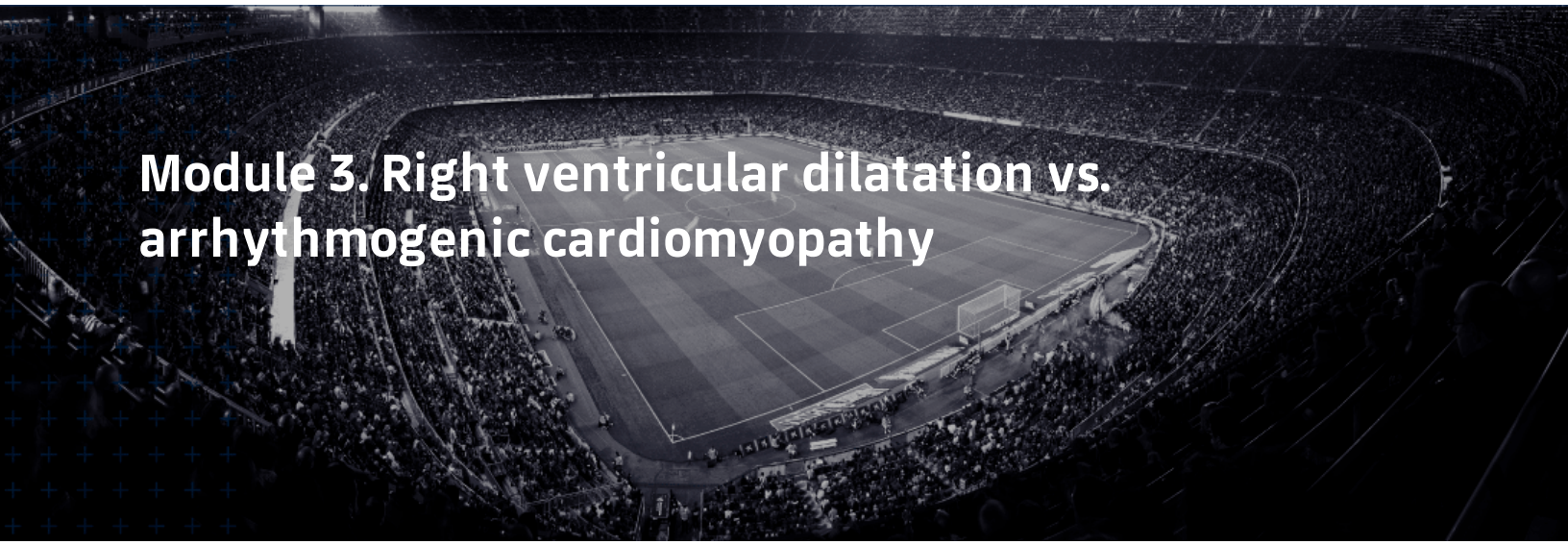

Module 3. Right ventricular dilatation vs. arrhythmogenic cardiomyopathy

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Unit 3.1 Adaptation of the right ventricle and pulmonary circulation to exercise

At rest, healthy pulmonary circulation is characterized by low resistance and high compliance, that is, it has great possibilities for distension and recruitment of new vessels. In contrast, under resting conditions, systemic circulation has a moderate compliance and operates with higher vascular resistance (Chamarthy et al., 2018). It is estimated that the pulsatile component of the pulmonary arterial load represents 25% of the power of the right ventricle compared to 10% in the systemic circulation for the left ventricle (Chamarthy et al., 2018). During high-intensity exercise, cardiac output increases up to five times, even reaching up to 40 l/min in highly trained athletes (La Gerche et al., 2011). This significant increase in flow is easily accommodated by the systemic circulation, which has a wide margin to reduce vascular resistance and recruit new vessels. In contrast, pulmonary circulation has a limited capacity to reduce vascular resistance which, at rest, are already low and experiences a much greater increase in pulmonary pressure than the systemic pressure. In fact, several studies have shown a linear relationship between increased cardiac output during exercise and increased pulmonary

arterial pressure (PAP) (La Gerche et al., 2011). In short, during exercise, right cavities are subjected to greater pressure and volume overload than left cavities, leading to greater wall stress for right cavities compared to left cavities (La Gerche et al., 2011). The healthy heart is able to adapt to intense, short-duration exercise, as it has sufficient contractile reserve to cope with it for short periods of time (La Gerche et al., 2012). However, when exercise and, therefore, overload are sustained for long periods of time, the functioning of the right cavities may be impaired. In fact, after the performance of intense long-term effort, such as during long-distance competitions (triathlon, marathon, open water races), several studies have documented a reduction in right ventricle (RV) performance in the form of reduced contractile function (Claessen et al., 2014; Sanz de la Garza et al., 2015; Martinez et al., 2019), cavity dilation (Claessen et al., 2014; Sanz de la Garza et al., 2015; Martinez et al., 2019) and increased cardiac biomarkers (Lewicka-Potocka et al., 2021).

This worsening in RV functionality was confirmed to be temporary, returning to baseline between 48 and 72 hours after the exercise stimulus (La Gerche et al., 2015). However, a murine model documented that high volumes of endurance exercise practiced over a long period of time could induce permanent structural change in the RV, in the form of myocardial fibrosis (Benito et al., 2011; Sanz de la Garza et al., 2017a) and ventricular arrhythmias originating from that ventricle (Benito et al., 2011). In humans, it is still controversial the hypothesis that high volumes of exercise may induce pathological RV

remodeling in initially healthy individuals. Heidbüchel et al. (2003) and, subsequently, La Gerche et al. (2010) evaluated two populations of highly trained endurance athletes who exhibited ventricular arrhythmias originating from the RV. Of these populations, 60% and 50%, respectively, met phenotypic criteria for a genetic heart muscle disease: arrhythmogenic cardiomyopathy. However, the percentage of these individuals who had a genetic component was much lower than expected in the general population, leading to the hypothesis that high volumes of sport could be sufficient to trigger pathological RV remodeling (Heidbüchel et al., 2003; La Gerche et al., 2010). Conversely, other studies conducted in other cohorts of elite athletes with similar training volumes do not confirm these findings (Aengevaeren et al., 2018; Bohm et al., 2016). Recent studies have documented a large variability in RV adaptation to exercise among individuals performing similar training volumes (Sanz de la Garza et al., 2015), which could partly explain this controversy. Mechanisms involved in the different RV adaptation to exercise are not well defined, which is considered to be the result of a complex combination of environment and genetic predisposition (Sanz de la Garza et al., 2020a).

Arrhythmogenic cardiomyopathy is a genetic disease characterized by an alteration in adhesive intercellular junctions called desmosomes (Corrado et al., 2017a). This alteration renders cells unable to stick together during stressful situations, such as exercise, leading to cell death and subsequent repair in the form of scar tissue and fat

deposits (Corrado et al., 2017a). The transformation of healthy myocardial tissue into fibrofatty tissue is progressive; initially, it is observed in the subendocardial region, and, in advanced stages, it affects the entire myocardial wall. This fibrofatty degeneration affects the cardiac muscle in a non-homogeneous manner (Corrado et al., 2017a). In the most classic variant affecting the RV, the degeneration is predominantly found in the so-called "triangle of dysplasia": outflow tract, inflow tract and apical region of the RV. Other variants affect both ventricles or predominantly the left ventricle (Sen-Chowdhry et al., 2008). In patients with a positive genotype but a negative phenotype for arrhythmogenic cardiomyopathy (AC), engaging in high volumes of endurance exercise accelerates the phenotypic expression of the disease (Mezzani et al., 2013). Moreover, in patients who have already phenotypically expressed AC, high-intensity exercise promotes disease progression and cardiac muscle degeneration, which in turn increases the risk of ventricular arrhythmias (Sawant et al., 2014) and heart failure (Saberniak et al., 2014).

For all of the above reasons, differentiating those individuals who have adaptive RV remodeling to exercise from those whose remodeling is pathological and potentially arrhythmogenic is essential and constitutes one of the most important challenges we face in sports cardiology in everyday clinical practice. The diagnosis of arrhythmogenic cardiomyopathy involves a combination of clinical, electrical, and structural parameters. The first criteria derived from the

AC Task Force were published in 1994. In 2010, these criteria were revised, significantly improving the diagnostic specificity and sensitivity for the RV-dominant variant of AC (Marcus et al., 2010). In 2020, the Padua criteria were published, with the aim of further improving the diagnostic sensitivity and specificity of the 2010 Task Force criteria for the RV-dominant variant and incorporating specific criteria for the diagnosis of the LV-dominant variant (Corrado et al., 2020). Endurance training induces a series of electrical and structural adaptive changes in the RV. In highly trained athletes, these changes can be so pronounced that they may complicate the applicability of some of the diagnostic criteria for AC. In this chapter, we will discuss the different diagnostic tools currently available to perform this essential task: differentiating between adaptive RV remodeling to exercise and pathological remodeling.

3.1.1 Clinical evaluation

The first step in evaluating an athlete is to know their sports history and to detail the type of sport they are practicing, the training volume and the level at which they compete. Endurance sports such as cycling, cross-country skiing or long-distance running, as well as mixed sports with a high dynamic component such as soccer are the sports where we would expect to find more pronounced electrical and structural RV remodeling (Pelliccia et al., 2018). Likewise, RV remodeling due to exercise is proportional to training volume; in other words, the most pronounced remodeling would be expected in

athletes who train longer hours, at higher intensity, and have been training at that level for longer (D'Ascenzi et al., 2019).

The anamnesis of symptoms must be detailed and thorough in the athlete, as sometimes symptoms are minimized or are nonspecific, such as a decrease in sports performance or generalized fatigue (Mont et al., 2016). Some symptoms that should serve as a warning and that require us to complete a diagnostic algorithm with complementary cardiological tests include the following:

- Oppressive chest pain, especially when it occurs during sports practice.
- Shortness of breath (dyspnea) during exercises of certain intensity that previously did not cause this symptom.
- Dizziness, especially if it occurs during exercise.
- Loss of consciousness (syncope).
- Palpitations or irregular heartbeat.

As for family history, we should ask about sudden cardiac deaths or the development of cardiac pathology before the age of fifty. Additionally, we should inquire about unexpected and unexplained

deaths of close relatives, even if their cardiac etiology has not been confirmed, such as an unexplained car accident. We should also consider the presence of multiple cases of sudden infant death syndrome as a factor when suspecting genetic cardiac pathology (Sawant et al., 2014)."

Electrocardiogram

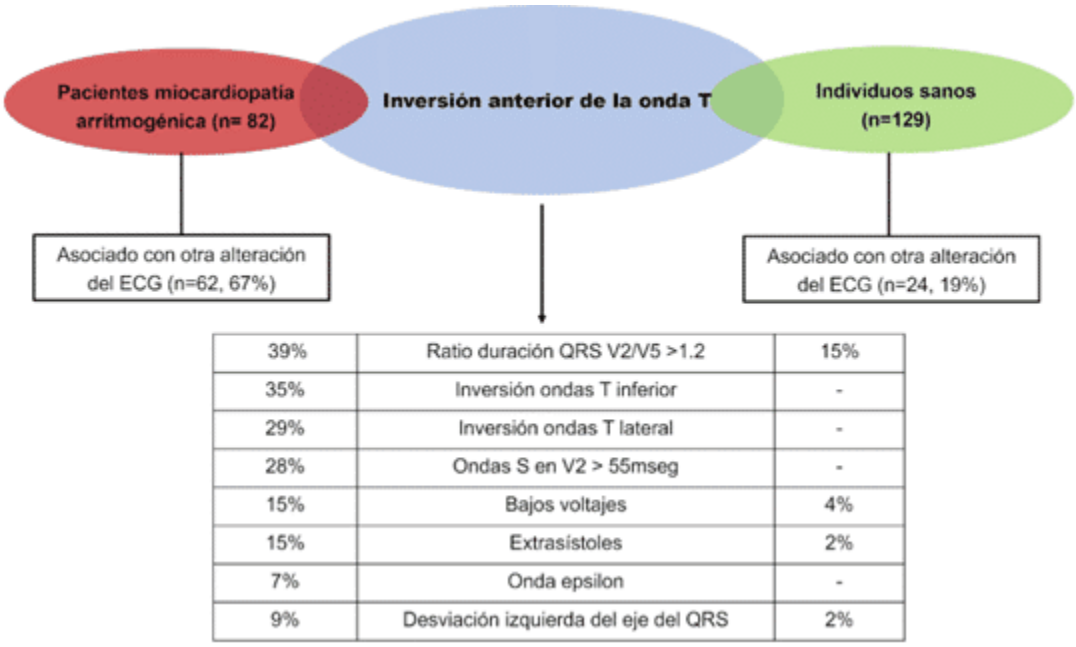
The electrocardiogram (ECG) is one of the first-line complementary tests in the assessment of the athlete (Mont et al., 2016). In order to accurately assess the athlete, it is key to know the electrocardiographic changes specific to sports practice so as to differentiate them from those changes that unrelated to sports practice and that could be the first sign of an underlying cardiomyopathy.

Regarding arrhythmogenic cardiomyopathy, ECG is highly useful in terms of diagnosis, as it shows pathological data in more than 80% of patients and may precede the characteristic structural abnormalities of the disease (Corrado et al., 2017a). T-wave inversion in precordial leads is the most common abnormality (Steriotis et al., 2009). The presence of negative T waves in precordial leads (V1-V3), and beyond V3 in the absence of complete right bundle branch block, constitutes a major criterion for AC according to Task Force criteria (Marcus et al., 2010). However, T-wave inversion in precordial leads may be present in healthy individuals (Malhotra et al., 2017). We should keep in mind

that its prevalence is higher in women (Malhotra et al., 2017). Additionally, in athletes and healthy individuals under sixteen years of age, the so-called juvenile repolarization pattern has been described, which is characterized by negative T waves in leads V1-V3 and is considered a benign, age-associated repolarization pattern (Sharma et al., 2017). Moreover, race has an important impact on the ECG repolarization pattern: up to 13% of Black athletes exhibit a wave inversion in leads V1-V4 characterized by being preceded by an elevated J point and a convex ST segment (Papadakis et al., 2011). That pattern is considered as normal in this ethnic group (Sharma et al., 2018). The volume and the type of training are also decisive when analyzing ECG repolarization. In highly trained endurance White athletes, wave inversion in precordial leads was confirmed: it is present in up to 7% without being associated with underlying cardiomyopathy (Brosnan et al., 2014).

In a recent study, the ECG characteristics of healthy individuals exhibiting anterior T-wave inversion were compared with those of patients with a definitive diagnosis of AC (Finocchiaro et al., 2019).

Figure 1. ECG abnormalities coexisting with T-wave inversion in patients with arrhythmogenic cardiomyopathy and in healthy individuals



39%	Ratio duración QRS V2/V5 >1.2	15%
35%	Inversión ondas T inferior	-
29%	Inversión ondas T lateral	-
28%	Ondas S en V2 > 55mseg	-
15%	Bajos voltajes	4%
15%	Extrasístoles	2%
7%	Onda epsilon	-
9%	Desviación izquierda del eje del QRS	2%

Source: Finocchiaro et al., 2019, p. 337.

As shown in the previous image, in patients with AC, anterior T-wave inversion is often accompanied by other electrocardiographic data considered pathological in athletes, such as T-wave inversion in inferior leads (II, III and aVF) and lateral leads (V5-V6), prolongation of the wave in V2, low voltage or the presence of ventricular extrasystoles.

The presence of an epsilon wave in the ECG is a major criterion of the Task Force for diagnosis of AC (Marcus et al., 2010) and a minor criterion in the new international guidelines (Corrado et al., 2020). It reflects a delay in the depolarization of part of the RV and manifests as low-amplitude electrical potentials, particularly in leads V1-V3 between the end of the QRS complex and the beginning of the T

wave. This wave is not present in the healthy or athletic population; the specificity of this electrocardiographic finding is 100%, but it is present in only a minority of patients with AC, especially in the early stages of the disease (Corrado et al., 2017b).

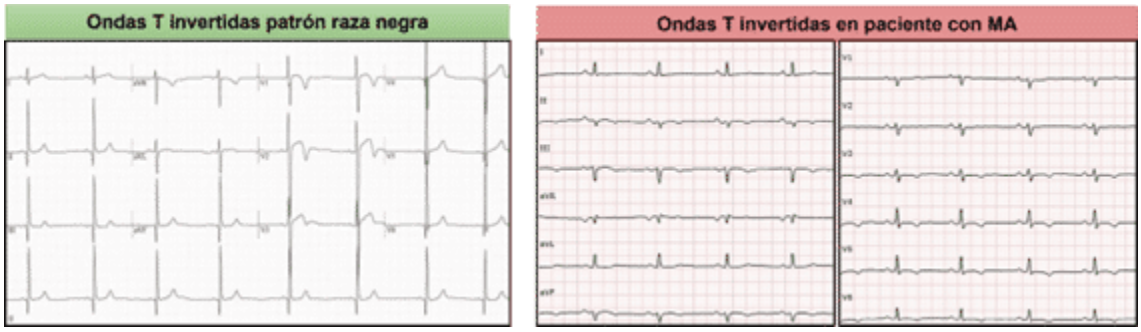
As noted above, the Black repolarization pattern is characterized by inverted T waves in leads V1-V4 preceded by an elevated J point (>0.1 mV). However, in White athletes, especially in female athletes, the fact that T-wave inversion is not preceded by J-point elevation is not a pathognomonic sign of pathology, as it is present in up to 65% of cases (Finocchiaro et al., 2019).

Up to 13% of athletes meet the Sokolow-Lyon voltage criteria for right ventricular hypertrophy (Zaidi et al., 2013): R wave in lead V1 + S wave in leads V5 or V6 >10.5 mV. It has been confirmed that such electrocardiographic finding is not associated with increased RV thickness (Zaidi et al., 2013). This is why it is considered a normal sign in the athlete's ECG (Sharma et al., 2017).

Traditionally, the presence of complete right bundle branch block was considered pathological in the sports ECG. However, later studies have documented that up to 3% of athletes have complete right bundle branch block in the absence of cardiac pathology (Kim and Baggish, 2015). This finding has been associated with a larger RV size, so it is considered another sign of adaptive electrical remodeling of the right

heart due to exercise (Sharma et al., 2017) and does not require further testing if this is the only differential finding on the ECG.

Figure 2. Normal T-wave inversion pattern in Black athlete's ECG vs. pathological pattern



Source: own source.

Inverted T-wave in Black athlete pattern

Inverted T waves in a patient with AC

Figure 2. A) Inverted T waves in leads V1 to V3 with elevated J point (>1 mV) and convex ST-segment elevation in an elite soccer player of mixed race (Caucasian/African-American). This is considered a normal pattern in Black or mixed-race athletes. B) T-wave inversion in leads V1-V6 extending to inferior leads, accompanied by left axis deviation of the QRS in a female recreational athlete with a confirmed diagnosis of arrhythmogenic cardiomyopathy with bi-ventricular involvement.

Echocardiogram

Dynamic training induces an increase in all cardiac cavities. This structural change is adaptive as a response to exercise and, therefore, it is proportional to the training practiced. We would expect to find the most dilated RVs in endurance athletes who engage in high volumes of training and those with a longer sports history (D'Ascenzi et al., 2019). Regardless of whether they are athletes or not, women tend to have smaller RV sizes compared to men, even after normalization for body surface area (Sanz et al., 2017). Therefore, when evaluating RV size, we must consider individual characteristics, such as body surface area and sex, as well as factors associated with the athlete's current and previous sports history.

In a population of young competitive athletes, Zaidi et al. (2015) documented that up to 61% of male athletes and 46% of female athletes met the Task Force minor criteria for RV outflow tract dilatation (RV outflow tract in the parasternal long axis view, 29-32 mm; and in the parasternal short axis view, 32-36 mm) whereas 37% of males and 24% of females met the major criterion (RV outflow tract in the parasternal long axis view, >32 mm; and in the parasternal short axis view, >36 mm). Sports-induced RV dilation is global, meaning it is proportional across the different segments of the RV; however, patients with AC show greater dilatation of the outflow tract compared to the rest of the segments. Thus, a predominant RV outflow tract dilatation with respect to the other segments would suggest pathological RV remodeling (D'Ascenzi et al., 2018). For these reasons, the European guidelines for the evaluation of athletes using

imaging techniques recommend that, for the echocardiographic assessment of the RV in athletes, only measurements indexed to body surface area should be considered, and an RV should be considered dilated only if it meets the major Task Force criterion, i.e., RV outflow tract >19 mm/m^2 in the parasternal long-axis view and >21 mm/m^2 in the parasternal short-axis view (Pelliccia et al., 2018). Additionally, emphasizing the need to evaluate RV size in the individual's clinical context, the new international criteria for AC diagnosis recommend considering an RV dilated only when the normal reference values for a given age, sex and body surface area are exceeded (Corrado et al., 2020).

Physical training induces a harmonic dilatation of all cardiac cavities and, therefore, cardiac remodeling is expected to be balanced between right and left cavities. In contrast, in classic arrhythmogenic cardiomyopathy, pathological remodeling predominantly affects the RV. Thus, an RV inflow tract to left ventricle diameter ratio (in the apical view for the RV and parasternal long-axis view for the left ventricle) greater than 0.9 is proposed as a cutoff value favoring pathological RV remodeling over adaptive remodeling (Pelliccia et al., 2018).

Global right ventricular systolic function is usually similar in athletes and the general healthy population. However, in highly trained athletes, where sports-induced cardiac remodeling can be very pronounced, a slightly decreased global RV function at rest may be

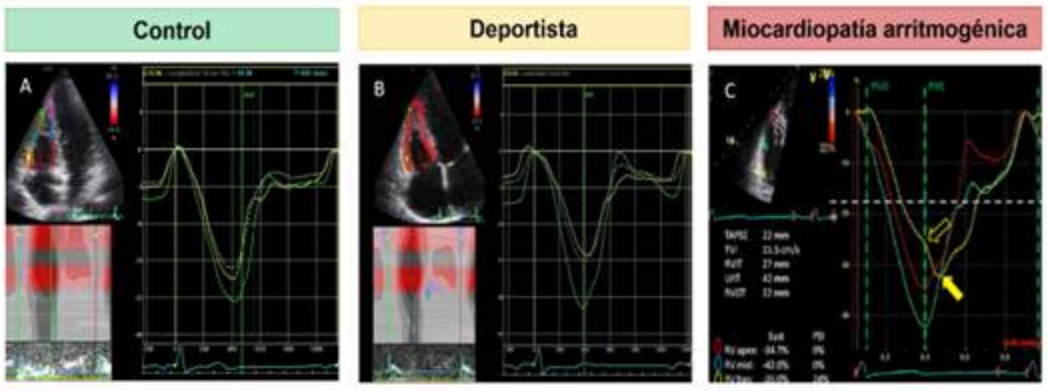
observed (Zaidi et al., 2015). A fractional area change of the RV (a parameter used in standard echocardiography to assess RV systolic function) of less than 30% was shown to have an 89% specificity for identifying arrhythmogenic cardiomyopathy vs. adaptive RV remodeling (Zaidi et al., 2015).

The training-induced change in RV function, while slight, affects the RV globally. Therefore, identifying an abnormality in RV motility should be considered a pathological sign that requires completing the diagnostic algorithm. It is true that, given the complex morphology of the RV, the qualitative assessment of segmental motility that can be performed with a standard echocardiography may not be adequate, especially at the apical segment, where up to 30% false positives have been reported (Teske et al., 2008). In the last decade, the development of new echocardiographic techniques has allowed us to evaluate myocardial deformation (strain), which provides a more direct measure of systolic function than the fractional area change of the RV.

In highly trained athletes, some studies have shown a slight reduction in myocardial strain at the basal segment and a higher value at the apical segment compared to non-athlete healthy individuals (Sitges et al., 2017). However, in all cases, myocardial strain values in healthy athletes were within normal ranges (Sitges et al., 2017). The European guidelines for the evaluation of athletes using cardiac imaging techniques recommend using global RV strain to

establish the differential diagnosis between pathological and adaptive RV remodeling, with a value <20% (in absolute terms) being suggestive of underlying pathology (Pelliccia et al., 2018). In addition, myocardial strain techniques allow us to assess the timing of cardiac muscle contraction in healthy individuals, whether athletes or not, the contraction of all RV segments occurs uniformly, in unison. In contrast, in patients with arrhythmogenic cardiomyopathy, a delay in contraction of some RV segments has been documented. This sign, known as mechanical dispersion, has been identified as an early sign of phenotypic expression of AC (Saberniak et al., 2017) and is associated with the development of ventricular arrhythmias (Sarvari et al., 2011).

Figure 3. Right ventricular myocardial strain in a healthy non-athlete individual, a highly trained endurance athlete and a patient with AC



Source: Figures A and B, own sources. Figure C, own source based on D'Andrea *et al.*, 2015.

Control

Athlete

Arrhythmogenic cardiomyopathy

Figure 3. A) Healthy non-athlete individual showing a global right ventricular strain of -26%, -27% at the basal segment, and -32% at the apical segment. B) Healthy athlete showing a normal global right ventricle strain value, similar to the one that shows the healthy non-athlete individual, but with a slightly lower basal strain of -25% (in absolute value), and a higher strain at the apical segment level of -37% (in absolute value). C) Patient with arrhythmogenic cardiomyopathy at an early stage of the disease. The global RV strain is normal—>20% (in absolute value)—, but the contraction of the basal segment is delayed compared to the other segments.

On the other hand, it should be noted that AC is a cardiac pathology that affects all cardiac cavities. The use of myocardial strain techniques has confirmed that even in patients with the classic variant of AC (predominantly affecting RV), the left ventricle myocardial strain can be reduced, especially in the mid and apical segments of the posterolateral wall of the left ventricle (Mast et al., 2015).

Exercise-induced structural remodeling reflects the RV structural adaptive changes to exercise. Thus, marked RV remodeling in the form of prominent RV dilation and borderline or slightly reduced global RV function would be expected in endurance athletes with high training volumes, where we would also expect excellent aerobic functional capacity. This marked RV dilation acts as an adaptive mechanism, providing the athlete with a greater volume reserve, while a borderline systolic function provides an increased contractile reserve during exercise. Exercise echocardiography would be highly useful in these cases of marked RV remodeling. In healthy athletes, we should observe an increase in RV systolic function in response to exercise stimulus, whereas in individuals with pathological RV remodeling, there will be little or no increase in this function, as assessed both by standard echocardiography (La Gerche et al., 2015) and more precisely by techniques that evaluate myocardial strain (Claeys et al., 2019).

Cardiac MRI

Cardiac resonance magnetic imaging (MRI) is the imaging technique of choice for the evaluation of global and segmental RV function. It allows for a more precise and reproducible estimation of RV mass and volumes compared to echocardiography. A meta-analysis that included 938 male athletes aged 18 to 55 years, assessed by cardiac MRI, provided reference values for bi-ventricular size and function in this population group (D'Ascenzi et al., 2018).

To date, there are very few cardiac MRI studies in female athletes, but the available studies confirm the findings of standard echocardiography. Female athletes have lower RV volumes than male athletes with similar sports histories, both in absolute terms and when indexed to body surface area (Domenech-Ximenos et al., 2020). In athletes engaged in high volumes of endurance training, it has been confirmed that RV volume often exceeds the normal limits established for the general population, meeting the minor Task Force criterion associated with the assessment of right ventricle size by means of cardiac MRI (D'Ascenzi et al., 2019).

This is why the European guidelines for the evaluation of athletes using cardiac imaging techniques (Pelliccia et al., 2018) recommend that the RV be considered dilated only if it meets the Task Force major volume criterion, i.e., an RV global volume →110 mL/m2 in males and →100 mL/m2 in females. In this regard, the new criteria for the AC diagnosis emphasize the need to use normal values for an athletic population with a given age, sex and body surface area (Corrado et al., 2020). As previously explained, exercise induces a harmonic dilatation of all cardiac cavities, so if a dilated RV is observed in an athlete, a similar dilation of the LV would be expected. Thus, for the differential diagnosis between pathological and adaptive RV remodeling using cardiac MRI, it is useful to evaluate the RV/LV volume ratio; if this is >1.2, it is suggestive of underlying pathology (Pelliccia et al., 2018).

Global RV function assessed by cardiac MRI is evaluated by the RV ejection fraction (percentage change between diastolic and systolic volumes). In highly trained athletes, the values of such parameters may be slightly decreased, but commonly remain within normal limits for the general population (D'Ascenzi et al., 2019, Domenech-Ximenos et al., 2020). So, as per a global RV function assessed by cardiac MRI, Task Force's both minor criterion (RV ejection fraction <45%) and major criterion (RV ejection fraction <40%) should be considered indicative of AC (Pelliccia et al., 2018; D'Ascenzi et al., 2019). On the other hand, cardiac MRI allows us for a more accurate assessment of RV segmental motility compared to standard echocardiography. The presence of segmental motility abnormalities detected by cardiac MRI should be considered pathological in all cases, requiring further diagnostic evaluation (Pelliccia et al., 2018; D'Ascenzi et al., 2019). In recent years, technological advancements in echocardiography have enabled the assessment of myocardial strain using magnetic resonance imaging with the feature tracking technique. This technique has recently been applied to the differential diagnosis between pathological and adaptive remodeling in athletes, with promising results, but established normal values for the athletic population are not yet available (Czimbalmos et al., 2019).

In highly trained athletes where we find extreme RV remodeling with dilation of the ventricle and borderline RV ejection fraction, performing a stress cardiac MRI can be useful to assess the contractile reserve of the ventricle. A reduced or absent RV contractile reserve

should raise suspicion of underlying pathology (Claessen et al., 2014; La Gerche et al., 2015).

Table 1. Summary of the most important studies providing average values and ranges of RV structural and functional parameters using two-dimensional echocardiography and cardiac MRI in endurance athletes, in whom right ventricular remodeling is expected to be more pronounced

2D echocardiogram	(D'Andrea *et al.*, 2013) (N = 395, 61% males)		(Oxborough *et al.*, 2012) (N = 102, 85% males)		(Sanz Garza 2017a) (N = 4 femal
Dimension parameters	**Mean ± SD**	**URL**	**Mean ± SD**	**URL**	**Mean ± SD**
Proximal RVOT (mm)	31.3 ± 6.3	43.9	34 ± 5	44	33.6 ± 2.9
Proximal RVIT (mm/m^2)	17.0 ± 3.4	23.8.	17 ± 3	23	21.8 ± 2.1

Distal RVOT (mm)	27.3 ± 7.3	41.9	N/A		N/A
RV basal diameter (mm)	38.1 ± 5.3	48.7	44 ± 5	54	36.5 ± 4.2
Mid RV diameter (mm)	33.3 ± 5.4	44.1	N/A		N/A
RV longitudinal diameter (mm)	80.1 ± 5.7	91.5	92 ± 9	110	61.8 ± 5.7
RV end-diastolic area (cm^2)	N/A		26 ± 5	36	18.6 ± 2.7
Indexed RV end-diastolic area (cm^2/m^2)	N/A		13 ± 2	17	11.6 ± 1.7
Function parameters	**Mean ± SD**	**LRL**	**Mean ± SD**	**LRL**	**Mean ± SD**
TAPSE (mm)	23.7 ± 2.8	18.1	N/A		N/A

RV FAC (%)	49.3 ± 3.7	41.9	47 ± 7	33	49.3 ± 5.1
RV s' TDI (cm/s)	14.8 ± 2.9*	9.0	11 ± 1.3[&]	8.4	9.8 ± 1.0[&]
Cardiac MRI	**(D'Ascenzi *et al.*, 2018)** **(N = 250, 100% males)**	**(Domenech-Ximenos *et al.*, 2020)** **(N = 44, 100% females)**			
Dimension parameters	**Mean ± SD**	**URL**	**Mean ± SD**	**URL**	
RVEDV (ml)	230 ± 7	244	145 ± 25	195	
Indexed RVEDV (ml/m^2)	120 ± 7	134	92 ± 16	124	
RVESV (ml)	101 ± 4	109	69 ±	93	

			12		
Indexed RVESV (ml/m^2)	55 ± 2	59	42 ± 8	58	
Function parameters	**Mean ± SD**	**LRL**	**Mean ± SD**	**LRL**	
RVEF (%)	54 ± 1	52	54 ± 4	46	

Source: Adapted from Sanz de la Garza, M., Carro, A., and Caselli, S. (2020b)

Table 1

SD: Standard deviation

RVOT: Right ventricular outflow tract

RVIT: Right ventricular inflow tract

TAPSE: Tricuspid annular plane systolic excursion

FAC: Fractional area change

TDI: Tissue Doppler imaging

RVEDV: Right ventricular end-diastolic volume

RVESV: Right ventricular end-systolic volume

RVEF: Right ventricular ejection fraction

URL: Upper reference limit

LRL: Lower reference limit

In addition to accurately assessing RV function and volumes, cardiac MRI allows us to characterize cardiac tissue. Late gadolinium enhancement sequences help us to identify areas of inflammation or fibrosis in the LV. Given the thin wall that characterizes the RV, interpretation of the late enhancement sequence in the RV is more challenging. Three-dimensional assessment of late enhancement (Gati et al., 2018) and the analysis of such sequence alongside the assessment of the affected segments motility facilitates the evaluation and allows for a more accurate assessment (Aquaro et al., 2016).

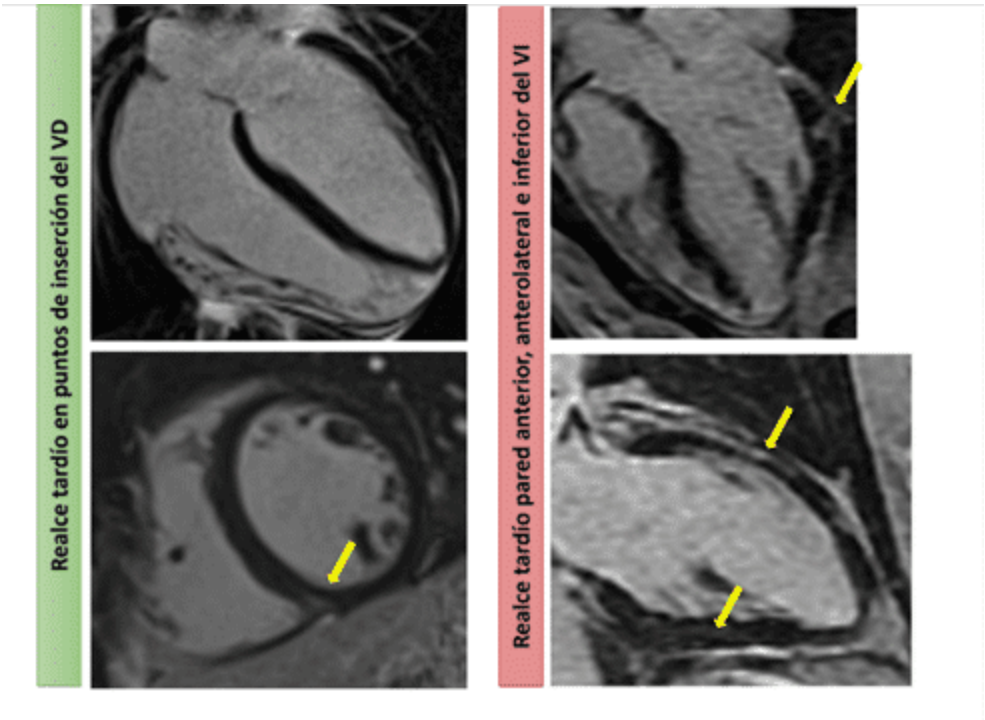
The presence of focal late enhancement at the RV insertion points has been observed in patients with RV volume overload, such as those with tetralogy of Fallot (Ylitalo et al., 2014), and in cases of

pressure overload, as seen in patients with pulmonary hypertension (Soma et al., 2013). However, this pattern has also been observed in the healthy general population. In athletes, recent studies have shown an increased prevalence of late enhancement at RV insertion points compared to healthy individuals of similar age and sex (Domenech-Ximenos et al., 2020). Currently, the significance of this finding in a healthy population, whether athletic or not, is still unclear, and therefore, it cannot be assigned clinical or prognostic value (Domenech-Ximenos et al., 2020).

In patients with AC, using the late enhancement sequence has allowed us to observe that, in the classic (RV-dominant) variant, LV involvement occurs earlier than initially believed, based on more traditional imaging modalities (Marra et al., 2012). Furthermore, in the LV-dominant variant, late enhancement may be the first pathological structural finding; in this group of patients, the characteristic late enhancement pattern affects the subepicardial and mid-wall regions of the posterolateral and inferior LV walls (Feliu et al., 2020). Given the usefulness of late enhancement, both in diagnostic and prognostic terms in AC, the new international guidelines incorporate as a new major criterion for diagnosing the classic (RV-dominant) variant the detection of transmural late enhancement affecting more than one region of the RV (outflow tract, inflow tract and apex in two orthogonal planes), and, for the LV-dominant variant, the presence of late enhancement in the LV free wall (subepicardial and mid-wall

regions), septum, or both (excluding the LV junction area) (Corrado et al., 2020).

Figure 4. Patterns of adaptive vs. pathological late gadolinium enhancement remodeling



Source: own source.

Realce tardío en puntos de inserción del VD	Late enhancement at RV insertion points
Realce tardío pared anterior, anterolateral e	Late enhancement of the anterior, anterolateral and inferior

inferior del VI	wall of the LV

Figure 4. The two cardiac MRI images on the left are from a 35-year-old male triathlete with high weekly training volumes. Cardiac MRI reveals focal late enhancement at the insertion of the RV into the interventricular septum, which is considered a pattern with no pathological significance. The two images on the right are from an asymptomatic female amateur athlete who, due to ECG abnormalities, underwent a cardiac MRI that confirmed the suspicion of arrhythmogenic cardiomyopathy with involvement of both ventricles. The enhancement shows a striated pattern in the mid-myocardial region of the anterior, anterolateral, and inferior walls of the left ventricle

Table 2. Differential diagnosis between adaptive and pathological remodeling of the right ventricle based on cardiac imaging tests

Remodelado adaptativo VD	Parámetros imagen cardiaca	Remodelado patológco del VD
Global	**Dilatación VD**	TSVD principalmente
<1.2	**Ratio volumen VD/VI**	>1.2
Normal o limítrofe	**Función global del VD**	Reducida <45% FEVD en RC <30% CAFVD en ecocardiograma
Ausente	**Alteraciones en la motilidad segmentaria**	Presente
Ausente o puntos de inserción VD	**Realce tardío**	Presente en pared libre VD y/o subepicárdico o medial en VI
Preservada	**Reserva contráctil del VD evaluación por ecocardiograma o RN de ejercicio**	Reducida o nula

Source: own source.

Columna 1	**Columna 1**
Remodelado adaptativo VD	Adaptive RV remodeling
Global	Global
<1.2	<1.2
Normal o limítrofe	Normal or borderline
Ausente	Absent
Ausente o puntos de inserción VD	Absent or RV insertion points

Preservada	Preserved
Columna 2	**Columna 2**
Parámetros imagen cardíaca	Cardiac imaging parameters
Dilatación VD	RV dilatation
Ratio volumen VD/VI	RV/LV volume ratio
Función global del VD	RV global function
Alteraciones en la motilidad segmentaria	Segmental motility abnormalities
Realce tardío	Late enhancement
Reserva contráctil del VD (evaluación por ecocardiograma o RN de ejercicio)	RV contractile reserve (assessment using echocardiogram or stress CMR)
Columna 3	**Columna 3**
Remodelado patológico del VD	Pathological RV remodeling

TSVD principalmente	Mainly RVOT
1.2	1.2
Reducida <45% FEVD en RC <30% CAFVD en ecocardiograma	Reduced <45% RVEF in CMR <30% RVFAC in echocardiogram
Presente	Present
Presente en pared libre VD y/o subepicárdico o medial en VI	Present in RV free wall and/or subepicardial or mid-wall regions of the LV
Reducida o nula	Reduced or absent

Table 2

RVOT: Right ventricular outflow tract

RVEF: Right ventricular ejection fraction

CMR: Cardiac magnetic resonance

3.1.2 Arrhythmia evaluation: Holter ECG recording and stress test

The most common ventricular arrhythmia in the healthy population, whether or not athletic, is the presence of ventricular extrasystoles. When ventricular extrasystoles are not associated with cardiac pathology, they tend to be relatively infrequent (<2 on a standard ECG and <500 on a 24-hour recording) (Sharma et al., 2017). However, finding frequent ventricular extrasystoles is not synonymous with poor prognosis or underlying cardiac pathology; other variables such as the morphology, behavior and complexity of these extrasystoles should be taken into account (Heidbüchel et al., 2021). The most common morphologies in the healthy population are those originating in the RV outflow tract (complete left bundle branch block with inferior axis) and fascicular types (right bundle branch block with QRS <130 ms); other morphologies are uncommon and should raise suspicion of underlying pathology. Likewise, the presence of more complex arrhythmias such as triplets of extrasystoles or non-sustained ventricular tachycardias are very rare in athletes and should therefore prompt completion of the diagnostic algorithm (Heidbüchel et al., 2021). Traditionally, arrhythmic burden assessment would be performed with an ECG Holter device. Today, technological advances have provided us with wireless ECG monitoring devices that are especially useful for ECG evaluation in athletes, as they allow us

to obtain an adequate ECG recording during sports practice (Fabregat, 2014).

When evaluating ventricular extrasystoles in an athlete, in addition to morphology, arrhythmic burden and complexity of these arrhythmias, we must assess their behavior during exercise. A peak stress testing will allow us to evaluate the behavior of extrasystoles during exercise and to assess whether additional arrhythmias are induced by the exercise stimulus, as well as to evaluate functional capacity and hemodynamic response. In the case of "benign" ventricular extrasystoles, the exercise stimulus reduces its frequency until it disappears at a certain heart rate. By contrast, "pathological" extrasystoles will persist or even increase with the adrenergic discharge induced by exercise (Heidbüchel et al., 2021). It is important to emphasize that, in the evaluation of arrhythmias in athletes, it is essential to take into account the clinical context; the presence of symptoms, a family history of early death or heart disease are key factors to take into account. Additionally, the presence of arrhythmias combined with pathological findings on ECG or cardiac imaging tests are suggestive of pathology and, therefore, necessitates completion of the diagnostic algorithm (Heidbüchel et al., 2021).

Table 3. Common and unusual features in ventricular extrasystoles in athletes

	COMÚN	NO COMÚN
Características extrasístoles		
Morfología	Origen en TSVD: BRI + eje inferior Fascicular: BRD con QRS <130ms	BRI + eje intermedio o superior BRD y QRS >130ms
Respuesta al ejercicio	Disminuyen/Desaparecen	Persisten/Aumentan
Complejidad	Aisladas, Monomórficas	Repetitivas, Polimórficas
Intervalo de acoplamiento corto	No	Si
Características clínicas		
Síntomas	No	Si
Historia familiar de MSC prematura o cardiopatía	No	Si
Hallazgos patológicos en el ECG	No	Si
Hallazgos patológicos en las pruebas de imagen cardiaca	No	Si

Source: own source based on Heidbüchel et al., 2021.

Columna 1	**Columna 1**
Características extrasístoles	Extrasystole characteristics
Morfología	Morphology
Respuesta al ejercicio	Response to exercise
Complejidad	Complexity
Intervalo de acoplamiento corto	Short coupling interval
Características clínicas	Clinical characteristics

Síntomas	Symptoms
Historia familiar de MSC prematura o cardiopatía	Family history of premature SCD or cardiopathy
Hallazgos patológicos en el ECG	Pathological findings on ECG
Hallazgos patológicos en las pruebas de imagen cardíaca	Pathologic findings on cardiac imaging tests
Columna 2	**Columna 2**
COMÚN	COMMON
Origen en TSVD: BRI + eje inferior Fascicular: BRD con QRS <130ms	Origin in RVOT: LBBB + inferior axis Fascicular: RBBB with QRS <130 ms
Disminuyen/Desaparecen	Decrease/disappears
Aisladas, Monomórficas	Isolated, monomorphic
No	No
Columna 3	**Columna 3**

NO COMÚN	UNCOMMON
BRI + eje intermedio o superior BRD y QRS >130ms	LBBB + intermediate or superior axis RBBB and QRS >130 ms
Persisten/Aumentan	Persists/increases
Repetitivas, Polimórficas	Repetitive, polymorphic
Sí	Yes

Table 3

RVOT: Right ventricular outflow tract

LBBB: Left bundle branch block

RBBB: Right bundle branch block

SCD: Sudden cardiac death

Invasive evaluation

If a comprehensive non-invasive evaluation still leaves the diagnosis uncertain, an invasive approach may be considered in specific cases. For ventricular arrhythmias originating in the right ventricle, a recent study found that an electrophysiological study can effectively distinguish between patients with arrhythmogenic cardiomyopathy and those with idiopathic ventricular arrhythmias, with high sensitivity and specificity (Dello Russo et al., 2022). Additionally, detecting fibrosis or fatty degeneration through an endomyocardial biopsy is a major diagnostic criterion for AC according to the Task Force. However, due to the procedure's low sensitivity —stemming from the challenge of obtaining a representative sample— and the inherent risks of an invasive approach, its use in clinical practice has declined in recent years (Cooper et al., 2007). Nonetheless, recent advances where endomyocardial biopsy is guided by electroanatomical mapping have shown promising results. The combination of both techniques not only improves the sensitivity of the test but also reduces the risk of technique-related complications, with only a 2% incidence of minor complications and no major complications (Casella et al., 2021).

Genetic testing

The use of genetic testing has increased exponentially in recent years in the field of cardiology. The recommendations for conducting genetic testing in athletes are similar to those for the general population. However, genetic testing holds additional value for athletes, as it

allows for the early identification of a genetic heart condition that could potentially lead to sudden death at an early stage (Castelletti et al., 2022). This is particularly important in the context of arrhythmogenic cardiomyopathy, as we know that both the intensity and duration of exercise are associated with an earlier onset of AC (James et al., 2013) and a worse prognosis (Sawant et al., 2014). In this context, genetic testing is recommended when there is a strong suspicion of AC or when a first-degree relative has been diagnosed with AC (Gray and Semsarian, 2020). It is important to note that a negative genetic test result does not exclude the diagnosis of AC, as 30-50% of patients with a confirmed diagnosis of AC may have a negative genetic test (James et al., 2020). This simply means that the genetic abnormalities associated with their AC have not yet been identified by the current genetic testing available at the time. Finally, it is crucial that genetic testing be conducted at a specialized center to ensure the correct selection of genetic targets for evaluation and to provide appropriate counseling for both the patient and their family members before and after the test (Castelletti et al., 2022).

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