a search was performed on Google Scholar and Pubmed for articles and clinical practice guides published by different European and American societies on ARVC, SCD and their relationship with sport. Next a search was performed of clinical practice guides and of systematic reviews of scientific literature in Pubmed using the search terms: *(arvd OR arvc) AND "sudden death"; (arvd OR arvc) AND "exercise"; (arvd OR arvc) AND "screening";* previously obtained from the MeSH Database. The search was restricted to articles published within the last 5 years in English and in Spanish. The studies had to provide significant data about the diagnostic tests of ARVC, or be related to the different methods that are useful in preventing SCD caused by ARVC in athletes < 35 years. The publications that did not refer to the object of our study were excluded.

Data extraction: After performing the initial search on Pubmed with the term *(arvd* OR *arvc) AND "sudden death"*, 593 articles were found, limi-

Table 1. Diagnostic criteria of ARVC/D reviewed Task Force 2010 AHA (Modified Ref.17).

I. Regional or global dysfunction and structural alterations	IV. Repolarisation / circulation abnormalities

Greater
2D ECHO
• Akinesia, dyskinesia or regional aneurysm of RV
• and 1 of the following (end-diastole):
  - EPL: Flow of RV outflow tract ≥32 mm
  (corrected by BA ≥19 mm/m²)
  - EPL: Flow of RV outflow tract ≥36 mm
  (corrected by BA ≥21 mm/m²)
  - or Ejection Fraction ≤33%
CRM
• Akinesia, dyskinesia or regional disynchrony of RV
• and 1 of the following:
  - End diastolic volume ratio RV/BA ≥110 ml/m² (Men)
   o ≥100 (Women)
  - or Ejection Fraction of RV ≤40%
RV angiography
• Akinesia, dyskinesia or regional aneurysm of RV
	Greater
	• Y-wave in right precordial leads (V1-V3). Replicable in low-amplitude signals between the end of QRS and the start of the T-wave

Lesser
2D ECHO
• Akinesia, dyskinesia or regional dyskinesia of RV
• and 1 of the following (end-diastole):
  - EPL: Flow of RV outflow tract ≥29 mm
  (corrected by BA ≥ 16 to <19 mm/m²)
  - EPL: Flow of RV outflow tract ≥36 mm
  (corrected by BA ≥21 mm/m²)
  - or Ejection Fraction >33% to ≤40%
CMR
• Akinesia, dyskinesia or regional disynchrony of RV
• and 1 of the following:
  - Ratio of end diastolic volume of RV/ BA ≥ 100 ml/m²
  (Men) or 90 to < 100 (Women)
  - or Ejection Fraction of RV >40% to ≤45%
	Lesser
	• Potential delays in SAECG in ≥1 parameter in the absence of QRS ≥110 ms in standard ECG
	• Duration of filtered QRS (fQRS) ≥114 ms
	• Duration of terminal QRS <40 µV (low-amplitude signal) >38 ms
	• Square root of the terminal voltage 40 µV ≤20 ms
	• Duration of the terminal activation of QRS ≥55ms, measured from the nadir of the S-wave to the end of the QRS including R' in V1, V2 or V3, in the absence of complete RBBB (Figure 3)

II. Tissue characteristics of the wall	**V. Arrhythmias**
Greater • Residual myocytes >60% in morphometric analysis (or >50% if it is estimated) with fibrous replacement of the free wall of the RV in ≥1 sample or with or without replacement of endomyocardial fatty tissue in biopsy	**Greater** • Sustained or non-sustained tachycardias with BBB morphology with superior axis (negative or undetermined QRS in ll, lll and in AVF, and positive in AVL)
Lesser • Residual myocytes 60-75% in morphometric analysis (or 50-60% if it is estimated) with fibrous replacement of the free wall of the RV in ≥1 sample or with or without replacement of endomyocardial fatty tissue in biopsy	**Lesser** • Sustained or non-sustained tachycardias with origin in the RV outflow tract, with BBB morphology with inferior axis (positive QRS in II, III and in AVF, and negative in AVL) • >500 ventricular extrasystoles in 24 hours (Holter)
III. Anomalies in repolarisation	**VI. Family history**
Greater • Inverted T-waves in right precordial leads (V1-V2) in individuals of >14 years in absence of complete RBBB (QRS ≥120 ms)	**Greater** • ARVC confirmed in first-degree relative that fulfils the TF criteria • AVRC confirmed by biopsy in 1st degree family member • Identification of mutation categorised as associated or probably associated with ARVC in assessed patients
Lesser • Inverted T-waves in right precordial leads (V1-V2) in individuals of >14 years in absence of complete RBBB (QRS ≥120 ms), or in V4, V5 or V6 • Inverted T-waves in V1, V2, V3 y V4 in individuals of >14 years in presence of complete RBBB.	**Lesser** • ARVC confirmed in first-degree relative in which it is not possible or practical to establish if the relative fulfils the TF criteria • Premature sudden death (<35 years) due to suspected ARVC, of a first-degree family member • ARVC confirmed in pathological analysis or that fulfils the criteria of the TF in 2nd degree family member

EPL: Eje Para-esternal Largo; SC: Área de Superficie Corporal; SAECG: ECG de Señal Promediada.
Diagnóstico Definitivo: 2 criterios mayores o 1 mayor y 2 menores o 4 menores de diferentes categorías; Limítrofe: 1 mayor y 1 menor o 3 menores de diferentes categorías; Posible: 1 mayor y 2 menores de diferentes categorías. Mutación patogénica: alteración del DNA asociada a ARVC que altera o se espera que altere la proteína codificada. No se observa o es raro observarla en un control no-ARVC, y altera o se espera que altere la estructura o la función de la proteína o se ha demostrado su *linkage* con el fenotipo de la enfermedad en un pedigrí concluyente.

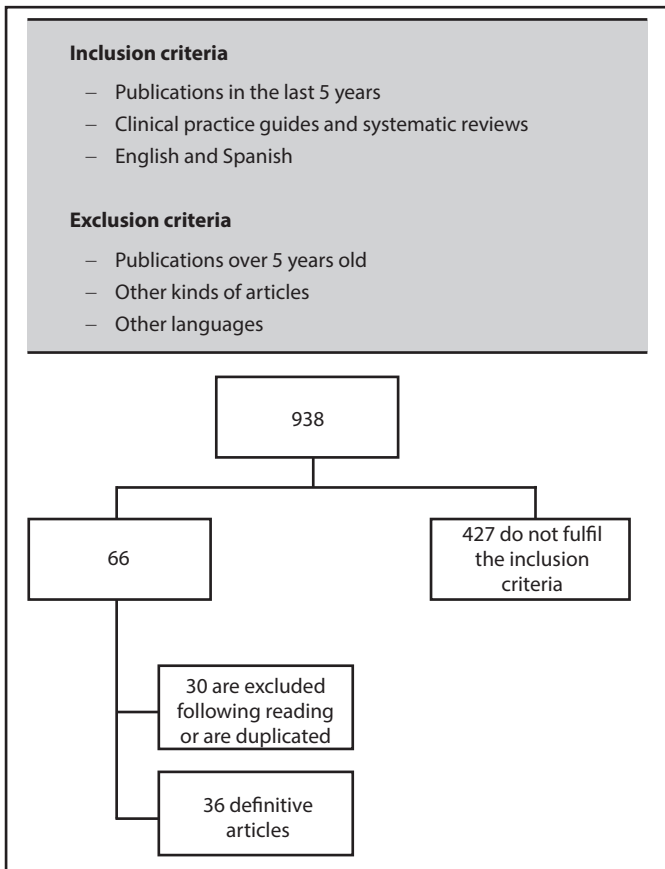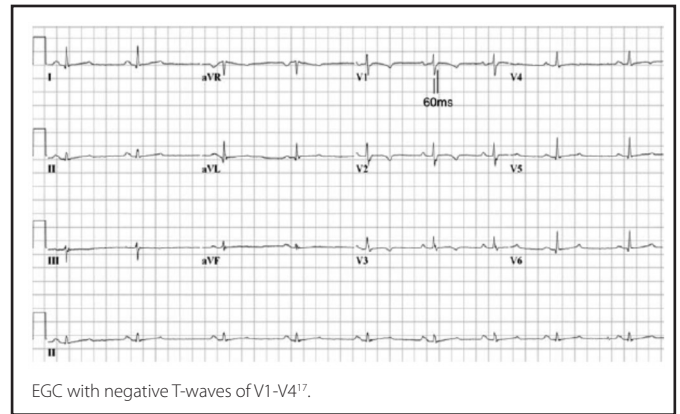**Figure 2. Inclusion and exclusion criteria and diagram of article selection.**

Inclusion criteria
- – Publications in the last 5 years
- – Clinical practice guides and systematic reviews
- – English and Spanish

Exclusion criteria
- – Publications over 5 years old
- – Other kinds of articles
- – Other languages

938

66

427 do not fulfil the inclusion criteria

30 are excluded following reading or are duplicated

36 definitive articles

Figure 3. ECG of patient with ARVC.

EGC with negative T-waves of V1-V4[17].

right-bundle branch block, it is considered a greater diagnostic criteria in those over the age of 14 years. In minors below this age, it may be a variety of normality. The presence of T-wave inversion in more than three precordial leads is a predictor of arrhythmic events. However, in 12% of patients the ECG is normal[12]. If ARVC is suspected with a normal ECG, a series of ECG must be carried out[13].

In severe phases, low amplitude signals may appear, defined as epsilon waves in V_1-V_3, which are also considered a greater diagnostic criteria[3,6-8]. The appearance of TV with morphology of the left bundle branch block is also characteristic6. The duration of the QRS of more than 120 ms is associated with ARVC[6-8,11,14]. These findings are highly sensitive (88-100%) but they have low specificity (46%), with the PPV being 61% and the NPV being 91-100%[6]. The application of the Seattle criteria gives over 97% sensitivity to the screening of athletes via ECG[15].

ted to 184 within the past 5 years. By only selecting the clinical practice guides and systematic reviews, a total of 48 publications were obtained, with 40 remaining upon selecting English and Spanish languages. With the search term *(arvd OR arvc) AND "exercise",* the initial number of 188 articles was reduced to 15 after applying the previously mentioned filters. Finally, with the formula of *(arvd OR arvc) AND "screening"* 157 were obtained, of which 11 remained after restricting the search.

Once 3 initial search equations were performed with the corresponding filters, a total of 66 articles remained, of which, after eliminating duplicates and excluding those that did not refer to the subject of our review, a total of 36 remained (Figure 2). To these, 5 general references were added about sudden death in sport.

Results

Diagnostic tests

Basal ECG

The ECG is the initial ARVC diagnostic method. The most common sign is T-wave inversion in the precordial leads V_1-V_3,[7-11] (Figure 3) and it forms part of the early diagnosis of the illness[7]. In the absence of a

Signal-averaged ECG

It contains the average of multiple QRS to filter noise and late potentials. The QRS duration of more than 114 ms, the terminal QRS duration of more than 38 ms, and a terminal voltage of less than 20 microV are considered abnormal. If any of these values are present, it is considered a lesser diagnostic criteria.

Holter monitoring (24 hours)

It is used in the diagnosis of ARVD, but especially, in its follow-up. A lesser criteria is considered to be less than 500 premature ventricular contractions in 24 hours or more than 30% of ventricular extrasystoles of the total heartbeats on the electrocardiographic record[3].

Echocardiography

Echocardiography is the most used image modality in the diagnosis and follow-up of ARVC[7]. The most common finding is the lengthening of the RV outflow tract[3,6,16]. A tract >30 mm has a diagnostic sensitivity of 89% and a specificity of 86%[16]. Ventricular dysfunction is also habitual, defined as an EF <32% and the abnormalities in the mobility of the wall[3,7,16]. The presence of akinesia, dyskinesia or aneurysm are also

considered greater criteria[12]. The extension of the hypokinesia, along with the measurement of the end diastolic volume, can give us an idea of the evolution of the illness[16].

Cardiac magnetic resonance

CMR is the test of choice as it provides information about the degree of fibrofatty replacement of the structure and of the ventricular function[3,7,17,18]. In comparison with the echocardiograph, it enables a better assessment of the previously mentioned characteristics[15,17-19]. The most common alterations are ventricular dilation (S77% and E95%), systolic dysfunction, dilation of the outflow tract, regional abnormalities in the wall movement, ventricular aneurysms, the presence of intramyocardial fat and late gadolinium enhancement[7,16,18].

The characterisation of the tissues is performed by assessing the images weighted in T2, indicative of recent myocardial injury (oedema); and by the characterisation of the late gadolinium enhancement, characteristic of irreversible tissue injury (scar). The percentage of the latter has been shown to be a powerful factor in the prediction of TV and of SCD caused by ARVC[20]. The CMR was positive in 100% of the patients diagnosed with ARVC, but it obtained a specificity of 29% due to the over-interpretation of the regional abnormalities of the movement[16]. The addition of quantitative parameters manages to raise specificity to up to 90-98%[12].

It is the ideal follow-up method in asymptomatic patients and is highly valuable for assessing symptomatic athletes[9,15]. However, there are inconveniences in terms of availability, cost, the need for experts to interpret the images and the tendency to over-diagnose[3,7,13,18]. This is why, despite its numerous advantages, it cannot be applied to the screening of large groups of athletes[15].

Computed tomography

The CT is an alternative for patients for whom the CMR cannot be used. In comparison to the CMR, the CT does not have resolution in the characterisation of the tissues and tends to over-estimate the final systolic and diastolic volume.

Electrophysiology

3D electro-anatomical mapping is a recent technique and is very sensitive when detecting areas of low voltage, which would indicate the loss of electrically active myocardium and their substitution with fibrofatty tissue, characteristic of this pathology[7,18,21]. If the signs of low voltage are present in the RV, this may help locate the area to perform a biopsy[6]. This technique has allowed for a greater understanding of the illness and for the assessment of the distribution of lesions, with the discovery that they are more frequent in the epicardium[21].

As it is an invasive test, it will only be performed in patients with suspected ARVC and ventricular arrhythmias of the RV, as well as for the differential diagnosis with idiopathic RV tachycardia[21]. In fact, some authors still consider it to be an experimental technique[3,7,13]. It is more sensitive than the CMR in cases in which the heart wall is thin, but it can cause confusion with other pathologies such as sarcoidosis[7,18].

Heart biopsy

In the typical ARVC biopsy, the myocytes are replaced by fibrofatty tissue, especially in the heart apex and the ventricular outflow tract, whether or not associated with atrophy of the ventricular myocardium[13,17]. The diagnosis can be made without the presence of fibrous tissue, as long as the infiltrated adipose is accompanied by inflammation and necrosis typical of myocytes[22]. Routine biopsies are taken from the interventricular septum, though the sample may provide a false negative as the process of the illness is frequently patchy[3,9,19,22]. Furthermore, the progression of the lesions is from sub-epicardium to endocardium, which is why the endocardial biopsy may not be positive in early stages. On the other hand, there is a major risk of perforation if it is performed on the free wall of the ventricle[3,7].

The diagnostic performance of the heart biopsy increases if it is carried out alongside electro-anatomical mapping; the sample should be collected from the affected area (low voltage)[7,12,13]. The immunohistochemical analysis reveals a reduction of the plakoglobin signal in the affected myocytes. It is considered to be a highly sensitive (91%) and specific (82%) diagnosis technique, but it is a tool that is still being researched due to its high rate of false positives and negatives (sarcoidosis and myocarditis of giant cells), which is why it is not usually performed today[7,9,21].

Clinical and genetic diagnostic criteria

The diagnosis of ARVC is based on the application of greater and lesser diagnostic criteria. Depending on the points scored, the patients are classified into possible, borderline or definite ARVC. Applying the diagnostic criteria updated by the AHA in the 2010 TFC, different publications have revealed an increase in sensitivity from 57 to 71% (p = 0.001), identifying 25 patients with defined ARVC and 64 with probable ARVC[14]. However, these criteria have limitations as they do not include cases with dominant left affection of the illness[7,19]. Infradiagnosis is probable due to the complexity of the cases and the existence of unknown variants[23].

The inclusion of genetic criteria was one of the changes made in the TFC. All patients with suspected or diagnosed ARVC must be genetically analysed, and in the event that they are positive, their family members must also be analysed[21,24,25]. The PKP-2 genes (plakophilin-2) located in the chromosome 12p11.21, and the DSG2 and DSP genes are responsible for over half of the cases of SCD due to ARVC. The mutation of the PKP2 gene is the most prevalent[26]. It follows an autosomal dominant inheritance model in the majority of cases[19]. Models of recessive autosomal inheritance have been described, linked to proteins such as plakoglobin[2]. In patients without a PKP2 mutation, additional tests in DSC2, DSG2, and DSP can identify a genetic cause in 5% to 10% of cases. When the participation of the LV is predominant in a family line, genetic tests for DSP, DSG2 and mutations of the transmembrane protein TMEM43 should be included in the first round of tests[27].

Of all the cases diagnosed using the TFC criteria, only 30-50% presented desmosomal anomalies, and of these, around 10% had more than one known mutation, a fact that has been associated to its greater severity[6,7,14,21]. Approximately 50% of mutations are unknown[2,8,14,19,28] and 16% of healthy controls revealed mutations characteristic of ARVC[19,21].

The interpretation of genetic tests is difficult due to their heterozygosity. Furthermore, the prognosis of ARVC according to the mutation is limited due to a lack of data[29]. Genetic diagnosis is considered a greater criteria, though the absence of identifiable mutations does not exclude the illness. It is most useful in family screening, in which asymptomatic carriers will require life-long monitoring, whilst non-carriers will not require serialised checks[9]. On the other hand, the genetic study of patients with diagnosed ARVC may be useful in establishing the importance and behaviour of the genes in the illness. The test should be considered for patients with possible ARVC (Recommendation level IIb) and is not recommendable for individuals with just one lesser criteria (Recommendation level III)[13].

First degree family members are considered to have a 50% risk of carrying the illness causing mutation with variable penetrance. Genetic testing is recommended for these patients (Level of evidence I)[3,13]. The follow-up of asymptomatic patients carrying a mutation is recommended from 10 to 50 years of age. This should be carried out with a complete screening every 1-2 years (history, ECG, echocardiograph, Holter, CMR)[19]. The clinical screening of family members of unexplained sudden death victims can identify ARVC in 7-9% of cases[19]. In second degree family members, the study is usually limited to an ECG, an echocardiograph and a Holter every 5 years[19].

Treatment

The handling of these patients must be orientated towards avoiding the appearance of arrhythmias that trigger syncopes or cardiac arrest. Patients with ventricular failure or ventricular tachycardias will be considered high risk and will receive a more aggressive treatment[13]. Currently, the majority of patients are recommended the implantation of an ICD as primary prevention, and the consumption of anti-arrhythmic drugs, or the excision via catheter of accessory circulation pathways to reduce the arrhythmic impact. Heart transplant could be recommended in terminal stages of heart failure or maintained ventricular tachycardias[10, 30].

Drugs

Beta blockers constitute the general treatment of these patients, despite their use being merely empirical[8,31,32]. As highlighted by Kantor et al[31], they are mainly used in the initial treatment of moderate or severe systolic failure of the LV. Within beta blockers, the most used in these patients is sotalol[6,7,12,13,31,33]. This pharmaceutical drug is also recommended to prevent electric shocks in patients fitted with an ICD[6,33], and is considered to be the only drug that reduces the risk, especially risk induced by exercise. The prescription of this drug is a prior requirement to the implantation of an ICD or to the excision via catheter in patients with ARVC[9,34]. However, some studies[13,34] did not show that beta blockers reduce the rate of TV in different series assessed. Another area of discrepancy radiates in the greater effectiveness of amiodarone compared to sotalol[7,13,24], relegating the latter to second place[34].

Implantable cardioverter defibrillator

The ICD is considered the most effective treatment in preventing sudden death, as it converts the VF into a sinus rhythm. It is therefore the fundamental pillar in preventing SCD in patients with ARVC[7,33,35,36]. As indicated by Schinkel et al.[35] and Saguner et al.[7], multiple studies have revealed that the ICD is effective in both primary and secondary prevention, despite not being exempt of risks. The complications associated with its implantation are a source of fatality in these patients. It is considered that complications appear in 58% of those implanted after 7 years, mainly related to the catheter[14]. Another problem with the ICD is that of inappropriate electrical shocks, though these shocks are appropriate in 94% of cases of TV[33].

The AHA recommends the implantation of an ICD (recommendation level IIA) to prevent SCD in patients with extensive illness, TV or sustained ventricular fibrillations, LV affection and patients with more than one family member with reanimated sudden death or unexplained syncope, as long as they are receiving optimum medical therapy and have a reasonable life expectancy[7,12,35].

The stratification of the risk continues to be the main challenge for the indication of ICD[21]. In accordance with international guidelines and expert consensus, the indications of the ICD in ARVC patients are well-established for high-risk patients with a history of SCD or episodes of sustained ventricular tachycardia (recommendation level IB), whilst the presence of unknown origin syncope, non-sustained ventricular tachycardia, a family history of sudden death, extensive illness including LV affection, are considered possible indications of ICD with an intermediate risk of SCD (Recommendation Level IIA, evidence level C)[31,32].

Excision via catheter

The excision of nerve channels via catheterisation has been considered a useful treatment for patients with poorly controlled ARVC. Excision via catheter cannot substitute ICD, but it can be useful in patients that already have one, in people resistant to medical treatment, in recurring monomorphic TV or in final stages with incessant ventricular tachycardias with palliative purposes[8,21,34]. It has been proven that better results are obtained if it is combined with electro-anatomical mapping to visualise the circulation pathways[24]. However, there is a high re-occurrence rate in the form of TV in the first 5 years of follow-up[14]. The application of current epicardium techniques along with endocardium techniques, has improved the success rate of eliminating TV, by not limiting the excision solely to the endocardiac lesion, less frequent in these patients[6,7,12]. This way, recurrence rates reduce by up to 30%[12].

Molecular therapy

A promising treatment for the future is the reprogramming of somatic cells in pluripotent cells. Skin fibroblasts can generate autologous cardiomyocytes, which can be implanted in a heart with ARVC[36].

Heart transplant

This is mainly used in the final stages, when the ARVC has progressed to extensive heart failure[13], or when faced with refractory disease to the medical treatment or other techniques[7,12]. It is not a frequent treatment, with an average age of 40 years and an 88% survival rate at 4.5 years[9].

Restriction of physical activity

The restriction of intense exercise is considered to be a hugely important treatment, as it has been demonstrated that exercise, especially when intense, increases the possibility of ARVC appearing, and is associated with a lower survival rate[9]. Competing athletes aged under 35 years with ARVC face a 5.4 times greater risk of SCD than non-athletes[2,30,34]. Recommendations from Lavine *et al.*[1] indicate that any exercise should be avoided apart from those of IA class, and in general any activity greater or equal to 4 METS. Although there are no studies on the progression rate of the illness, restricting exercise is considered the most important factor[9,19].

The limitation of physical activity is also recommended for family members of those affected by ARVC that have the mutation, whilst there is discrepancy in family members in which the genetic screening is not possible or in which no mutation has been identified. In this situation, an individualised series of assessments is recommended, mainly if they are high-level athletes[37]. Exercise and lifestyle recommendations should be given with the consensus of the patient and the family. The psychological impact of the diagnosis and the treatment, along with recommendations, poses a challenge for patients[32].

Prognostic factors

The possibility of SCD in patients with ARVC can be favoured by the presence of the following factors: Family history of SCD; Early onset of the illness[7]; Malignant arrhythmias or spontaneous or inducible unstable TV[34]; Heart attack or syncope, especially in stress[7], as it reflects the existence of malignant arrhythmias; Serious dysfunction of the RV (EF < 50% or thinning or aneurysm of the wall); QRS dispersion >50 ms (Increase of the QRS dispersion is considered to be from 40 ms and is the strongest independent predictor, with a sensitivity of 90% and a specificity of 77% according to Cadrin-Tourigny *et al*[34]); and the failure of anti-arrhythmic pharmaceuticals[2,34]. Furthermore, patients with the combination of spontaneous sustained TV, signs of right heart insufficiency and/or LV dysfunction are classified as being at the greatest risk of sudden death and have the worst long-term outlook[14].

On the other hand, for patients with an implanted ICD, the main risk factors related to secondary prevention are an aborted SCD and unstable TV, the presence of which implies a 10% annual risk of fatal TV[34].

Screening

Along with the antecedents, the resting ECG is the foundation for prevention of SCD in sports. When a basal ECG detects negative T-waves of V_1 to V_3, the study should be completed with an echocardiograph and a maximum stress test. Depending on the result of these tests, the study can be continued with CMR, with late gadolinium enhancement (LGE) and 24-hour Holter. Also a 12-lead ECG and echocardiograph of first-degree family members under the age of 10 years[38].

The European Sports Medicine Society, the European Society of Cardiology (ESC), the International Olympic Committee and FIFA recommend the carrying out of screening tests on athletes to prevent SCD, orientated at discovering the most frequent pathologies in athletes under 35 years. In the case of the ARVC, it is complex and difficult to perform, due to the low prevalence of the illness, the high cost of implementation and possible false positives. However, the success of screening and preventive measures in reducing SCD in athletes with ARVC has been proven. In the region of Venetto (Italy), screening with clinical history, physical examination and annual ECGs, and in high-risk cases, the limitation of sport, are factors that have led to an 89% reduction in ARVC-based SCD[16].

The ESC recommends screening of all athletes before starting intensive sporting activity to prevent cardiovascular-origin SCD. Basic cardiovascular assessment includes all federated athletes, is based on anamnesis, a physical examination and a 12-lead ECG, and should be carried out every two years. In turn, advanced cardiovascular assessment, within that found in high-risk athletes and professionals, requires the addition of the echocardiograph and the maximum stress test to the previous tests, and should be performed annually[39]. However, the AHA only recommends a clinical-family history and a physical examination. This discrepancy could be due to the greater weight of cost-efficiency issues in the United States in terms of healthcare. Despite this, and in contrary to most algorithms, different sporting bodies such as FIFA or the NBA place image tests in the initial screening, with the aim of ruling out heart anomalies, aortopathies or some cardiomyopathies with normal ECG readings[15] (Figure 4).

In terms of the age for starting the tests, the screening of patients with ARVC should be performed at around 12 years, given that if it is later, some cases of SCD may appear or the illness may progress[16,19]. On the other hand, initial assessment is recommended for all patients with suspected ARVC with a physical examination, clinical history, family antecedents with clinically compatible cases, ECG, signal-averaged ECG, Holter and echocardiograph[2].

Finally, the study by La Gerche *et al*[40] questions the evidence of screening programmes, indicating the researchers' concern for the long-term repercussion of the unnecessary exclusion from sport with

Figure 4. Algorithm of screening of 100,000 asymptomatic athletes[25].
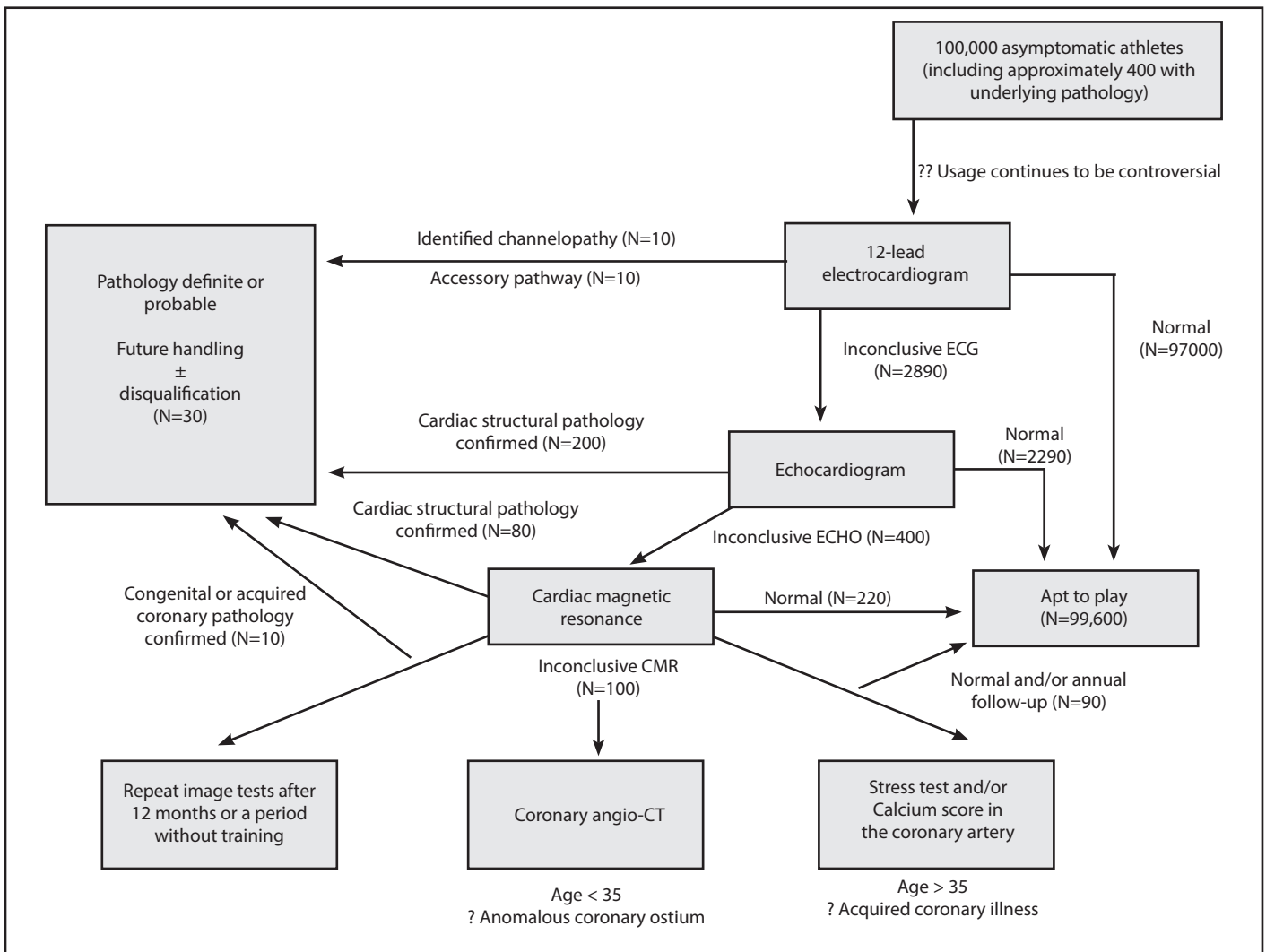
the aim of avoiding SCD, stating that it is a very uncommon pathology and is difficult to diagnose. The study also confirms that if generalised screening is to be carried out, it should be developed in parallel with the creation of centres of excellence in sporting cardiology so as to facilitate the task, with the creation of a record of SCD considered necessary.

Discussion

ARVC is one of the most frequent causes of SCD in athletes under 35 years of age, and therefore it is necessary to discover their natural history and the different diagnostic criteria with the aim of preventing SCD via screening and treating it appropriately. Unfavourable prognostic factors of the illness are considered to be: a previous heart attack, a history of exertional syncope or family SCD, the early onset of symptoms, physical exercise, the presence of TV, RV dysfunction or affection of the LV and resistance to pharmaceutical drug[s2,7,34].

Its diagnosis is based on the TFC criteria of the AHA, with this being difficult as those affected may remain asymptomatic and may suffer SCD as the first symptom. Genetic tests are indicated in patients with suspected ARVC or with a definitive diagnosis. In the case that any of the mutations are present, genetic tests should also be carried out on patients' family members as a screening method[21,24].

Following the anamnesis and the performance of a complete clinical history, ECG is the first diagnostic tool, with T-wave inversion in right precordial leads being the most common symptom[7-11]. Its presence in the ECG requires the study to be completed with a stress test and an echocardiograph[15]. Echocardiogram is considered to be the first and most used image test in ARVC[7], with the lengthening of the RV outflow tract being the most common anomaly[3,6,16].

CMR is the test of choice as it provides detailed information about the detail of the structure, ventricular function and the degree of fibrofatty replacement, characteristic of ARVC[3,7,16-18]. It is the most useful

follow-up method in asymptomatic patients[9]. In the event it cannot be performed, CT is considered an alternative. 3D electro-anatomical mapping is a useful diagnostic technique as it detects areas with a loss of electrically active myocardium, though it is used individually in patients with suspected ARVC with ventricular arrhythmias[7,18,21].

ARVC treatment is complex, as there is no clear evidence about the effectiveness of the different therapies. Current recommendations indicate the implantation of an ICD and the consumption of anti-arrhythmic drugs (sotalol or amiodarone) and/or excision via catheter of accessory pathways[3,10]. ICD is the most effective preventive treatment for SCD[7,33,35,36], which is indicated in patients with a history of SCD or episodes of sustained TV (high risk). The presence of unknown-origin syncope, non-sustained TV, a family history of SCD and extensive illness are considered to be intermediate risk indications[31,32].

According to the current bibliography, physical exercise should be restricted in patients with a possible, borderline, or definite diagnosis of ARVC, only permitting those of class I-A[1]. This prohibition should be made with the security that the patient has the illness, as this restriction entails a significant limitation on the lifestyle of these athletes. To assess the degree of progression, an ECG and an echocardiograph should be performed each year, along with a Holter and a CMR, the regularity of which depends on the patient[25].

The main sporting organisations and medical societies recommend the carrying out of biannual screening tests to prevent SCD in all athletes from the age of 12 years, before initiating sporting practice[16,19]. The basic cardiovascular assessment is performed systematically on all federated athletes and includes an anamnesis, a physical examination and a 12-lead ECG. On the other hand, advanced testing is only carried out on professional athletes and those with a high risk of SCD. To this latter group, a stress test and echocardiograph are added. If there is suspected ARVC, an initial assessment is recommended via a physical examination, clinical history and compatible family antecedents, ECG, signal-averaged ECG, Holter and echocardiograph[2].

For first-degree family members of patients with ARVC, the necessary tests are considered to be an ECG, an ergometry, an signal-averaged ECG, a Holter and a CMR; performed every 2-3 years if the results are normal. In second degree family members, the study is usually limited to an ECG, an echocardiograph and a Holter every 5 years[19]. The genetic test should be considered in patients with possible ARVC and first-degree family members[3,13], but it is not recommended on those with a single lesser-diagnostic criteria[13]. In patients carrying asymptomatic mutation, an annual or biannual follow-up should be carried out with a clinical history, ECG, echocardiograph, Holter and CMR[19]. In the case of asymptomatic patients without mutation or without a genetic study, follow-up will be every 3-5 years[13].

This systematic review is limited by heterogeneity and the reduced size of the populations studied, as currently no large-scale studies have been carried out in our media, and those that do exist do not include the echocardiograph as an initial screening test for all athletes, with this being highly recommendable for the detection of structural heart disease causing SCD. As well as this, there are no established records of sudden death in athletes; which is why there is no solid evidence of the prevalence of the different illnesses responsible for SCD.

Conclusions

– Carry out screening on all athletes using: anamnesis, family history, thorough physical examination and 12-lead ECG with the aim of detecting possible causes of SCD. In the case of ARVC, adding the echocardiogram is highly recommendable.

– In cases with anomalies detected via pre-participative screening, it is recommendable to continue the study with an echocardiogram, though this test has diagnostic limitations[41].

– The CMR will be reserved for patients with suspected ARVC without a firm diagnosis using the previously mentioned tests.

– Restrict physical exercise over 4METS in patients with a possible, borderline, and definitive ARVC diagnosis, as well as practising sports, apart from those in I-A class.

– Use sotalol and amiodarone as medical treatment, along with the implantation of an ICD in high-risk patients.

– Perform a periodic follow-up of patients with suspected or diagnosed ARVC, as well as of their first degree family members.

– Create a SCD register with the aim of quantifying the main causes with our means, so as to create a suitable prevention programmes and facilitate the research of these pathologies.

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