Recommendations for physical exercise in athletes with inherited heart diseases (first part)

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Summary

The safety of physical activity and sports in patients with inherited heart disease is not well established. The recommendations on physical exercise in these patients are usually quite restrictive without clear evidence for this, despite the fact that sport has shown important cardiovascular benefits. Participation in sports in adults with inherited heart disease is considered a relatively little known territory and many clinicians find it difficult to advise their patients. The development of current medicine has meant a significant improvement in the study of inherited heart diseases, as well as in their early diagnosis and treatment. In addition, genetic studies have assumed a fundamental aspect in the follow-up of these heart diseases, guiding more appropriately the therapeutic attitude that we must follow. Until recently, patients with such heart disease have been frequently disqualified from competitive sports, and in many cases, complete cessation of physical activity, including recreational sport, is recommended. However, current recommendations are less restrictive, insisting on individualizing the different cases depending on the type of pathology, the type of physical activity performed, whether they present the disease or are only carriers of causal genetic mutations, etc. Current research focuses primarily on the safety of physical activity in patients with inherited heart disease and the fear that the practice of competitive physical activity can significantly increase the risk of adverse events, especially arrhythmic events and sudden death. In this review, we analyzed numerous studies and clinical practice guidelines, in order to establish the recommendations of physical activity, as well as their restrictions depending on the different types of inherited heart disease.

Key words:
Sport cardiology.
Inherited heart disease.
Sporting activity.
Cardiomyopathies.
Channelopathies.

Recomendaciones para el ejercicio físico en deportistas con cardiopatías familiares (primera parte)

Resumen

La seguridad de la actividad física y deportiva en pacientes con cardiopatías familiares aún no está bien establecida. Las recomendaciones sobre el ejercicio físico en estos pacientes suele ser bastante restrictiva sin que haya clara evidencia para ello, a pesar de que el deporte haya demostrado importantes beneficios cardiovasculares. La participación en deportes en los adultos con cardiopatías familiares se considera un territorio relativamente poco conocido y muchos clínicos se encuentran con dificultades en el asesoramiento a sus pacientes. El desarrollo de la medicina actual ha supuesto una mejoría significativa en el estudio de las cardiopatías familiares, así como en su diagnóstico precoz y tratamiento. Asimismo, los estudios genéticos han supuestos un pilar fundamental en el seguimiento de estas cardiopatías, guiando de manera más adecuada la actitud terapéutica que debemos seguir. Hasta hace poco tiempo, los pacientes que presentan dichas cardiopatías han sido descalificados de manera frecuente de los deportes competitivos y en muchas ocasiones, se recomienda el cese completo de la actividad física, incluido el deporte tipo recreacional. Sin embargo, las recomendaciones actuales son menos restrictivas, insistiendo en individualizar los diferentes casos en función del tipo de patología, del tipo de actividad física realizada, si éstos presentan la enfermedad o son únicamente portadores de mutaciones genéticas causales, etc. Las investigaciones actuales se centran fundamentalmente en la seguridad de la actividad física en pacientes con cardiopatías familiares, y el temor a que la práctica de actividad física a nivel competitivo pueda aumentar significativamente el riesgo de eventos adversos, especialmente de eventos arrítmicos y muerte súbita. En esta revisión, analizamos numerosos estudios y las guías de práctica clínica, con el fin de establecer las recomendaciones de actividad física, así como sus restricciones en función de los diferentes tipos de cardiopatías familiares.

Palabras clave:
Cardiología deportiva.
Cardiopatías familiares.
Actividad deportiva.
Miocardiopatías. Canalopatías.

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Introduction

Inherited heart disease is the term used for a group of cardiovascular diseases (cardiomyopathies, channelopathies, certain aortic diseases, etc.) that share a series of common characteristics: they have a genetic base, a familial presentation, follow a heterogeneous clinical course and, finally, they can all be associated with sudden death[1].

The participation in sports of adults with inherited heart diseases is considered to be a relatively unknown area and many clinicians do not find it easy to advise their patients. The fundamental concern is based on patient safety and the fear that the practice of competition level sports could increase the risk of adverse events[2]: potentially lethal arrhythmias, sudden death, etc. However, in this field there is still no extensive experience to make it possible to establish definitive recommendations. Given the proven benefits of physical activity, it would be extremely restrictive to limit this population to purely recreational sports activities.

Until recently, patients with inherited heart diseases were frequently disqualified from competitive sports and, on many occasions, patients were recommended to completely stop physical activity, including recreational sports. However, we need to consider the disadvantages of the lack of physical exercise, predominantly in young people. For this reason, current recommendations are less restrictive, insisting on individualising the different cases, based on the type of pathology, the type of physical activity performed, whether they have actually developed the disease or are solely carriers of causal genetic mutations, etc.

In short, it is extremely important for physician to be aware and to know how to recommend an adequate level of exercise for these athletes, which offers the benefits of physical activity without increasing the risk of sudden death or other adverse events. Therefore, the current challenge would consist in ensuring that patients of this type can safely take part in regular physical activity. This review describes the recommendations for physical activity based on the different types of inherited heart disease.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a hereditary autosomal dominant condition with a marked variation in phenotypic expression and a prevalence of 1:500 in the general population[3]. It is the prime cause of sudden death of athletes under the age of 35 in the United States and many European countries, such as Spain.

Although the presence of ventricular hypertrophy generally appears between the ages of 12 to 20, in some cases, it can also be detected at older ages. Likewise, it is relatively frequent that many carriers never develop the disease.

Intense exercise over prolonged periods of time has been shown to cause adaptive physiological changes (increase in the thickness of the walls, dilatation of the atria and right ventricle, etc.), which is commonly known as "athlete's heart". For this reason, it is essential to conduct an exhaustive study and to be particularly careful when establishing a diagnosis of HCM. This is because, on many occasions, we find ourselves in a grey area in which it is difficult to differentiate between adaptive changes and the presence of structural heart disease. Traditionally, the proposed limit for physiological adaptations is a wall thickness of less than 15 mm. However, different findings need to be studied, helping us to tip the scale and to establish a definitive diagnosis. Findings such as a reduction in the wall thickness with detraining, electrocardiographic changes, diastolic dysfunction, presence of a family history of sudden death, genetic study, etc.

Likewise, some works have described the appearance of myocardial fibrosis in some athletes subjected to a high sports load, favouring the appearance of ventricular arrhythmia[4]. In general, for HCM, there is currently little evidence to associate the intensity of exercise with the progression of the disease.

Today, echocardiography is considered to be the gold standard tool in the diagnosis of this pathology. This study makes it possible to estimate the level of hypertrophy, the ventricular function as well as the degree of obstruction of the left ventricular outflow tract (LVOT). We should point out that those factors affecting the systemic blood pressure (reduced pre-load and after-load) as well as an increase in myocardial contractility increase the degree of obstruction. Therefore, exercise generally increases the obstruction of the LVOT, when present. The exercise-related physiological changes produce an increase in the sympathetic activity, resulting in an increase in cardiac contractility and can lead to an increased obstruction of the LVOT. It has therefore been associated with increased symptomatology during exercise.

Today it has been described that only a minority of those patients having a set of symptoms for sudden death, actually die during exercise[5]; however, strenuous physical exercise is considered to be an important adverse event trigger. Moreover, while exercising, patients with HCM may develop an increased obstruction of the left ventricular outflow tract, myocardial ischaemia, diastolic dysfunction, etc. This can cause these athletes to exhibit important symptomatology such as exertional dyspnoea, angina or syncope. For this reason, faced with these symptoms, we need to rule out the presence of this disease.

In most cases, these cases of sudden death appear to be due to arrhythmic events (ventricular tachycardia, ventricular fibrillation, etc.). A number of articles establish that, for this pathology, the underlying electrophysiological substrate capable of triggering potentially lethal ventricular arrhythmias is unpredictable[6]. Many different triggering factors such as stress interaction resulting from competing, hydroelectrolytic disorders and the excessive discharge of catecholamine may play an important role.

To estimate the risk of sudden death, a score is available which assess the probability of the said adverse event occurring based on a series of criteria (family history, syncopal episodes, nonsustained ventricular tachycardia, etc.)[7]. If the said score gives a probability greater than 6% for sudden death after 5 years, then the implant of an implantable cardioverter defibrillator (ICD) is appropriate. To do so, it is necessary to conduct an exhaustive study of those patients with suspected hypertrophic cardiomyopathy, which should include a

transthoracic echocardiogram, 24-hour Holter monitoring, ergometry, cardiac resonance, etc.

Likewise, we need to take account of the fact that HCM patients could be at risk of sudden death even if they do not exhibit the conventional risk factors, although with a significantly lower incidence. In fact, high-intensity sports practice could in itself cause arrhythmic events, therefore acting as a powerful, modifiable and independent sudden death risk factor.

At present, it is complicated to apply these known risk criteria to competitive athletes with hypertrophic cardiomyopathy. The views expressed at the Bethesda conference of 2005[8] as well as those of the most recent American[9] and European[7] guidelines all have a strong similarity with regard to exercise restrictions in their recommendations, establishing that athletes with a probable or unequivocal diagnosis of HCM should not participate in competitive level sports. Thus, only low-intensity, low-dynamic and low-static (class IA) or leisure sports would be permitted. These recommendations are considered to be independent of a number of characteristics such as age, prior medical or surgical interventions, level of hypertrophy, type of mutation, etc. (class III, level of evidence C).

However, we should clarify that the possibility of a fully informed athlete with this pathology taking part in competitive sports would not be completely ruled out, provided that a joint multidisciplinary decision has been taken, basically between the athlete, the doctor and the sports organisation responsible.

For these athletes with HCM, drugs must not be administered (beta blockers, calcium antagonists, etc.) to alleviate the symptomatology or to prevent arrhythmic events, in order to participate in high intensity sports (Class III, level of evidence C).

Moreover, patients with an ICD are advised to follow the same restrictions as those that have no ICD. The implant of an ICD for the purpose of allowing these athletes to participate in high-intensity sports is not considered appropriate. We need to take account of the possible complications derived from the implant and monitoring of these devices (pocket haematoma, generator replacements, device infections, etc.). The indications for the implant of the ICD in competition sports should not be different for non-athletes with HCM (class III, level of evidence B).

At present, the performance of genetic studies is widely extended, leading to the frequent discovery of carriers of the family mutation who have not yet shown signs of the disease. In this regard, it is difficult to assess genotype positive-phenotype negative cases, in other words those healthy carriers of this disease who, even though they exhibit a genetic mutation, do not have ventricular hypertrophy or any other type of structural heart disease.

According to the current recommendations of the Bethesda Conference and the American Heart Association (AHA), asymptomatic patients with a positive genotype and who have not developed hypertrophy, with no family history of HCM-related sudden death or other risk factors, can participate in competitive sports (class IIA, level of evidence C). However, the European Society of Cardiology (ESC) is more restrictive in this respect, advising against their participation in competitive sports, while allowing them to participate in leisure activities.

Furthermore, for this patient subgroup, the recommendation is to assess ventricular hypertrophy by both transthoracic echocardiogram and cardiac magnetic resonance, given the fact that, in many cases (such as apical hypertrophic cardiomyopathy, etc.) this diagnosis may go unnoticed. Likewise, we need to take the different types of mutation into account, given the fact that the gene aggressiveness and the prognosis for the said pathology can be estimated on the basis of the variant.

With regard to the recommendation for sports activity, the ESC and the AHA establish similar recommendations for these patients[7,8]. Activities with an aerobic component (running, swimming, etc.) are primarily recommended with a light-medium intensity. Those sports with an intense static predominance (isometric) such as weightlifting, with potential rapid acceleration and deceleration should be avoided as there is an increased risk of induced LVOT obstruction due to the Valsava manoeuvre performed with this activity.

There is thus a need to consider the possibility of minimising the dynamic obstruction risk, the provocation of fatal arrhythmias and the progression of the disease. Moreover, there is a need to explain to athletes the importance of doing physical exercise in a suitable environment, given that adverse environmental conditions (excessive heat, dehydration, hydroelectrolytic disorders, etc.) could cause a greater risk of the aggravation of the induced symptomatology in relation to a reduction in the preload and afterload alike.

However, it has been described that exercise helps to improve the symptomatology of patients with HCM. These symptoms (dyspnoea, angina, syncope) typically occur during effort, probably related to diastolic dysfunction, cardiac insufficiency, etc. Studies exist which, although not specific to patients with this pathology, have demonstrated an improvement in the diastolic function and in the measured exercise capacity for oxygen uptake and quality of life after prolonged, regular physical exercise.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is generally characterised by the dilation and dysfunction of the left ventricle or, on occasions, of both ventricles. It can have a number of causes, such as aetiology of an idiopathic, genetic, metabolic, viral (prior myocarditis), alcoholic, ischemic nature, etc. Although not very frequent, dilated cardiomyopathy represents a cause of sudden death in the athletic population, predominantly due to lethal arrhythmic events.

An exhaustive study should be conducted on athletes with suspected dilated cardiomyopathy, including a physical examination, personal and family history, in addition to complementary tests: electrocardiogram, echocardiogram, 24 hour monitoring, ergometry, etc. In some cases, it is possible to identify the presence of supraventricular or ventricular tachycardias, conduction disorders, left bundle branch block, etc. For this reason, it is important to rule out the presence of arrhythmic events during the electrocardiographic monitoring, at rest and under effort.

It is currently considered that around 30-50% of dilated cardiomyopathies have a genetic or familial component[10]. Current guidelines do not recommend genetic studies for this population. However, in the index case, once a genetic dilated cardiomyopathy diagnosis has been established (or another type of cardiomyopathy), it would be useful to conduct a genetic study of relations, even if these are completely asymptomatic. Today it is described that, for certain more aggressive genes such as laminin, pathogenic mutation carriers show a higher incidence of adverse events[10], such as ventricular arrhythmias, sudden death, etc. at early ages, even without having developed a ventricular dysfunction.

Particular care should be taken in relation to the valuation of findings compatible with DCM, given the fact that it is essential to differentiate this disease from the physiological dilatation caused by high-performance training[11]. As mentioned above, prolonged aerobic exercise can cause the marked dilatation of the chambers of the heart, although this generally most frequently occurs at the expense of the right chambers.

There are a series of findings in the echocardiographic study that can help us to differentiate between the physiological adaptations of an athlete and the presence of this cardiomyopathy. For the DCM, for example, the ventricular cavity generally expands disproportionately in relation to the wall thicknesses, which are either normal or thinner (moreover, athletes frequently exhibit a slight increase in the ventricular walls). Likewise, systolic and diastolic dysfunctions are generally identified in athletes with this pathology, unlike the case of other athletes. The presence of significant valve diseases (for example mitral insufficiency due to cardiac remodelling, ring dilatation, etc.) or segmentation should direct us towards structural cardiomyopathy.

In certain cases, ventricular dilatation in athletes can be associated with a slight ventricular dysfunction. This can be explained by the fact that the increase in chambers produces a greater volume per beat, so that the ejection fraction at rest can either be at the lower limit of normality or slightly below it (<55%). To differentiate between both situations, it is extremely useful to use imaging techniques to evaluate the ventricular function during exercise (echocardiogram, heart gammogram, etc.). A significant increase in the ejection fraction would support the diagnosis of an "athlete's heart" while the lack of improvement in the ventricular function would direct us towards a pathological dilatation of the left ventricle.

Numerous studies have been published in which an analysis is made of the different echocardiographic findings in populations of elite footballers[12], objectivising that around 15% of trained athletes can have diastolic diameters of up to 70 mm in men and 60 mm in women. Likewise, the mean diameter is also generally at the high limit of normality, at around 55 mm, so we should not make a hasty diagnosis. The greatest ventricular dilatations are objectivised in men with a high body surface area, and in athletes practising sports with a high aerobic component (biking, marathon, etc.).

So, although there is little information available at the moment, the guidelines recommend that those symptomatic athletes with DCM, restrictive cardiomyopathy or cardiac infiltrative diseases (sarcoidosis, Fabry's disease, etc.) should not take part in most competitive sports with the exception of those of low intensity (class IA) in selected cases (Class III: level of evidence C). These recommendations are independent of the demographic characteristics, phenotypic appearance, and they do not differ for those asymptomatic athletes or those that have received prior treatment with drugs, surgical interventions or an ICD implant. Likewise, as mentioned above for hypertrophic cardiomyopathy, the presence of an ICD in high level sporting events must not be considered as either primary or secondary prevention, and should not be a justification for athletes with DCM to participate in competitive sports.

Arrhythmogenic right ventricular dysplasia / cardiomyopathy

This is considered to be a primary myocardial disease histologically characterised by the fibroadipose replacement (fatty tissue) of the ventricular myocardium (predominantly the right one). This is a disease of the desmosome generally resulting from the mutation of defective cell adhesion proteins. From a clinical point of view, it usually appears as potentially lethal ventricular tachyarrhythmias in young individuals, in most cases it is associated with exercise and participation in sports.

This pathology has been traditionally known as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD/C). However, for some years now, it has also been termed "arrhythmogenic cardiomyopathy" due to the fact that both ventricles are frequently affected or, even on some occasions, only the left ventricle. It is estimated that ARVD/C affects 1 in every 1,000 - 1,250 individuals[13], although it is possible that there is a certain infradiagnosis due to the difficulty in detecting it in asymptomatic individuals or with slight symptoms, with sudden death being its first manifestation. ARVD/C is usually inherited as an autosomal dominant disorder. However, the phenotype of this disease is widely variable, with certain patients who, despite exhibiting the mutation and the disease, do not strictly meet the criteria.

ARVD/C currently represents the most frequent cause of sudden death in athletes under the age of 35 in Italy[14]. Today, the identification of ARVD/C is a great challenge, particularly with regard to asymptomatic individuals. Its diagnosis basically depends on the presence of a family history, electrocardiogram alterations or right ventricular morphological abnormalities using different imaging techniques. Nowadays, there are a series of minor and major criteria that help us to establish the definitive diagnosis[15]. Thus, based on the minor and major criteria presented by the patient, we can consider that the patient has definite ARVD/C, borderline ARVD/C, or possible ARVD/C. We should take into account the fact that a carrier of a mutation related to this pathology constitutes in itself a major criterion in the diagnosis. Therefore a carrier of these mutations would already have a possible diagnosis of ARVD/C[15].

Some experimental experience exists for animals (mice) and observational experience for athletes, in connection with physical exercise increasing the risk of developing the disease (penetrance) and the arrhythmic risk in healthy carriers. This has been demonstrated both in high performance sport and in moderate leisure physical activity.

With regard to the performance of diagnostic tests, the electrocardiogram proves highly useful in its identification, given the fact that different electrocardiographic anomalies (inverted T waves in right precordial leads, epsilon wave, etc.) may be present in 50% of patients. Likewise, on many occasions, these electrocardiographic findings may precede the clinical manifestations of the disease. However, we need to exercise particular care when using this tool to make the diagnosis, given the fact that multiple findings frequently encountered in athletes, such as the incomplete right bundle branch block, negative T waves in V1-V3, etc. could simulate this pathology.

The premature ventricular ectopic beats and ventricular tachyarrhythmias usually have a left bundle branch block morphology (given that the ectopic focus generally comes from the right ventricle) and are frequently associated with exercise. Therefore, ergometry is an essential test that will help us in the diagnosis and risk stratification of this disease.

Today, for the definitive diagnosis of arrhythmogenic cardiomyopathy, imaging techniques are an essential tool. The echocardiogram offers us a considerable amount of information, given the fact that it allows us to identify the marked dilatation or dysfunction of the right ventricle which must lead us to suspect this pathology. However, the use of this technique to evaluate the morphological study of the right ventricle requires greater validation, due to the localised extension of morphological abnormalities, poor ultrasound windows, etc. For this reason, the detection of abnormalities in the contractility or dimensions of the right ventricle in the echocardiogram often has a limited diagnostic value.

Today, cardiac magnetic resonance imaging is the gold standard tool for the definitive diagnosis of ARVD/C. This technique has greater spatial resolution and therefore allows us to make an exhaustive study of the presence of right ventricular dysfunction as well as localised morphological abnormalities such as aneurysms, dyskinesias or the thinning of the right ventricular free wall. Furthermore, this test allows us to identify areas of fibrosis or the fibrofatty replacement of the ventricular wall. As mentioned earlier, we must not forget the evaluation of the left ventricle in the study of this pathology.

Likewise, we should remember that high-resistance athletes, predominantly with a greater aerobic component, may exhibit a marked dilation of the heart chambers (predominantly the right ones) as a consequence of the significant cardiac remodelling resulting from their high performance training[12]. There are certain criteria that can help to distinguish between physiological adaptations and findings compatible with arrhythmogenic cardiomyopathy. Athletes show normal right ventricular wall thicknesses with no dyskinetic or aneurysmatic areas. The absence of dysfunction, delayed enhancement or fatty tissue would go in favour of physiological adaptations related to an "athlete's heart".

A genetic study must be conducted on those athletes with a highly suspected presence of arrhythmogenic cardiomyopathy. Today, the mutation of the PKP2 gene is the principal cause of this pathology, with a prevalence of mutations in index cases of up to 43%[15]. However, as outlined in the literature, only 30% of these cardiomyopathies exhibit an identification of the causal mutation.

In short, the current recommendations for patients with this pathology are:

- Athletes with a definite diagnosis of ARVD/C should not participate in most competitive sports, with the possible exception of low-intensity sports (IA) (Class III: level of evidence C), proven absence of symptoms or arrhythmias related to exercise.
- Athletes with a borderline diagnosis of ARVD/C should not participate in most competitive sports, with the possible exception of low-intensity sports (IA) (Class III: level of evidence C).
- Athletes with a possible diagnosis of ARVD/C should not participate in most competitive sports, with the possible exception of low-intensity sports (IA) (Class III: level of evidence C).

These recommendations are also independent of age, gender and phenotypic appearance and do not vary from asymptomatic athletes, or those treated with drugs, surgical interventions, ablation or ICD implant. Likewise, the prophylactic implantation of a defibrillator in patients with ARVD/C should not be made for the simple purpose of participating in high-intensity sports, due to the possible complications derived from the implantation of these devices. (Class III; level of evidence C).

Non-compaction cardiomyopathy

Non-compaction cardiomyopathy (NCC), also called spongiform cardiomyopathy, is a genetic-based cardiomyopathy that is due to the arrest of the embryonic myocardial development[16], characterised by the presence of a left ventricular hypertrabeculation. As this entity has only recently been described within the history of cardiology, at the time being there are no extensive studies that make it possible to apply a special risk stratification for athletes.

Its diagnosis is doubtful in many cases, and it therefore entails a certain difficulty in studying IT. For this reason, different criteria are used to help us try and establish a definitive diagnosis[17]:

- TT echocardiograms, the use of validated criteria (marked trabeculae, more than three, with a compacted - non-compacted myocardium ratio greater than 2 (in systole), trabecular perfusion, etc.
- Cardiac magnetic resonance: nowadays it is established that there should be a ratio between non-compacted and compacted layers of more than 2.3 (diastole), trabeculated IV mass of more than 20% of the normal VI mass, etc.
- Genetic test, neurological evaluation, screening in first degree relatives, etc.

The transthoracic echocardiogram and electrocardiogram are currently used as the main tools to establish an initial diagnosis. However, magnetic resonance imagining is recommended for suspected cases of NCC, given the fact that it offers greater image resolution and therefore helps in the myocardial qualitative study and in the evaluation of the non-compacted layer.

However, the actual sports-related ventricular remodelling can simulate different cardiomyopathies, particularly the non-compacted cardiomyopathy. Although the most frequent physiological adaptations

consist in an increase in the diameters of the chambers and wall thickness, exceptionally we could find a case of a marked hypertrabeculation, which is generally more frequent in the left ventricular apical segments.

In a Spanish study of more than 6,000 athletes[18], the echocardiogram only revealed the presence of 6 cases of hypertrabeculated myocardium, with a proportion of compacted/non-compacted greater than 2 in the telesystole. In all these cases, the segments affected were normocontractile and presented a conserved ventricular function. Likewise, no structural cardiopathy was detected in first-degree relatives for any of these athletes.

This study concluded that the absence of symptomatology and family history and also the absence of alterations in the complementary study (electrocardiogram, echocardiogram, etc.) should make us doubt the diagnosis of NCC. We should therefore be aware that myocardial trabeculation could be an uncommon form of adaptation to intense exercise in certain predisposed individuals.

So, we know that there are severe forms of the disease, particularly in patients with symptomatology, family history or known genetic mutations, where it is simpler to make a definite diagnosis. However, there are generally serious problems in those minor forms, particularly in high-level athletes. Other populations for which the said hypertrabeculation findings are described could be: black athletes, patients with sickle cell anaemia, etc.

Likewise, great genetic heterogeneity has been described for this pathology with different inheritance patterns and an overlapping with other cardiomyopathies, particularly with dilated cardiomyopathy and hypertrophic cardiomyopathy. There are currently no long term studies on the evolution of athletes with NCC. As a result, no criteria have been established with regard to the risk of sudden death that could be applied to competition athletes. For this reason, there is very little evidence on this disease and its natural history still remains unknown, particularly for those with a normal systolic function.

Current recommendations establish that, until more relevant clinical information is available, asymptomatic patients with an NCC diagnosis and conserved systolic function, with no important ventricular arrhythmias in the ambulatory monitoring or in the effort test, and with no unexplained syncope history, can participate in competitive sports (Class IIB, level of evidence C).

However, the very presence of one of these parameters in these patients would exclude the athlete from competing. In other words, those athletes with a clear diagnosis of NCC with systolic dysfunction or important atrial and ventricular arrhythmias in the ambulatory monitoring or in the effort test (or history of syncope) must not participate in competitive sports with the exception of low-intensity sports (class IA), at least until there is more clinical information (Class III: level of evidence C).

Marfan syndrome

Marfan syndrome is a dominant autosomal hereditary disease that generates an alteration of connective tissue, producing different levels of affectation: cardiovascular, ocular, musculoskeletal or pulmonary. It has an estimated prevalence of around 1 in every 5,000 live births[19].

The cardiovascular manifestations are of particular interest, given the fact that they entail a high risk of sudden death for individuals with this condition. The most frequent manifestations are aortic root dilatation, mitral valve prolapse, coarctation of the aorta or the CIA. On the other hand, the worst finding is aneurysm or aortic dissection.

Approximately 60% of patients with Marfan syndrome exhibit aortic root dilatation, predominantly males. In general, medical treatment for these patients is based on avoiding aortic root dilation and dissection by endeavouring to reduce blood pressure and cardiac inotropism. Treatment with beta blockers[20] has been widely recommended in a number of studies in order to prevent the progressive dilatation of the aorta. Moreover, recent studies have focussed on the use of ARA II (angiotensin II receptor antagonists) to antagonise TGF-B signalling, involved in the aortic root dilatation in Marfan syndrome.[21].

Currently, the revised Ghent criteria are used for the diagnosis of Marfan syndrome (Table 1)[22]. The transthoracic echocardiogram and the CAT/MR scan of the thorax are the basic tools to assess the cardiovascular impact. Stable patients require an annual check-up with an echocardiogram. A CAT/MR is recommended every 5 years if there is no aortic dilation. In the event of aneurysm or aortic dilation, these imaging tests should be conducted on an annual basis[23].

Given the greater vulnerability of patients with this disease, the limits for intervention and surgery are different from those of the general population. With regard to surgical repair, according to the 2014 European guidelines on the diagnosis and treatment of the pathology of the aorta, surgery is recommended for patients with Marfan syndrome and a maximum aortic diameter greater than or equal to 50 mm, or else 45 mm if there are risk factors such as family history of dissection, growth > 3mm/year (in various examinations using the same technique and with confirmation in another), serious aortic regurgitation or childbearing intention. Patients exhibiting Marfanoid manifestations due to connective tissue disease, with incomplete Marfan criteria, must be treated as patients with Marfan.

With regard to the participation of athletes with Marfan syndrome, the most important consideration is the early detection of individuals with this condition. Athletes with a Marfanoid phenotype or with family history must be examined immediately to rule out this pathology prior to commencing sporting activity. More aggressive screening strategies are recommended for sports that are typically practised by athletes with this specific profile and a certain Marfanoid habit, such as basketball and volleyball. Given the fact that the prevalence of Marfan syndrome is generally higher in this population, the screening of these high-risk groups could improve the early detection of this pathology and prevent the progression of the disease among these athletes.[24].

Today, important restrictions on physical activity have been established for patients with Marfan syndrome. For example, activities involving collisions or intense contact sports are considered to be of particularly high risk for these individuals, given their cardiovascular and

Table 1. Diagnostic criteria of the Ghent nosology for the diagnosis of Marfan Syndrome.

Organ/System	Requirements for the classification of major criteria	Requirements for the affectation of organ/system
Skeletal	At least four of the following: 1. *Pectus carinatum* 2. *Pectus excavatum* requiring surgery 3. Reduced upper to lower segment ratio or arm span to height ratio (<1.05) 4. Positive wrist and thumb signs 5. Scoliosis (20º) or spondylolisthesis 6. Reduced extension at the elbow (<170º) 7. Medial displacement of the internal malleolus causing flat feet. 8. Protrusio acetabuli	At least two major criteria findings or one from this list and two from the following minor criteria: 1. *Pectus excavatum* of moderate severity 2. Joint hypermobility 3. High arched palate or crowding of teeth 4. Characteristic facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures).
Ocular	Ectopia *lentis*	At least two of the following minor criteria: 1. Abnormally flat cornea 2. Increased axial length of the ocular globe 3. Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis
Cardiovascular	At least one of the following: 1. Dilation of the ascending aorta with or without regurgitation, involving the sinuses of Valsava 2. Dissection of the ascending aorta	At least one of the following minor criteria: 1. Mitral valve prolapse with or without regurgitation 2. Dilatation of the pulmonary artery, in the absence of stenosis or other cause in individuals under the age of 40 years 4. Dilatation or dissection of the descending thoracic or abdominal aorta in individuals under the age of 50 years.
Pulmonary	None	At least one of the following minor criteria: 1. Spontaneous pneumothorax 2. Apical blebs
Teguments	None	At least one of the following minor criteria: 1. Stretch marks not associated with marked weight changes, pregnancy or repetitive stress. 2. Recurrent or incisional hernia
Dura	Lumbosacral dural ectasia	None

For the diagnosis of Marfan Syndrome in patients with no family history of the disease, two organs / systems must be involved which comply with the criteria and at least an impact on a third organ / system. For patients with a family history of Marfan Syndrome, only one major criterion is required, with data that suggest the involvement of a second system (De Paepe, *et al*).

skeletal sensitivity. Likewise, athletes who are carriers of this syndrome should not perform high-risk activities, or at least try and minimise their exposure to activities of this type (class III; level of evidence C).

With regard to current recommendations, isometric exercises should be prohibited for athletes with Marfan syndrome, given the damaging haemodynamic effects of increased aortic wall tension, leading to a considerable increase in the risk of aortic dissection or rupture. According to the recommendations established in the 36th Conference of Bethesda[8], these athletes should only practice low-intensity activities with a low dynamic and static component (such as rambling, bowling, golf, etc.). Likewise, the more recent American recommendations (AHA 2015)[9] establish that patients with this syndrome can practice type IA or IIA sports (Class I; level of evidence C) if they do not have more than one of the following characteristics: aortic root dilation (Z score >2, 40 mm or >2 DS children and minors under 15), moderate-severe mitral insufficiency , left ventricular systolic dysfunction (FEVI<40%) and/or family history of aortic dissection with diameter <50 mm.

The bibliography is published in the second part of the work.