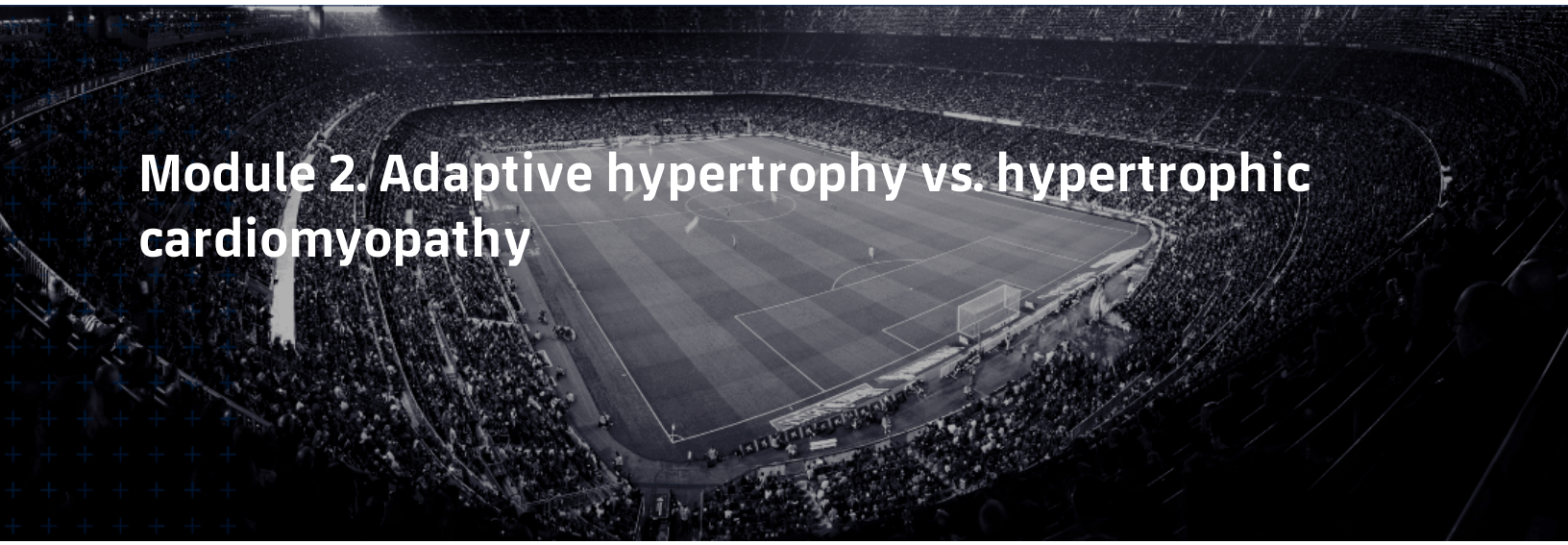

Module 2. Adaptive hypertrophy vs. hypertrophic cardiomyopathy

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Left ventricular hypertrophy (LVH) is a possible adaptive response to physical exercise. Therefore, it is important to differentiate it from the main pathological causes: mainly, hypertrophic cardiomyopathy (HCM), both sarcomeric and non-sarcomeric, and other phenocopies. This difference, which may seem simple, is of vital importance due to its repercussions: in terms of sports practice, it may prompt its cessation at a professional level; in terms of prognosis, it is one of the main causes of sudden death (SD) in athletes; and in terms of family, there may be a genetic component with family aggregation. HCM is the most frequent cause of SD in young athletes, since the adrenergic discharge associated with high-intensity sport favors the appearance of malignant ventricular arrhythmias and SD in these individuals.

In this chapter, we will focus on the keys to performing a correct differential diagnosis.

Unit 2.1 Left ventricular hypertrophy

Adaptive

Any increase in left ventricular afterload sustained over time can lead to a ventricular adaptive response. In this case, hypertrophy could not be defined as a cardiomyopathy, since it is secondary to a hemodynamic change, and is therefore considered an adaptive change.

Within this group, we find LVH secondary to a sustained increase in blood pressure, either as a primary condition or secondary to other processes, such as pheochromocytoma or drugs such as cyclosporine. In this case, it usually presents as symmetrical hypertrophy and can manifest with either an eccentric or concentric pattern. Another typical phenotype in elderly individuals or those chronically hypertensive is the presence of sigmoid hypertrophy, predominantly at the basal septal level, which is generically referred to as “septal bunch” (Ganau et al., 1992). This phenomenon also occurs in left ventricular outflow tract obstruction, such as aortic stenosis or sub-valvular aortic membrane (Rader et al., 2015).

But the most representative form of this adaptive LVH is the so-called athlete's heart.

- **Adaptive hypertrophy in athletes**

In athletes, LVH is one of the adaptive changes observed at the cardiac level, secondary to intense and regular sporting activity. Thus, the main challenge in these cases is to differentiate this adaptive process from a pathological LVH, such as the one observed in HCM, from both a structural and an electrical standpoint.

It is important to keep in mind that these changes are also influenced by other factors, such as gender, race or ethnicity and age, so we will below analyze the effects they have on both ECG and cardiac morphology.

Age:

In the case of young athletes, under 16 years of age, we can define an electrocardiographic pattern known as the juvenile pattern (typical in athletes under 16 years old in the absence of signs, symptoms or family history of heart disease). This pattern is defined by negative T waves in anterior precordial leads from V1 to V4 and is present in up to 10-15% of young athletes (D'Ascenzi et al., 2019).

Over time, this pattern evolves into the adult ECG, where inversion does not extend beyond V1 and up to V2 in the case of women. If the pattern persists, a differential diagnosis with specific cardiomyopathies, particularly those affecting the right ventricle (RV), such as arrhythmogenic cardiomyopathy, should be performed.

According to a study by Papadakis et al. (2009), T-wave inversion in inferolateral leads was rare in young athletes, representing only 0.1% to 0.9% of participants, and, in this group, several cases of arrhythmogenic cardiomyopathy and HCM were observed. In fact, T-wave inversion is a frequent electrocardiographic finding in cardiomyopathies and is present in up to 85% of affected patients.

Thus, finding these possible age-related alterations makes follow-up over the course of months very relevant for these individuals.

Regarding ventricular thickness, in a study by Sharma et al. (2000) involving 720 elite White adolescent athletes (with a mean age of 15.7 ± 1.4 years old), the thickness of the left ventricular walls and cavity dimensions were compared by means of an echocardiography with 250 sedentary controls of the same gender, age and body surface area. On average, the athletes had a 13% greater left ventricular wall thickness and a 6% greater left ventricular cavity diameter compared to the controls. Although left ventricular wall thickness exceeded the upper limits of normal in 38 athletes (5%), only 0.4% had a thickness >12 mm (all male), and all of them exhibited concurrent left

ventricular cavity dilatation. None of the controls exhibited a ventricular wall thickness >11 mm (Sharma et al., 2002).

These data suggest that the upper limit of normal for left ventricular wall thickness can be considered as ←12 mm in White male adolescent athletes.

Sex:

Sex also plays an important role in the changes observed in athletes, although the underlying mechanisms are still unclear. The most widely accepted hypothesis is that differences in the levels of sex hormones, as well as the density and sensitivity of their receptors, are responsible for these variations.

Thus, the adaptive modifications described in female athletes are more subtle compared to male athletes. In a comparative study of athletes including 600 women and 738 men, as well as 65 sedentary women as controls, no ventricular thicknesses greater than 12 mm were observed in any of the female athletes, compared to up to 2% of the male athletes (Pelliccia et al., 1996).

Race:

Racial diversity in sports has made it possible to evaluate the influence of this variable on cardiac adaptations to intense physical

exercise. Specific structural changes have been identified in Black athletes, mainly in electrocardiographic patterns. These changes are up to twice as frequent as in the White population.

T-wave inversion in precordial leads V1-V4 and convex ST-segment elevation can be considered as racial variants, but T-wave inversion in lateral leads cannot. However, there is no sufficient information regarding T-wave inversion in inferior leads, so prolonged patient follow-up is recommended (Papadakis et al., 2011).

New studies in patients of Asian origin show that there is also a higher prevalence of electrocardiographic abnormalities in this population compared to the White race, without this indicating pathology. Some studies reveal electrocardiographic abnormalities in up to 6.7% of the population, predominantly, T-wave inversion beyond V2 in Asian female athletes. In this particular case, the prevalence was up to 9%, without this resulting in a higher prevalence of myocardial disease (Yeo et al., 2022).

In terms of structural changes, different studies have demonstrated greater ventricular wall thickness in Black individuals; thickness →15 mm has been described in up to 3%. In the particular case of Black female athletes, a greater ventricular thickness is also observed compared to their White female counterparts. Based on these studies, it has been established that the upper limits of normal for ventricular thickness in Black athletes are ←15 mm for adult men and ←12 mm for

adult women. For adolescent athletes, these values correspond to ←14 mm for males and ←11 mm for females.

Sport discipline:

Morganroth determined how the sport discipline and the type of exercise performed are directly related to the changes observed at the cardiac level, which has been defined as the Morganroth hypothesis (1975). In a study using cardiac ultrasound, he observed how isotonic exercise was associated with an increase in left ventricular mass and volume, as well as with a wall thickness that does not exceed normal limits in most cases (eccentric hypertrophy). This type of exercise includes dynamic sports such as cycling or cross-country skiing. Electrical changes are also frequent, mostly caused by an increase in vagal tone, resulting in a decrease in sinus node and a delay in atrioventricular conduction. On the other hand, isometric exercise is mainly related to an increase in ventricular mass and thickness, while end-diastolic volume remains within normal. Even though Morganroth's dichotomous division does not strictly correspond with reality in sports field, since all sports disciplines combine dynamic and strength training in order to achieve the best sports performance, this simplified division is useful to understand the predominant cardiac remodeling that we would expect to find in an athlete based on their sport discipline.

We must remember that all these forms of adaptation are physiological, so we have to differentiate them from pathological ones, such as hypertrophic cardiomyopathy and its phenocopies.

Hypertrophic cardiomyopathy

Cardiomyopathies have been defined by the working group of the European Society of Cardiology, which define cardiomyopathies as heart diseases in which there is an alteration in the structure or function of the myocardium, without the presence of coronary artery disease, hypertension, valvular disease or congenital heart disease that could explain the observed alteration (Elliott et al., 2007).

In the case of hypertrophic cardiomyopathy, its main feature and diagnostic criterion is the determination of a ventricular wall thickness of →15 mm in one or more myocardial segments, measured by any imaging technique, and which cannot be explained solely by loading conditions. This value is reduced to →13 mm in patients with a family history of HCM.

Its prevalence is estimated to be between 0.5% and 0.2% in the general population, although most cases are asymptomatic and go unnoticed (Ommen et al., 2020). Despite this, it is of particular importance in the field of sport, since, unfortunately, sudden death may be the first manifestation. HCM is the leading cause of SD in

young athletes under 35 years old. The risk of SD is estimated to be between 1-2% per year (Elliott et al., 2006).

There are multiple predictors of SD, such as the presence of a family history of SD in young relatives; history of unexplained syncope, especially if recurrent and recent; non-sustained ventricular tachycardia on Holter monitoring; abnormal blood pressure response during stress test; severe hypertrophy greater than 30 mm; and severe dynamic obstruction with gradients exceeding 90 mmHg. Currently, we have risk calculators such as the one from the European Society of Cardiology, which allows estimating the 5-year risk of SD based on some of these parameters (O'Mahony et al., 2014).

A sarcomeric mutation can be identified in up to 60% of cases, mostly in the MYH7 and MYPC3 genes, with autosomal dominant inheritance pattern. In addition, 5-10% of patients have other genetic abnormalities, sometimes related with metabolic and neuromuscular diseases, the so-called phenocopies or non-sarcomeric HCM.

Common symptoms of HCM include exertional dyspnea, palpitations, anginal chest pain and syncope. Only syncope has been shown to be a reliable predictor of SD in adults.

The electrocardiogram (ECG) shows alterations in about 90% of cases, although the isolated presence of high voltage QRS complexes should

not be considered as diagnostic, since it can be found in young individuals and athletes, as previously mentioned.

Echocardiography is a valuable tool to evaluate LVH, which is septal in 70% of cases and concentric in up to 15%, making it difficult to differentiate from athletic cardiac adaptation. Additionally, functional study makes it possible to determine the presence of a dynamic systolic gradient in the left ventricle outflow tract (LVOT) (see Figure 1). In some cases, we can also find mid-systolic gradients, which are typically less symptomatic. In addition, it may be accompanied by valvular abnormalities of the sub-valvular apparatus and dynamic changes such as systolic anterior motion (SAM) of the mitral valve.

Figure 1. Transthoracic echocardiography

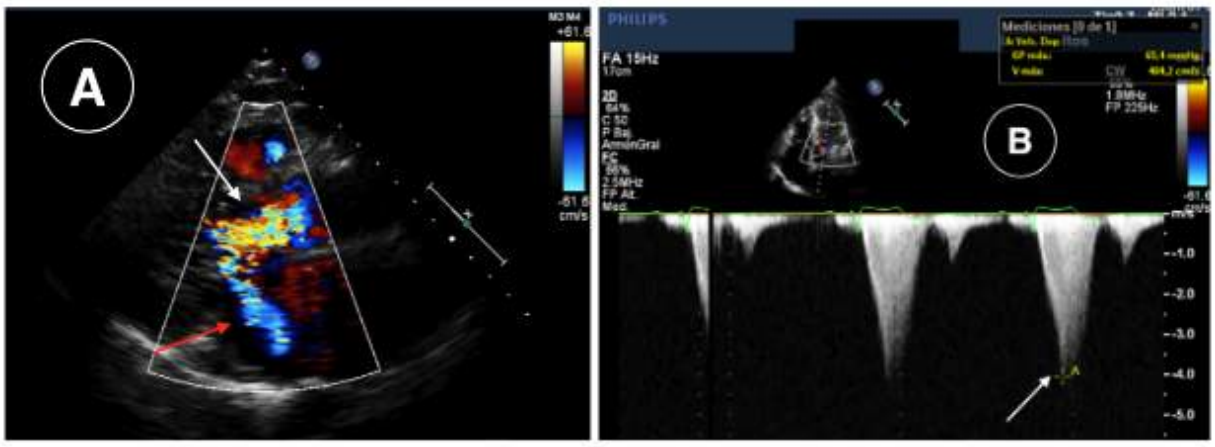

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Figure 1. A 44-year-old woman with hypertrophic cardiomyopathy, transthoracic echocardiography. (A) Parasternal long axis view showing obstruction at the level of the left ventricular outflow tract (white arrow) and mitral regurgitation secondary to systolic anterior motion of the mitral valve (red arrow). (B) Doppler image showing the obstructive gradient at the level of the left ventricular outflow tract (white arrow).

The treatment of these patients can be divided into treatment to reduce obstruction and treatment to prevent SD. As for the treatment of obstruction, it is based on beta-blockers or dihydropyridine calcium antagonists. If obstruction persists, disopyramide can be added as a second drug, although its anticholinergic effects and QT interval prolongation limit its use. New drugs, such as mavacamten (MYK-461), a myosin inhibitor, have shown promising results (Olivotto et al., 2020) in terms of obstruction control and are pending approval in Europe.

Invasive options are reserved for elevated gradients (>50 mmHg) along with severe symptomatic impairment (NYHA III-IV). Myectomy is the best option for young patients with severe hypertrophy or associations with valvular abnormalities. In contrast, alcohol septal ablation (ASA), while being a less invasive option, is less specific and requires the presence of septal coronary arteries directed at the site of maximum obstruction. The use of pacemakers to increase the degree of asynchrony and reduce obstruction has been virtually abandoned.

Treatment of sudden death risk relies on the implantation of a cardioverter-defibrillator, based on the individual risk of each patient, usually calculated using the European Society of Cardiology (ESC) risk calculator.

Phenocopies

As previously mentioned, HCM is a broad term encompassing a variety of pathologies characterized by an increase in ventricular wall thickness. Unlike sarcomeric pathology, phenocopies are characterized by homogeneous and symmetric hypertrophy, which poses the differential diagnosis with athlete's heart or cardiac adaptation to exercise. Multisystemic manifestations of these syndromes can aid in their diagnosis. These include LVH secondary to metabolic disorders and infiltrative diseases.

Metabolic disorders:

The most common metabolic disorder related to HCM is Anderson-Fabry disease or lysosomal storage disease, an X-linked disease that mainly affects men. This pathology is characterized by an alteration in the enzyme α-galactosidase-A, which results in the deposition of globotriaosylceramide in tissues. This leads to a variety of conditions: renal conditions that may require dialysis; ocular conditions (whorl keratopathy); dermatological conditions in the form of angiokeratomas which typically occur in a bathing trunk distribution;

and ventricular hypertrophy with a typical pattern of enhancement on magnetic resonance imaging (MRI), generally affecting the inferolateral wall. The prevalence of Fabry disease varies between 0.5% and 1%, and it is estimated that it may be present in up to 3% of patients diagnosed with HCM. The importance of diagnosis lies in the availability of a disease-specific enzyme replacement therapy.

Other glycogen deposition pathologies include Danon disease, caused by mutations in the LAMP2 gene, which is inherited in a sex-linked manner and mainly affects males. This disease is characterized by very severe hypertrophy with concomitant musculoskeletal and neurocognitive involvement. Pompe disease, caused by a deficit of α-1,4-glucosidase, leads to musculoskeletal and cardiac conditions. A specific case is found in mutations related to PRKAG2, which are associated with conduction abnormalities, including blockages and pre-excitation phenomena, due to glycogen deposition in the *annulus fibrosus*.

- **Infiltrative disorders:**

Cardiac amyloidosis is a condition caused by the deposition of amyloid fibers in the heart. There are several varieties of amyloidosis, with the most common in developed countries being light-chained amyloidosis. These chains are generated in plasma cells, subsequently deposited in different tissues, and they usually affect younger individuals. We will also highlight transthyretin (TTR) amyloidosis, which may or may not

have a hereditary component. Although it usually manifests in the last decades of life, there are cases, generally associated with genetic mutations, with an earlier onset.

Although cardiac amyloidosis mainly affects the heart, it can exhibit specific characteristics on a surface ECG (see Figure 2), because the deposition of this amorphous protein is widespread; its buildup in various organs and systems is associated with specific symptoms. So, its buildup in the gastrointestinal system is linked to abdominal pain and alterations in intestinal motility; at the nervous system level, it is related to numbness in the lower extremities, decreased skin temperature perception and impaired cognitive abilities.

Figure 2. A male's ECG with hereditary amyloidosis

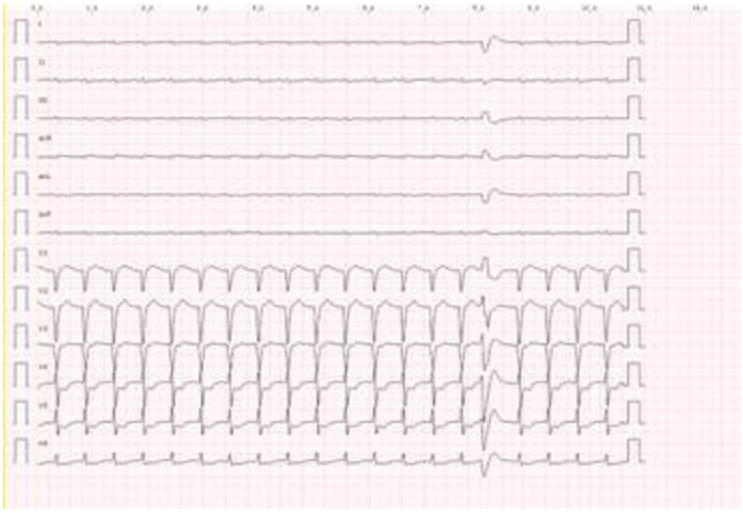

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Figure 2. A 55-year-old male with hereditary amyloidosis. ECG: pseudo-anterior infarct pattern typical of this pathology. Precordial leads with low voltages and absence of R waves in the anterior precordial leads.

Due to advances in diagnostic techniques, cardiac amyloidosis is gaining more attention and the paradigm surrounding this disease is changing. Additionally, the development of new drugs in the last decade is improving the prognosis of the disease, which remains underdiagnosed today.

- **Others**

There are other disorders that, because they are associated with other extracardiac manifestations, such as neuromuscular involvement, are less common in athletes. Among them, we can highlight neuromuscular disorders such as Duchenne and Becker muscular dystrophies, which can also show LVH as a feature of myocardial involvement, mitochondrial disorders such as MELAS syndrome, which causes skeletal myopathy, encephalopathy, lactic acidosis and stroke; or Friedreich's ataxia, a disorder related to abnormalities in mitochondrial iron metabolism and frataxin. Cases secondary to pharmacological treatments are rare and generally mild, with anabolic steroids and hydroxychloroquine being notable examples.

2.1.1 Differential diagnostic algorithm of adaptive hypertrophy vs. HCM

Accurate diagnosis of HCM is key to protect the athlete's health, as it is one of the leading causes of SD in young athletes under 35 years of age and is a disqualifying criterion in several professional sports. Despite this, current evidence does not allow us to determine whether, in general, the cessation of sporting activity reduces the risk of arrhythmic events (Pelliccia et al., 2018). The manifestation of the disease is variable, with different degrees of severity, even within the same family, which represents a challenge for diagnosis, especially in mild cases.

Both personal and family history are very important in the identification of cases of HCM compared to adaptive hypertrophy. Dyspnea disproportionate to the level of exercise is often associated with pathology, as these patients are unable to sustain an increase in stroke volume for long periods of time. Palpitations, chest pain and, especially, loss of consciousness during or immediately after exercise should raise suspicion of an underlying pathology that could be related to both arrhythmic events and LVOT obstruction phenomena.

Autosomal dominant inheritance makes the presence of other cases of HCM in the family frequent. In these cases, creating family trees in large families can be particularly useful, as probability increases the likelihood of more cases being present. The presence of SD in first-

degree relatives (those who share at least 50% of their genetic material) under the age of 40 is another factor that raises the index of suspicion.

Furthermore, when evaluating each case, it is important to consider the specific characteristics of the athletes based on age, gender, race, and sport discipline. This is why there is no single valid criterion; rather, it is the set of data obtained from each patient that will allow us to make a decision regarding the presence or absence of pathology.

ECG

The presence of abnormalities in ECG is a common finding in cases of HCM, observed in up to 98% of affected patients. However, ECG changes have also been found in healthy athletes, with a higher incidence in certain populations, such as Black athletes, where prevalence can reach up to 40%.

As already mentioned, one of the most frequently observed abnormalities is T-wave inversion. In a study by Schnell et al. (2015), where 155 asymptomatic athletes with deep T wave inversion were evaluated, 137 of them were found to have an inversion in lateral leads. The researchers concluded that the presence of this deep inversion in these leads was associated with an increased likelihood of developing cardiomyopathy (41%), with HCM being the most frequently diagnosed. Additionally, in a study by Pelliccia et al.

(2008), which included 12,550 athletes, 81 of whom had a diffuse T-wave inversion and normal imaging test results, after 9 years of follow-up, those patients who developed HCM had a T-wave inversion in the lateral leads.

T-wave inversion in two or more lateral leads (I, aVL, V5, V6) or extending to inferior leads always requires a more detailed patient evaluation, especially, if the inversions are deep (→2 mm). The lack of evidence establishing the benignity of inversions <2 mm in isolated leads requires a similar follow-up.

In the case of isolated T-wave inversion in the inferior leads, this pattern can be observed both in patients with cardiomyopathy and in up to 6% and 2% of healthy Black and White athletes, respectively. Because this pattern is indeterminate, it requires follow-up and investigation.

ST-segment depression is an uncommon finding in healthy athletes occurring in less than 0.5% of cases; this is why its finding warrants further study. Indeed, its presence in lateral leads in patients with known cardiomyopathy is associated with a higher risk of SD.

As for the electrocardiographic criteria for LVH, the most frequently used are the Cornell or Sokolow-Lyon criteria. The fact that these findings are associated with other electrical abnormalities, such as T-wave inversion or ST-segment depression, is the factor that truly

suggests pathogenicity. Therefore, the exclusive presence of LVH criteria in the absence of other electrical abnormalities is considered a normal ECG change in athletes and does not require further investigation.

- **Echocardiography:**

Echocardiography is a simple, fast, inexpensive and bloodless test for cardiac assessment. It allows both structural (cavity size, wall thickness, valve morphology) and functional assessment, including both systolic and diastolic functions and valve function.

Among the most useful data we can observe is the pattern of hypertrophy and its relationship to ventricular diameter. In athletes, hypertrophy is generally symmetrical and is accompanied by physiological dilatation of the cardiac chambers (eccentric hypertrophy), whereas in HCM an asymmetric and concentric growth occurs (concentric hypertrophy) that reduces ventricular end-diastolic diameter (EDD) (see Figure 3).

Figure 3. Asymmetric hypertrophy

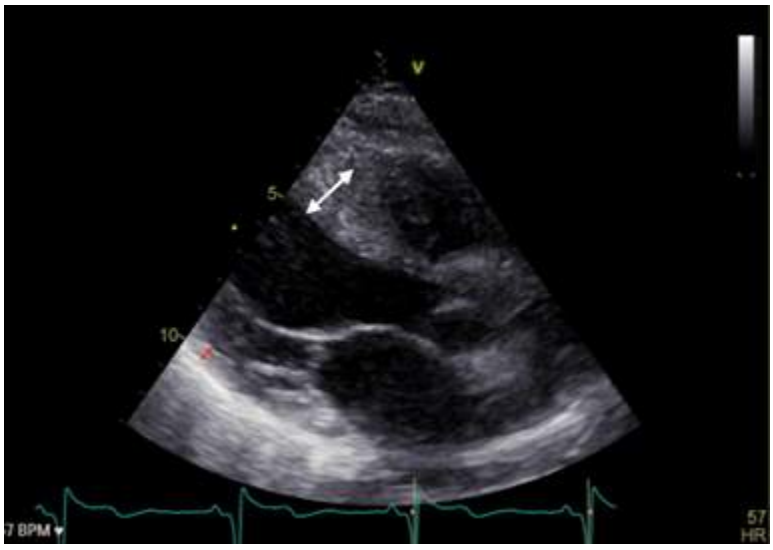

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Figure 3. Echocardiographic image of a parasternal long axis view showing asymmetric hypertrophy, predominantly at the septal level (white arrow), with respect to the posterior wall (red arrow), in a 53-year-old woman affected by hypertrophic cardiomyopathy.

Structural changes include the development of hypertrophy and ventricular dilatation. As for hypertrophy, it is characterized by a concentric and diffuse pattern with rare occurrence of obstruction at the LVOT level in cases of adaptive hypertrophy, unlike what occurs in HCM. In addition to LVH, a reduction in end-systolic diameter (ESD) and an increase in ventricular end-diastolic diameter (EDD) are observed, which result in an increase in stroke volume and cardiac output. Some studies have shown that left ventricular (LV) EDD can be greater than 55 mm in up to 50% of athletes, with values reaching up to 70 mm in some extreme endurance sports. In general, values

less than or equal to 64 mm in White males are considered to be the upper limit of normal (Pelliccia et al., 1999).

Up to 15% of athletes may have increased myocardial thickness compared to sedentary controls, but most cases do not exceed 12 mm, which would be considered normal in isolated cases or with diagnosed family members.

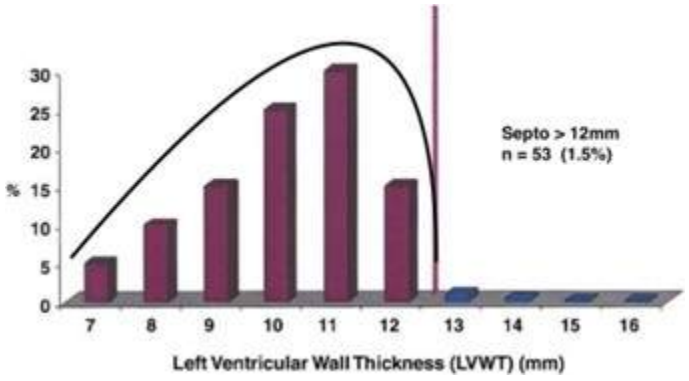
However, a small percentage of athletes, especially those engaged in cycling, swimming, cross-country skiing and rowing, may have myocardial thickness greater than 12 mm, up to nearly 2%, according to some studies involving multiple sports disciplines. In specific populations, such as the Black race, this figure can be even higher, up to 18% for values greater than 12 mm.

These figures create a gray zone in athletes, which requires further and more detailed evaluation, as there may be overlap with up to 15% of patients with a mild phenotype HCM.

We can consider values of up to 12 mm of thickness in White male athletes and 15 mm in the case of Black athletes as normal. In women, values of up to 11 mm in White athletes and 13 mm in Black athletes would be found. In addition, the pattern is symmetrical, with a difference <2 mm between the portion of greatest and least myocardial diameter (see Figure 4). Furthermore, it is important to highlight that hypertrophy in athletes with HCM is usually lower

than in sedentary HCM patients (15.8 mm vs. 19.7 mm, p <0.001) (Sheikh et al., 2015).

Figure 4. Left ventricular hypertrophy values in 3500 elite athletes



Source: Adapted from Basavarajaiah et al., 2008.

Figure 4. Left ventricular hypertrophy values in 3500 elite athletes.

Recent studies have established a cutoff point for left ventricular size at diastole of 54 mm, with 100% sensitivity and specificity. Values exceeding 54 mm are rare in cases of HCM, found in about 14% of early stages. Additionally, at the end stages of the disease, ventricular dysfunction and a decrease in hypertrophy, usually accompanied by overt clinical symptoms, may be observed Relative wall thickness, defined as the ratio of the sum of the thickness of the interventricular septum and posterior wall to the left ventricular EDD,

is useful to differentiate between the two conditions. In general, the athlete's heart has a relative wall thickness of less than 0.45.

Echocardiography also allows for the identification of structural valvular and sub-valvular apparatus abnormalities, such as elongation of the leaflets, changes in the chordae, accessory papillary muscles or atypical locations of these, which guide to the diagnosis of HCM.

Another relevant finding is the LVOT obstruction. This is present in about 30% of patients with HCM and can be induced in up to 50%, according to some studies, with exercise. Both obstructive phenomena and SAM are extremely rare findings in physiological or sport-induced LVH. Its absence at rest does not rule out the pathology, and, in cases of high suspicion, an assessment is recommended with a stress echocardiogram.

In addition, there are specific variants of HCM, such as isolated apical hypertrophy, which can be identified on an ECG with deep negative T waves, especially in the lateral precordial leads (known as Yamaguchi syndrome).

Ventricular function in HCM is often superior to that of healthy controls, at least in the early stages. However, by using tissue Doppler imaging techniques, an alteration in longitudinal systolic function can be detected compared to the athlete's heart. In addition, there is

also dysfunction in diastolic function due to a loss of relaxation capacity in the ventricular cardiac muscle. These alterations are related to myofibrillar disorganization and tissue fibrosis, a typical histological feature of HCM. Preserved diastolic function is a constant in the athlete's cardiac physiology and, as previously mentioned, it is even improved compared to controls.

Even though tissue Doppler has low sensitivity levels for differentiating between patients with HCM and exercise adaptations, its specificity levels are higher. Values of S' <9 cm/s, E' <9 cm/s, E/E' >12 and E/A <1 have a specificity of 84%, 100%, 100% and 95%, respectively. The absence of these parameters does not rule out the presence of a pathology; isolated values of these parameters have not proven useful, since, in athlete with HCM, diastolic function may be preserved.

The two-dimensional strain technique, based on speckle tracking, allows for the early detection of alterations and is less sensitive to artifacts produced in Doppler imaging due to the angle of the images. A global longitudinal strain value <10 is clearly pathological in both athletes and the general population, and it appears in advanced stages of HCM. New assessments, such as mechanical dispersion, have proven useful at rest, with higher values in HCM patients compared to athletes (Schnell et al., 2017).

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) overcomes the main limitations of echocardiography, such as poor echocardiographic windows (see Figure 5). However, it is a more expensive, time-consuming test and, in cases of claustrophobia, it can be unpleasant for the patient.

Figure 5. Asymmetric hypertrophy at the anteroseptal level in a short axis view

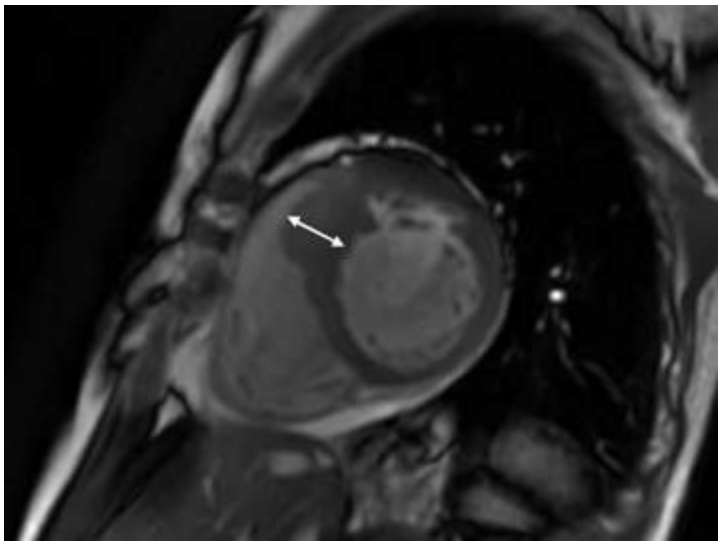


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Figure 5. A 28-year-old man with HCM. MRI showing asymmetric hypertrophy at the anteroseptal level in a short axis view.

Besides, the use of contrast in some cases requires further evaluations, such as renal function and allergies, which may limit its use.

Cardiac MRI offers greater temporal and spatial accuracy compared to echocardiography. It is very useful in cases of borderline hypertrophy and allows for the unmasking of areas of hypertrophy that are difficult to visualize, such as the anterior, apical and posterior septum. It will allow us to observe features typically associated with HCM, such as elongated mitral leaflets or the presence of crypts, as well as extra or incorrectly positioned papillary muscles. Finally, left atrial dilatation, although it is present in athletes, exhibits a specific pattern in HCM, since, in cases of cardiomyopathy, dilatation is isolated and not accompanied by ventricular dilatation, which does occur proportionally in athletes (D'Ascenzi et al., 2015).

In cases of HCM, apart from assessing cardiac function and structure, dynamic functional studies can be performed with adenosine, which will allow us to detect alterations in microvasculature, which are typical of this disease and not found in the athlete's heart (Rudolph et al., 2009).

The use of contrast, such as gadolinium, enables the detection of fibrous replacement tissue, which is present in approximately 40% to 60% of HCM patients in areas of maximal hypertrophy (see Figure 6). Furthermore, this finding will help us in the risk stratification of our

patients, as its presence is associated to a higher frequency of SD. This feature may also be present in cases of LVH secondary to arterial hypertension (Kuwahara et al., 2004).

Besides, the pattern of late gadolinium retention can assist in the differential diagnosis, since some pathologies exhibit more or less specific patterns. In amyloidosis, gadolinium enhances an area of the interstitium occupied by amyloid material instead of collagen, and its distribution pattern is characteristically subendocardial (specifying patterns of HCM and other phenocopies, and briefly also of hypertension).

Figure 6. Patchy fibrosis at the level of the basal septum

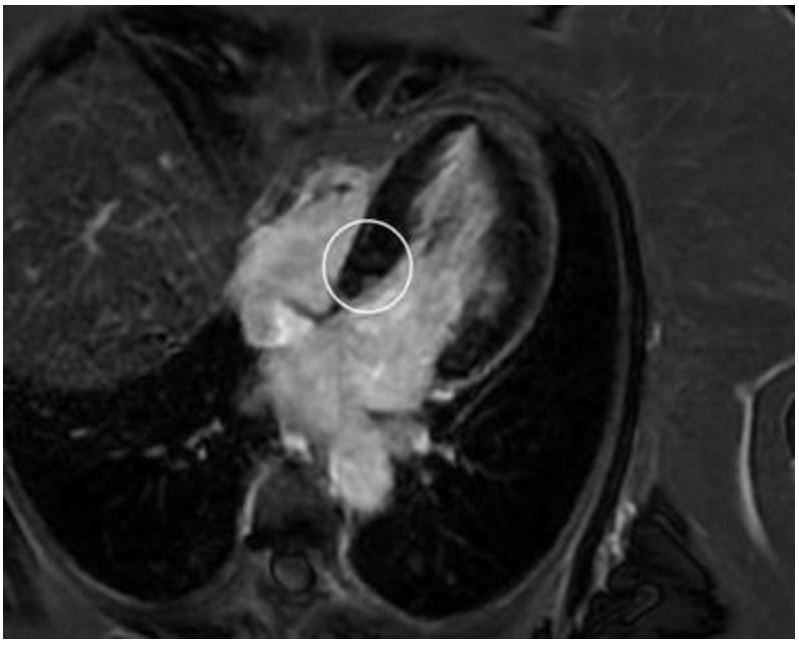

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Figure 6. A 35-year-old man with obstructive HCM. MRI in a four-chamber view showing patchy fibrosis at the level of the basal septum (white circle).

Based on the pathophysiology of the disease, given that in HCM there is increased extracellular tissue fibrosis, as opposed to myocyte hypertrophy in athlete's heart, we can observe an increase in T1 time and extracellular volume in the case of the pathology (Swoboda et al., 2016).

- **Cardiopulmonary exercise test:**

Due to LVOT obstruction, tissue and microvasculature impairment, as well as the SAM phenomena present in HCM, these patients often exhibit reduced exercise capacity. Therefore, cardiopulmonary tests that measure oxygen consumption during exercise may be a useful tool to differentiate between HCM and other conditions (Kawasaki et al., 2008).

In patients with HCM, a decrease in oxygen consumption (VO2 max) is observed compared to athletes with adaptive hypertrophy. This is the result of a reduced ability to increase stroke volume, which is related to macro and microstructural changes in HCM. Generally speaking, indicators such as VO2 max greater than 120% of predicted value for age and gender or greater than 50 ml/kg/min can be used to

differentiate between the two conditions, although these assumptions are mainly based on studies in Caucasian populations, and peak values lower than 84% of the predicted value suggest the presence of HCM (Sharma et al., 2000).

We should bear in mind that these data are mostly derived from comparative studies between athletes and sedentary patients with HCM. Therefore, athletes with HCM may have above-average capacity, in line with their sport discipline, especially in the early stages of the disease (Sheikh et al., 2015).

Approximately one-quarter of patients with HCM experience an abnormally flat systolic blood pressure response during a stress test (an increase of less than 20 mmHg from baseline to peak exercise). For accurate assessment, it is important to discontinue the use of antihypertensive medicines, especially beta-blockers and calcium channel blockers, before the test.

- **Holter:**

Ambulatory monitoring with a Holter can be valuable in the assessment of athletes with LVH, as the presence of multiple ventricular extrasystoles or non-sustained ventricular arrhythmias for 24 to 48 hours are indicative of underlying pathology. Admittedly, the usefulness of this study is limited by the short monitoring time, but increasingly advanced devices are becoming available on the

market that allow for prolonged monitoring and are compatible with the athlete's sporting activity (Weissler-Snir et al., 2016).

- **Genetic testing:**

Although the genetic testing is not decisive in the diagnosis of HCM, it can be useful in uncertain cases, although its indiscriminate use is not recommended if there is no diagnosis of HCM or a high suspicion. It should be taken into account that up to 40% of patients with HCM may have a negative result in genetic testing, so a negative result does not exclude the diagnosis. Currently, the indication for genetic testing in diagnosed cases, according to European and American guidelines, carries a Class IB recommendation (Ommen et al., 2020).

- **Biomarkers:**

Although the use of biomarkers has been proposed to differentiate between HCM and adaptive hypertrophy, there are currently no conclusive studies. Some of the suggested biomarkers include high-sensitivity troponin T, B-type natriuretic peptide and messenger RNA, whose elevation would be related to an underlying pathology. While these biomarkers have promising potential, their use in clinical practice in this context has not yet been fully validated (Matthia et al., 2022).

- **Detraining:**

In cases where doubts persist regarding the presence of HCM, temporary interruption of sport may be a useful tool to differentiate between adaptive and pathological hypertrophy.

Studies with serial cardiac echocardiography and MRI show a reversal of adaptive hypertrophy after 3 months of cessation of sporting activity (though changes can be observed as early as 6 to 8 weeks), while pathological hypertrophy in HCM persists (Maron, 2005).

Nonetheless, for high-performance athletes, stopping their sporting activity for such a long time may have professional consequences, making it more difficult to implement this measure.

Another factor to consider is the fact that there are also athletes with HCM in which partial regression of hypertrophy has been described during periods of exercise cessation. Therefore, a comprehensive evaluation using various complementary tests is necessary to establish a differential diagnosis.

In summary, it is important to evaluate all the possible parameters of the different tests (Table 1) in order to establish an accurate differential diagnosis.

Table 1. Comparison between findings that allow for a diagnosis

	Athlete's heart	High blood pressure	Hypertrophic cardiomyopathy
Left ventricular hypertrophy	Symmetrical	Symmetrical +/- septal bunch	Asymmetric
Reduction of LVEF	-	+/-	+/-*
Diastolic pattern alteration	-	+	+
Reduction of e'	-	+	+
Bi-ventricular hypertrophy	+	-	+/-
Bi-auricular dilatation	+	-	++
Late gadolinium enhancement	-	Patchy	Areas of maximum hypertrophy

Reduction of hypertrophy with deconditioning	+	-	-
Oxygen consumption, lower than expected	-	+/-	+/-
Negative T waves in lateral leads	-	-	+/-
Genetic testing	-	-	+/-

Source: own source.

Table 1. Comparison between the findings that allow us to make a differential diagnosis between athlete's heart, hypertrophic cardiomyopathy and arterial hypertension.

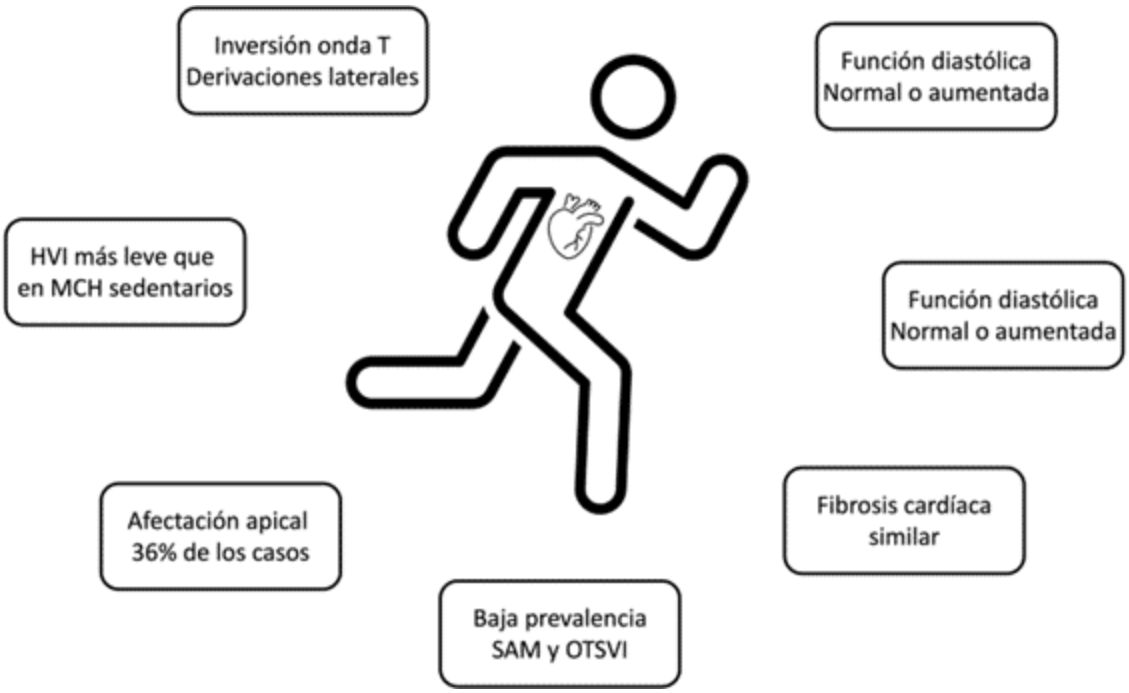
*In advanced stages.

2.1.2 Athlete with hypertrophic cardiomyopathy

It is worth noting that these differences are based on comparisons between athletes and generally sedentary patients with HCM. There is limited scientific literature comparing the profile of sedentary patients with HCM and athletes with HCM. However, in the latter, the structural and functional differences seem to be less pronounced due to exercise adaptation compared to sedentary patients with HCM (see Figure 7).

In terms of morphological findings, athletes with HCM generally exhibit less hypertrophy than sedentary patients (15.8 mm vs. 19.7 mm, $p < 0.001$), and it is more frequently localized to the apex. The presence of obstruction is also uncommon in patients who perform high-intensity exercise. As for diastolic function, most of the affected athletes exhibit parameters within the normal range. The parameter that has shown the greatest sensitivity is the presence of an s' wave <9 cm/s. Other findings, such as fibrosis detected by MRI, are also less frequent in athletes.

Figure 7. Main characteristics of the athlete with HCM



Source: own source based on Malhotra & Sharma, 2017.

Inversión onda T Derivaciones laterales	T-wave inversion in lateral leads
Función diastólica Normal o aumentada	Normal or increased diastolic function
HVI más leve que en MCH sedentarios	Less severe LVH compared to sedentary HCM
Función diastólica Normal o aumentada	Normal or increased diastolic function

Afectación apical 36% de los casos	Apical involvement in 36% of cases
Fibrosis cardíaca similar	Similar cardiac fibrosis
Baja prevalencia SAM y OTSVI	Low prevalence of SAM and LVOTO

Figure 7. Main characteristics of the athlete with HCM vs. sedentary profile. LVH: left ventricular hypertrophy. HCM: hypertrophic cardiomyopathy. LVOTO: left ventricular outflow tract obstruction. SAM: systolic anterior systolic motion of the mitral valve (Malhotra & Sharma, 2017).

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