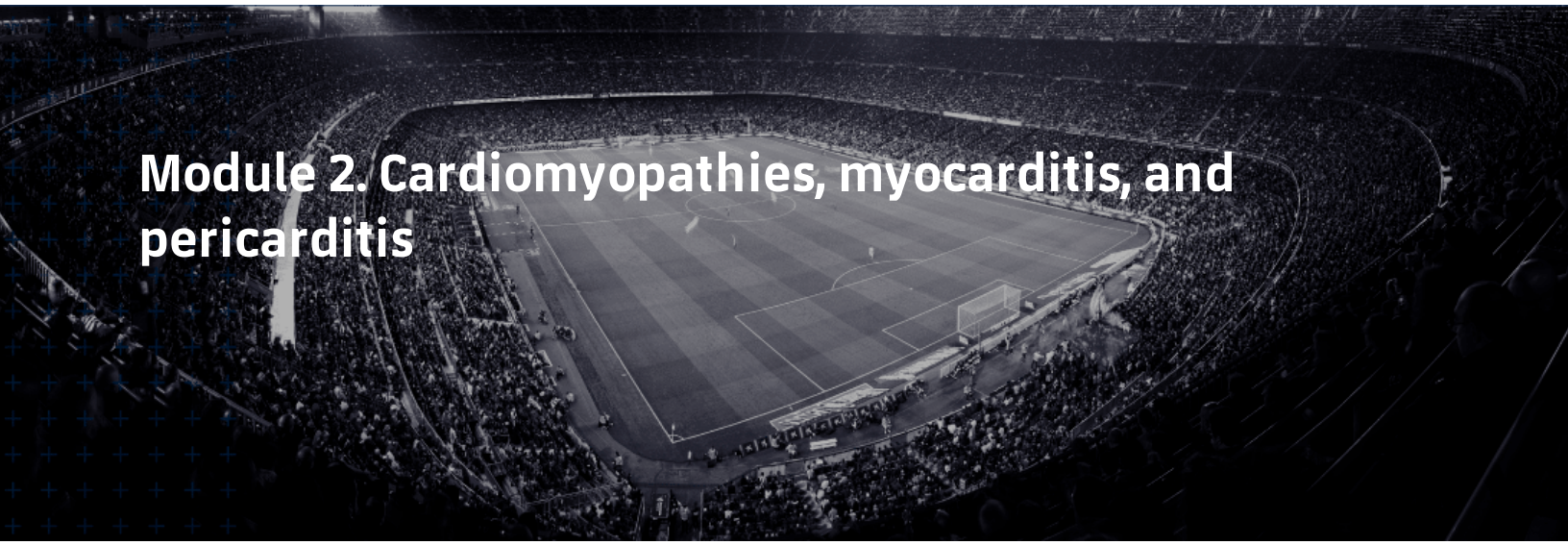

Module 2. Cardiomyopathies, myocarditis, and pericarditis

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Cardiomyopathies, myocarditis, and pericarditis are an important cause of sudden cardiac death (SCD) in athletes, appearing, on many occasions, in previously asymptomatic individuals (Maron et al., 2009). In addition, sport can accelerate the evolution of some of these pathologies.

Previous chapters addressed the issue of making a correct differential diagnosis of cardiomyopathies with the adaptive changes that occur in the athlete's heart. Once the diagnosis of the underlying pathology is established, risk stratification and sports counseling are of vital importance in these patient groups.

It is also important to remember that we are dealing with a spectrum of disease that includes from patients in early stages (even genetic carriers without phenotype) and asymptomatic to those in later stages of the disease. This means that the indications regarding exercise must be established in the most individualized and specific way possible.

Unit 1. Hypertrophic cardiomyopathy (HCM)

References

Unit 1. Hypertrophic cardiomyopathy (HCM)

In the general population, the leading cause of SCD in individuals over 35 years old remains HCM. Sport and high-intensity exercise were considered a trigger for the development of malignant arrhythmias and, therefore, SCD in these patients. For this reason, previous consensus recommendations restricted the participation of all individuals with HCM in competitive sports (Maron et al., 2004; Pelliccia et al., 2005).

However, recent studies have shown that there is no evidence of the development of lethal arrhythmias in individuals with HCM during exercise. Series with patients with HCM who continued their sports practice after implantation of implantable cardioverter defibrillators (ICDs) in primary prevention did not show an increase in the number of cardiovascular shocks during exercise. (Lampert et al., 2017). Cohort studies of young patients with HCM (mean age of 15 years old) who participated in high-intensity exercise and even competition show no difference in major events at a 9-year follow-up, compared to those who dropped out of exercise (Pelliccia et al., 2018). In necropsy studies of patients with HCM, only 23% of deaths occurred during sports

practice, affecting males with a mean age of 30 years (Finocchiaro et al., 2016). Moreover, cardiac rehabilitation studies began to be performed in patients with HCM, showing a significant increase in functional capacity, without presenting major events (Klempfner et al., 2015).

From these analyses, it is important to stratify the risk of malignant arrhythmias in all patients with HCM to offer individualized counseling, since there will be high-risk patients in whom physical activity will have to be limited or even contraindicated, and others who, after evaluation, will be considered low-risk patients and will be able to perform exercise, even competitive exercise. Within the initial evaluation, the basic aspects would include the following:

- **Anamnesis:** Ask about family history (of heart disease or sudden death), as well as personal history regarding cardiac comorbidities that may affect prognosis (arterial hypertension, ischemic heart disease, diabetes *mellitus*, dyslipidemia, smoking) (Saberi et al., 2017). Also, it is important to evaluate the sports practice prior to the evaluation (type of sport, intensity and duration of training, years of exercise). Finally, ask about symptoms associated with HCM (mainly SCD and cardiogenic syncope).

- **Physical examination:** Evaluate the presence of systolic murmur of HCM at baseline or after Valsalva maneuver, the presence of signs of heart failure or syndromic phenotypes associated with ventricular hypertrophy.

- Complementary tests:

  - **Baseline electrocardiogram (ECG) and, above all, 48-hr Holter monitoring**, including an exercise session, to detect supraventricular arrhythmias (due to the high association of HCM with atrial fibrillation) and ventricular arrhythmias, since nonsustained ventricular tachycardias (NSVT) increase the risk of lethal arrhythmias, especially in individuals over 35 years old (**Zamorano** *et al*., 2014).

  - **Stress test** (conventional or cardiopulmonary): The development of symptoms or exercise-induced arrhythmias or an abnormal tension response (hypotension or increase in systolic blood pressure (SBP) <20 mm Hg with exercise) are markers of high risk (**Olivotto** *et al*., 1999).

The cardiopulmonary stress test, also known as ergospirometry or stress test with oxygen consumption (CPET), constitutes one of the most important tests in the diagnosis of cardiopulmonary diseases, in the determination of baseline functional capacity and risk stratification, as well as in exercise prescription guidance, both in cardiac rehabilitation programs and in elite athletes (**Herdy** *et al*., 2016).

The CPET is a conventional ECG-guided stress test, in which pulmonary ventilation and respiratory gas exchange are monitored through an oropharyngeal mask placed on the patient and connected to a gas analyzer. The test is preceded by a previous baseline spirometry that, in an integrated manner with the results obtained, provides essential information to globally assess the behavior of the cardiovascular, respiratory, and metabolic-energy apparatus (**Levett** *et al*., 2018).

The exercise can be performed on a treadmill or on a cycloergometer. These test contraindications are the same as those of the conventional stress test. The test will be stopped if the maximal oxygen consumption (VO_2 max) value is considered to have been reached or if clinical, ECG, or hemodynamic problems are detected (**Herdy** *et al*., 2016). In order to consider that the test has been maximal, four conditions must be met: VO_2 reaches plateau values; >85% of the theoretical maximum heart rate has been reached;

respiratory exchange ratio (RER) >1.1; lactate >18 millimoles (not always available). The RER refers to the state of the energetic processes during exercise, so that as its value increases, anaerobic participation increases, being predominant in values >1 close to reaching VO_2 max.

The main parameters obtained in a CPET are oxygen consumption (VO_2) and CO_2 production (VCO_2), which will later be integrated with other variables (heart rate, exercise time, workload achieved, ventilation) to obtain Wasserman graphs (**Change** *et al.*, 2007).

Oxygen consumption (VO_2) is the most studied parameter and the one that best assesses functional capacity, providing an objective value of it. It can be expressed as an absolute value (l/min; ml/min; ml/min/kg; ml/min/kg lean mass) or, preferably, as a percentage of the predicted value for that subject, depending on age, sex, weight, height, and ethnicity. VO_2 → 85% of the predicted value is considered normal, being pathological a value which is <50% of the predicted one.

The most commonly used parameter is VO_2 max (if a maximal test is achieved). In case of submaximal tests, the peak VO_2 value (the highest value reached in the submaximal test) will be studied, with the VO_2 value being also essential in the so-called ventilatory thresholds. The VO_2 value at the first threshold, or VT1, corresponds to

the beginning of anaerobic metabolism, and the VO_2 value at the second threshold, or VT2, when aerobic metabolism is exhausted, is close to the VO_2 max or peak.

VO_2 max is directly related to cardiac output, so that lower VO_2 max values correlate with worse cardiac output and worse prognosis. Weber's classification relates these two parameters, differentiating between functional class A (VO_2 max >20 ml/min/kg), B (VO_2 16-20 ml/min/kg), C (10-15 ml/min/kg), D (6-10 ml/min/kg) and E (<6 ml/min/kg) (**Guazzi** *et al*., 2017).

There are other parameters associated with worse prognosis and higher cardiovascular mortality, such as O2 pulse (low values and flattening of the curve are associated with ischemia and heart failure), oxygen uptake efficiency slope (OUES) (ratio between VO_2 and ventilation; low values are associated with poor prognosis), slow VO_2 recovery dynamics (VO_2 RD) with high O2 debt, as well as the presence of ventilatory oscillations. Ventilatory inefficiency parameters, mainly represented by the minute ventilation (VE)/VCO_2 slope (ratio between ventilation and CO_2 production) are also pathologically elevated in conditions such as heart failure, pulmonary hypertension, or in some cardiomyopathies, being an independent prognostic factor for cardiovascular mortality (**Sinagra** *et al*., 2020). In the prognostic stratification of patients with heart failure, all these parameters obtained by the CPET are integrated, with the aim of

estimating the risk of cardiovascular mortality at 1 year and, thereby, guiding clinical action in these patients (**Malhotra** *et al*., 2016).

The VO_2 max (or VO_2 peak in submaximal tests) is also the main parameter for guiding exercise (together with the maximum heart rate [HR] obtained, in the case of conventional stress tests) both in cardiac rehabilitation programs and for counseling competitive athletes (both for those without pathologies to increase their performance and those with concomitant cardiological pathologies). In this way, exercise intensity and safety training zones can be delimited in each case, as specified in Table 1 (Pelliccia et al., 2021).

Likewise, high-risk individuals who can only perform low-intensity exercise will have a limit of 40% of VO_2 peak or 55% of maximum HR (aerobic training zone, below the first ventilatory threshold). Those who can reach moderate-to-high intensity will be between 40-85% of VO_2 peak or 55-90% of maximum HR (predominant aerobic training zone, but the first ventilatory threshold is already reached). Finally, athletes or patients at low risk who can reach high intensities will be able to reach VO_2 peak >85% and >90% of maximum HR, entering the zone of predominant anaerobic metabolism. The heart rate reserve (HRR) is the maximum HR – resting HR, and can also be used to guide training.

Table 1. Intensity and training zones based on VO_2 peak, HR max, or heart rate reserve (HRR)

Intensity	VO_2 peak (%)	HR max (%)	HRR (%)	Effort scale	Training area
Low	<40	<55	<40	10-11	Aerobic
Moderate	40-69	55-74	40-69	12-13	Aerobic
High	70-85	75-90	70-85	14-16	Aerobic + lactate
Very high	>85	>90	>85	17-19	Aerobic + lactate + anaerobic

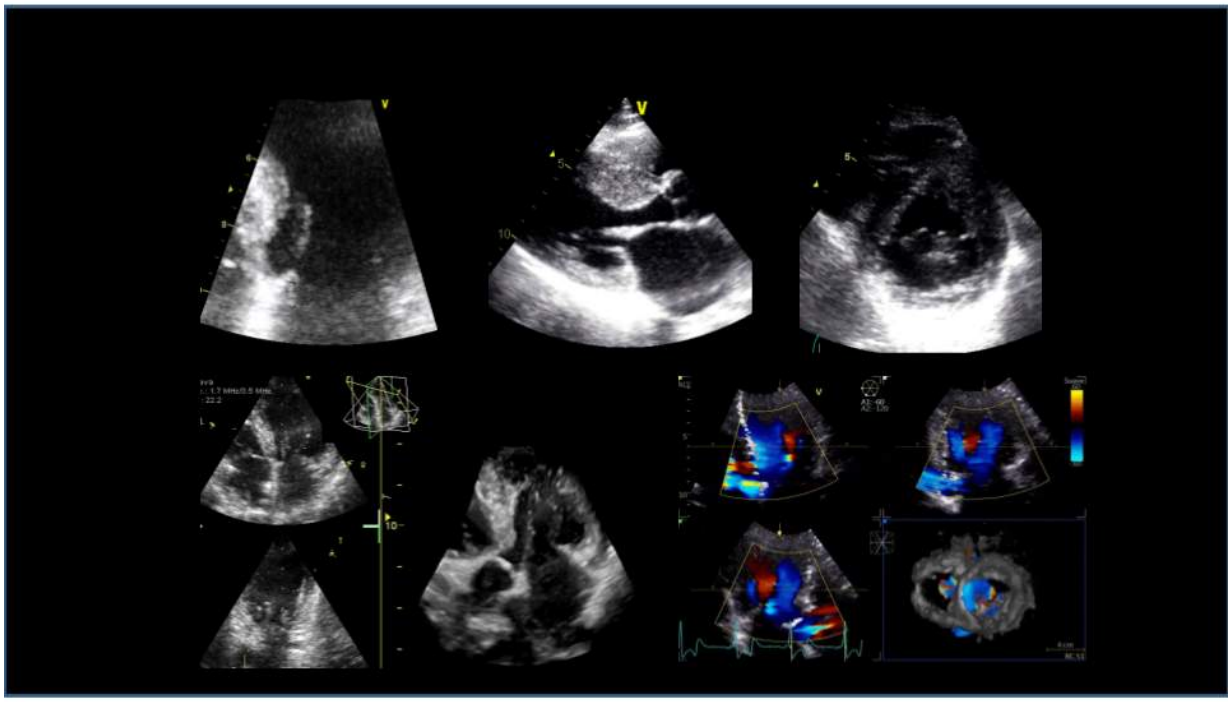
Source: **own source based on Pelliccia** *et al.*, 2021, https://goo.su/m705a.

On the other hand, equally important are strength or endurance exercises, which are not guided by the aforementioned parameters in this case (they are useful for aerobic exercises), but by the patient's subjective effort on the Borg scale (score 10-20). It is recommended to do sets of repetitions, ideally of exercises that involve large muscle groups. A progressive increase in intensity and duration of exercise sets should be prescribed, starting from a Borg scale score of <15 and a progressive increase according to tolerance in low-to-moderate risk patients (**Williams** *et al.*, 2007).

In the case of HCM, the CPET may provide additional characteristic information, such as the presence, in some cases, of chronotropic incompetence, flattening of the O2 pulse curve, and increased pulmonary artery pressure. A VO_2 peak <50% and a VE/VCO_2 slope >31 have been associated in several studies as independent predictors of heart failure and cardiovascular mortality (**Sinagra** *et al*., 2020).

- Baseline echocardiogram: It evaluates the left ventricle wall thickness, left ventricular outflow tract (LVOT) gradient (LVOT) at baseline and during the Valsalva maneuver (defined as obstructive HCM when it exceeds 30 mm Hg, with values above 50 mm Hg considered hemodynamically significant), and the dimensions of the left atrium (LA) (**Zamorano** *et al*., 2014). If systolic anterior motion is observed, without detecting a significant gradient in the baseline echocardiogram, an exercise echocardiogram can be considered (Figure 1).

Figure 1. Echocardiography of a 24-year-old female endurance athlete, asymptomatic

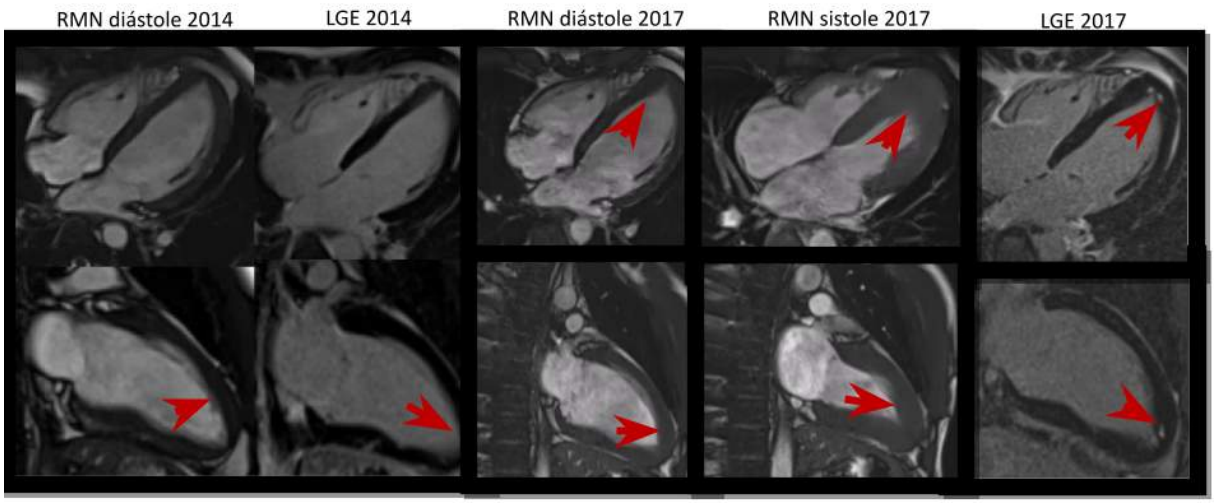


Source: own source.

The figure shows an echocardiogram referred for cardiovascular screening due to a family history of hypertrophic cardiomyopathy. The echocardiogram shows septal thickening and mitral valve involvement, thus establishing the diagnosis of hypertrophic cardiomyopathy in the patient. In the absence of risk markers for sudden death, in consensus with the patient and after explaining the potential risks of sports in the specific case of her cardiomyopathy, it

was decided to keep practicing competitive endurance sports with a close annual follow-up.

- **Cardiac MRI:** A late gadolinium enhancement >15% of the left ventricular myocardium significantly increases the risk of ventricular tachycardias and SCD (**Weng** *et al.*, 2016), as shown in Figure 2.



Source: **Weng** *et al.*, 2016, https://goo.su/7fI8UUP.

In the case shown in the figure, the initial magnetic resonance imaging (MRI) evaluation conducted in 2014 detected no alterations. In the 3-year control (2017), the presence of hypertrophy at the apical level with focal fibrosis is observed in the sequences with late gadolinium enhancement (LGE), so the patient is diagnosed with apical hypertrophic cardiomyopathy. In addition, the patient reported episodes of presyncope with intense exertion, which were observed in a Holter ECG recording and included a training session with nonsustained ventricular tachycardia. In view of the above, antiarrhythmic treatment was started and the patient was considered unfit for competitive sport. Low-to-moderate intensity exercise was recommended.

- **Genetic testing:** They should only be used for cascade screening of relatives, but not for deciding exercise-related stratification.

- **European Society of Cardiology (ESC) risk scale:** It is estimated with a calculator found online (https://doc2do.com/hcm/webHCM.html). This calculator allows for the estimation of the 5-year risk of SCD based on 7 variables (age, LV thickness, left atrium (LA) size, LVOT, family history of SCD, NSVT, and unexplained syncope) (Zamorano et al., 2014). The 5-year SCD risk is low if it is <4%, intermediate if it is 4-6%, and high if it is >6%. It should be

considered that this scale is created from evidence in mainly non-athlete populations (**O'Mahony** *et al.*, 2014), so it would not be completely extrapolable to these patients, and a joint decision-making process with the patient would be necessary.

Based on this analysis, the 2020 ESC guidelines (*Pelliccia et al.*, 2021) establish five basic risk markers: a) cardiac symptoms, history of cardiac arrest, syncope of unknown origin; b) ESC risk >4% at 5 years; c) LVOT gradient at rest >30 mm Hg; d) abnormal BP response to exercise; and e) exercise-induced arrhythmias, based on which the following recommendations are established (Table 2).

Table 2. Exercise and sports participation recommendations for patients with HCM

Recommendation	Class	Level
Competitive exercise/sport may be considered, if desired (with the exception of those for whom syncope could mean harm or death) for patients with hypertrophic cardiomyopathy who do not have increased risk markers after expert evaluation.	IIb	C
Low- or moderate-intensity exercise may be considered, if desired, for patients with hypertrophic cardiomyopathy who have any increased risk markers after expert evaluation.	IIb	C
Participation in all competitive sports may be considered, if desired, in patients with hypertrophic cardiomyopathy with positive genotype/negative phenotype for hypertrophic cardiomyopathy-related genes.	IIb	C
Participation in high-intensity exercise (both recreational and competitive) is not recommended for patients with hypertrophic cardiomyopathy who have any increased risk markers.	III	C

Source: own source based on Pelliccia *et al*., 2021, https://goo.su/m705a.

Patients without the phenotype or risk markers mentioned above can participate in all types of sports. As special considerations, patient age may influence risk stratification. In most SCD series, the average age of the deceased is 18 years, with 65% of deaths occurring in athletes under 17 years old (**Maron** *et al*., 2009). Moreover, there are very dynamic stop-start sports (basketball, soccer), which involve a higher risk of SCD. As a result, although age is not a factor that contraindicates high-intensity exercise, if there is no other associated risk factor, it is important to reach a consensus with athletes with HCM who are ←17 years old and with their parents on the decision to perform competitive exercise and its modality.

An annual follow-up should be done in patients with positive phenotype and every 6 months in high-risk individuals, including adolescent or younger patients, who are more vulnerable to exercise-related SCD (**Pelliccia** *et al*., 2021). For those individuals with a negative phenotype, an annual follow-up should be done which focuses on the development of the phenotype, in order to monitor the onset and evolution of the disease. In this way, risk stratification is dynamic and may vary from one clinical review to another.

There is evidence of safety and efficacy of cardiac rehabilitation programs in individuals with HCM without risk markers (**Wasserstrum** *et al*., 2019), primarily based on aerobic exercise, improving functional capacity and VO2 peak (**Saberi** *et al.*, 2017).

2. Dilated cardiomyopathy (DCM)

DCM presents a risk of SCD of 2-3% per year, increasing with lower left ventricular ejection fraction (LVEF), worse New York Heart Association functional class (NYHA FC) and in specific genotypes, such as laminin alpha (LMNA) and filamin C (FLNC) (**Halliday** *et al*., 2017). Training and cardiac rehabilitation programs improve functional capacity, LVEF, and quality of life and should therefore be considered a fundamental part of treatment (**Holloway** *et al*., 2012). In some cases, however, intense

exercise and competitive sports have been found to be associated with SCD in patients with high-risk DCM (**Finocchiaro** *et al*., 2016).

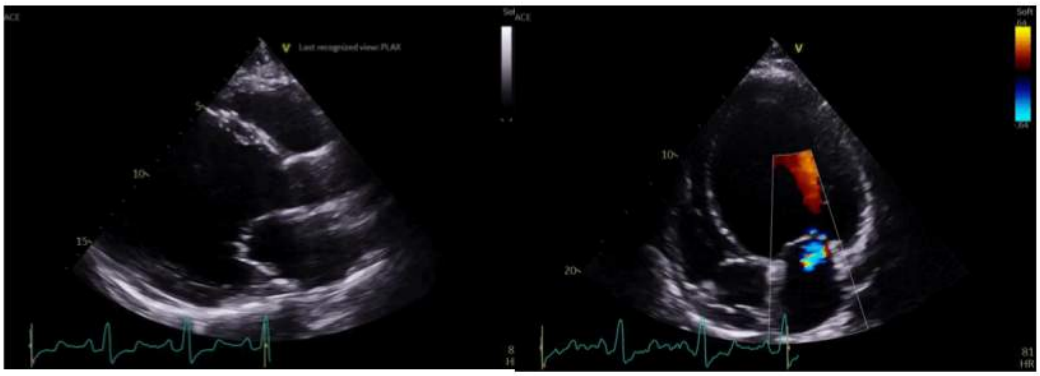
Consequently, as with other cardiomyopathies, a correct and detailed evaluation of these patients is essential, which should include the following aspects:

- **Anamnesis:** Detail the presence of family history of heart disease, symptoms (arrhythmic or heart failure), and sports history.
- **Physical examination**: Look for signs of heart failure or tachyarrhythmias.
- **Complementary tests**
- **Baseline ECG and 24-hr Holter monitoring:** For evidence of atrial or ventricular tachyarrhythmias with which it may be associated or abnormalities in the QT or PR intervals.
- **Stress test:** To detect arrhythmias with exertion or during recovery. Additionally, the stress test with oxygen consumption (CPET) has diagnostic value, since the presence of reduced VO_2 peak is indicative of DCM, as well as a prognostic value. A VO_2 peak <60% of that predicted for age, ethnicity, and sex or

a VE/VO_2 slope >29 have been shown to be independent predictors of cardiovascular mortality or need for heart transplantation, as well as being associated with pulmonary arterial hypertension (**Sinagra** *et al*., 2020).

- **Baseline echocardiogram:** To determine the degree of left ventricular dilatation and LVEF, as well as secondary mitral insufficiency (MI) or right ventricle (RV) involvement and possible associated pulmonary hypertension. There are cases of athletes with mild ventricular hypertrophy and LVEF of 45-50%, in which there is doubt as to whether it is an adaptation to sport or incipient DCM (**Pelliccia** *et al*., 2018). In these cases, the use of a stress echocardiogram is particularly helpful. An increase during peak exercise of less than 10% can indicate a pathological process (**Claessen** *et al*., 2018). Likewise, diastolic dysfunction can also be indicative of DCM (Figure 3).

Figure 3. Echocardiogram. Male, 45 years old, amateur endurance athlete, referred for worsening of functional capacity



Source: own source.

The 2D ECG in the previous figure shows severe dilatation of the left ventricle not compatible with an athlete's heart. There is also a disproportionate dilatation of the left ventricle, with severe systolic dysfunction of the left ventricle. Once coronary involvement was ruled out, the patient was reassessed and confirmed a family history of dilated cardiomyopathy; his father and paternal uncle were diagnosed at 40-50 years old. Genetic testing was performed, and a pathogenic variant was located in laminin A/C. Given the diagnosis and the documentation of a gene associated with high arrhythmic

risk, the patient was advised to avoid competitive sports and/or high-intensity exercise, and was referred to an individualized cardiac rehabilitation program for exercise prescription.

Taking into account analytical, imaging and CPET parameters, there are validated prognostic scales, such as the MECKI score (metabolic exercise test combined with cardiac and kidney indexes), which calculates the risk of cardiovascular mortality at two years (calculator: https://www.cardiologicomonzino.it/en/mecki-score/) based on a database of more than 75,000 patients with HF and reduced LVEF (**Salvioni** *et al*., 2020).

- **Cardiac MRI:** To more accurately estimate ventricular volumes and LVEF and right ventricular ejection fraction (RVEF), and, above all, to document the presence, location, and extent of late gadolinium enhancement, highly related to the risk of SCD (*Gulati et al*., 2013).

- **Genetic testing:** LMNA and FLNC carriers are high-risk genotypes for SCD (**Mestroni and Taylor**, 2008).

General recommendations, according to the ESC guidelines (Pelliccia et al., 2021) (Table 3) indicate that patients with DCM should refrain from high-intensity or competitive exercise, except those that meet

the following conditions: 45-50% LVEF, asymptomatic and without LMNA or FLNC mutation, without arrhythmic events in stress test or Holter monitoring, and without fibrosis >20% in MRI. In the rest of the patients, low-to-moderate intensity exercises are recommended, and higher intensity may be considered in selected asymptomatic cases, except for those with LMNA and FLNC mutations.

Table 3. Exercise and sports participation recommendations for patients with DCM

Recommendation	Class	Level
Participation in low- to moderate-intensity recreational exercise should be considered for patients with dilated cardiomyopathy, regardless of their left ventricular ejection fraction, if there are no limiting symptoms or exercise-induced ventricular arrhythmias.	IIa	C
High- or very high-intensity exercise, including competitive sports (with the exception of those for whom syncope could involve harm or death), may be considered for patients with dilated cardiomyopathy who are asymptomatic and who meet all of the following conditions: Left ventricular ejection fraction ≥45%; absence of frequent or complex ventricular arrhythmias during ambulatory Holter monitoring or during ergometry; absence of late gadolinium enhancement on cardiac MRI; 10-15% increase in left ventricular ejection fraction is achieved with exercise; no evidence of high-risk genotype (laminin A/C or filamin C).	IIb	C
Participation in all competitive sports can be considered in patients with dilated cardiomyopathy and positive genotype/negative phenotype, with the exception of carriers of high-risk mutations (laminin A/C or filamin C).	IIb	C
High- or very high-intensity competitive sports practice is not recommended in patients with dilated cardiomyopathy and any of the following: Symptoms or personal history of cardiac arrest or unexplained syncope; left ventricular ejection fraction <45%, frequent or complex ventricular arrhythmias on ambulatory Holter monitoring or ergometry; late gadolinium enhancement >20% on cardiac MRI, or high-risk genotype (laminin A/C or filamin C).	III	C

Source: own source based on Pelliccia *et al.*, 2021, https://goo.su/m705a.

The key parameter to guide training, as explained in the previous section, is the VO2 max or peak obtained by CPET (or maximum HR reached in the case of conventional ergometry). Low risk patients will be able to reach high work intensities (VO_2 peak >85% or >90% of

maximum HR), while, in the rest of patients, low-intensity aerobic exercises (40% of VO_2 peak or 55% of maximum HR) should be started in high-risk individuals, and may be increased to 70% of VO_2 peak or 75% of maximum HR if well tolerated and in the absence of complications. The modality can be either continuous (largest number of endorsed studies) or intervallic exercises, particularly indicated in low-risk patients to reach a higher VO_2 peak more quickly and be able to resume high-intensity exercise (**Cornelis** *et al*., 2016).

Regarding strength training, there is strong evidence for safety and efficacy in patients with DCM, including those at high risk, helping to regain muscle mass and improvement of VO_2 peak in numerous studies, mostly combined, with aerobic exercise (**Wittekind** et al., 2018). It should generally be started at an intensity of 15 out of 20 on the Borg subjective scale in each patient, progressively increasing the intensity and duration of the training, according to the patient's tolerance (**Lin** *et al*., 2020).

Breathing exercises are also important in individuals with DCM, especially in those patients with heart failure and advanced functional class, high risk individuals (Neto et al., 2016), or as the only training, or genotypes associated with muscular dystrophies such as LMNA (Taya et al., 2019), ideally as a bridge to the aerobic and strength training previously explained.

Follow-up is annual and includes patients with positive genotype and negative phenotype, in order to characterize the phenotype and stratify risk. In turn, follow-up should be closer in adolescent or young individuals in whom the pathology is still developing and there is a greater risk of SCD, as in the case of other cardiomyopathies. Likewise, in those patients with DCM who want to do competitive and high-intensity sport and are able to do so, according to previous recommendations, closer follow-up is recommended.

3. Arrhythmogenic cardiomyopathy (ACM)

Arrhythmogenic cardiomyopathy (ACM) is one of the exceptions in which regular, high-intensity exercise involves acceleration in disease progression and a worse prognosis (Maupain et al., 2018). In fact, ACM accounts for a significant percentage of SCD in young athletes (Finocchiaro et al., 2016).

Disease progression is accelerated if exercise is initiated at an early age, even in asymptomatic carriers (positive genotype, negative phenotype) (James et al., 2013).

The relationship of progression in RV dysfunction and malignant arrhythmias is greater the longer the duration of training in sports involving acceleration and especially in high-intensity exercise. A twofold increase in the risk of malignant arrhythmias, SCD, and early disease onset has been documented in patients with ACM who

participated in competitive sports, when compared to patients who practiced recreational or sedentary sports (Ruwald et al., 2015). In studies in which intense exercise is even more restrictively defined (→6 METs for →4 hr/week for at least 6 years) (Saberniak et al., 2014), acceleration of the clinical course of the disease has also been documented.

Also, reduced exercise activity in these patients is significantly associated with fewer episodes of VT and SCD, reaching the same level as sedentary patients with ACM (Ruwald et al., 2015).

Consequently, unlike low-risk patients with HCM, who can even engage in competitive sports in selected cases, patients with ACM receive much stricter recommendations, with early diagnosis, close follow-up, and contraindication of high-intensity and competitive exercise being essential. Therefore, the baseline evaluation of patients with suspected ACM must include the following aspects.

- **Anamnesis**: Including family history of ACM or SCD, personal history indicating severity of ACM (previous sudden cardiac arrest, syncope without prodrome or with exercise, tachyarrhythmias, especially ventricular) and history of sports practice (from what age, intensity, duration, symptoms).

- **Physical examination:** Especially to check for signs of heart failure or arrhythmias on auscultation.

- **Complementary tests:**

  - **Baseline ECG and Holter monitoring, including an exercise session:** In the baseline ECG, the presence of extensive T-wave inversion in 3 or more precordial leads or T-wave inversion in 2 of the 3 inferior leads indicates more risk of SCD (Bhonsale et al., 2011). Likewise, Holter monitoring is critical to detect NSVT or a ventricular extrasystolic load >1,000/24 hr, which indicates a worse prognosis, even in asymptomatic individuals (Orgeron et al., 2017).

  - **Conventional stress test and CPET:** The presence of induced arrhythmias in the stress test also implies worse prognosis and higher risk of SCD (Orgeron et al., 2017). As for CPET, up to 25% of patients cannot reach maximal exercise (beta-blocker treatment, exercise-induced arrhythmias), so results are usually based on submaximal parameters. Of these, it appears that the VE/VCO2 slope is the one most associated with right ventricular dysfunction and symptomatic heart failure, although further studies are needed to clarify the prognostic

stratification of ACM with CPET (Sinagra et al., 2020).

- **Baseline echocardiogram and cardiac MRI:** Mainly focused on left and right ventricular dilatation and motility and, in the case of MRI, on fibrofatty infiltration of the myocardium. The more widespread the infiltration, the greater the risk of arrhythmias (Wichter et al., 2004).
- **Genetic testing:** Unlike HCM, in ACM the presence of 2 or more mutations in desmosomal genes or multiple pathogenic variants in the same gene confer an arrhythmic risk up to 4 times higher than those with a single mutation (Gandjbakhch et al., 2018). In addition, certain genotypes, such as desmoplakin (DSP), filamin C (FLNC), laminin (LMNA), and transmembrane protein 43 (TMEM 43), confer high arrhythmic risk (Merner et al., 2008).

There is no defined risk scale, unlike HCM, for ICD implantation. In these patients, established SCD risk factors that presuppose the indication for ICD implantation are recovered sudden cardiac arrest, syncope without prodrome, VT, and left/right ventricular dysfunction (**Calkins** *et al*., 2017).

As previously discussed, the general recommendations, according to the 2020 ESC guidelines (**Pelliccia** *et al*., 2021) (see Table 4) advise against high-intensity sports and any competitive sport for all patients with ACM, even in asymptomatic carriers of ACM-associated variants. Low-intensity exercise (150 min/week) is recommended for all patients, with moderate-intensity exercise allowed if there are no risk factors: sudden cardiac arrest, unexplained syncope, >500 VE on 24-hr Holter monitoring, or exercise-induced ventricular arrhythmias or minimal structural abnormalities. Special considerations that confer greater risk are male sex, the presence of symptoms at early ages, and highly dynamic stop-start exercises, such as basketball or soccer.

Table 4. Exercise and sports participation recommendations for patients with ACM

Recommendation	Class	Level
Participation in low-intensity exercise (150 min/week) should be considered in all patients with arrhythmogenic cardiomyopathy.	IIa	C
Participation in low-to-moderate intensity recreational exercise/sport may be considered in patients with arrhythmogenic cardiomyopathy in the absence of all of the following: History of cardiac arrest or ventricular arrhythmias; unexplained syncope; minimal structural cardiac abnormalities; <500 ventricular extrasystoles in 24 hr; and evidence of exercise-induced complex ventricular arrhythmias.	IIb	C
Participation in high-intensity recreational exercise/sport or any competitive sport is not recommended in patients with arrhythmogenic cardiomyopathy, including those with positive genotype/negative phenotype.	III	B

Source: own source based on Pelliccia *et al.*, 2021, https://goo.su/m705a.

There is very little scientific evidence on the safety or efficacy of cardiac rehabilitation programs, both aerobic and strength training, in patients with ACM. There are hypotheses about possible improvement of diastolic function and functional capacity, especially in those patients with ICDs who could be protected in case of exercise-induced arrhythmias (La Gerche, 2015). However, more observational studies are needed to obtain general conclusions on safety and efficacy in real life for these patients.

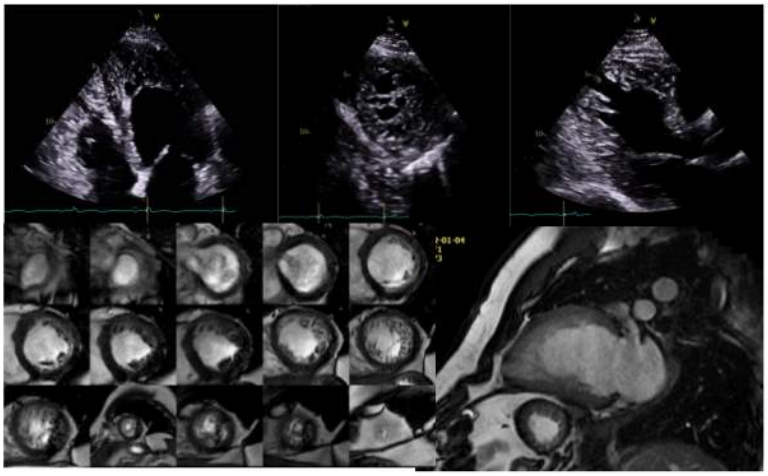
Follow-up should be annual, being biannual in adolescents and young individuals in whom the clinical form of ACM is still evolving,

as well as in particularly aggressive genotypes, such as TMEM 43, DSP and carriers of multiple pathogenic variants.

4. Non-compaction cardiomyopathy (NCCM)

The occurrence of LV hypertrabeculation is common in athletes; it is thought to be due to increased preload (Gati et al., 2013). Up to 8% meet echocardiographic criteria for the diagnosis of NCCM, although to be considered diagnostic of NCCM in athletes, these criteria must be associated with the presence of any of these factors: LVEF <50% or impaired myocardial relaxation (E' <9 cm/s on tissue Doppler imaging) (Gati et al., 2013); very thin compacted epicardial layer (on cardiovascular magnetic resonance [CMR], 5 mm in end diastole or <8 mm in systole); abnormal ECG; symptoms suggestive of heart disease, or family history of NCCM or heart disease (**Zemrak** *et al.*, 2014) (Figure 4).

Figure 4. Echocardiogram. Asymptomatic 21-year-old female elite athlete referred for cardiovascular screening prior to sports practice



Source: own source.

The 2D echocardiogram (top row) shows marked hypertrabeculation at the level of the left ventricular apex, suggestive of non-compaction cardiomyopathy. These findings were confirmed by an MRI (bottom row), fulfilling criteria for such cardiomyopathy. Given that the patient had a normal ejection fraction and no arrhythmias on the Holter monitoring, competitive exercise could be considered subject to annual cardiovascular reassessment.

In these patients, a thorough echocardiographic evaluation, MRI (presence of fibrosis, thrombi), Holter monitoring, and stress test (inducible arrhythmias) are important.

No adverse cardiac events have been documented in patients without ventricular dysfunction, regardless of the number of trabeculation severity (**Zemrak** *et al.,* 2014). Consequently, according to the 2020 ESC guidelines (Pelliccia et al., 2021) (Table 5), asymptomatic patients with NCCM, including carriers (with the exception of LMNA and FLNC), with LVEF >50% and absence of inducible ventricular arrhythmias, can perform high-intensity sport. Low-to-moderate intensity is reserved if LVEF is 40-50%, and low intensity is reserved if LVEF<40%, if there is positive genotype for FLNC or LMNA, or there are inducible arrhythmias or symptoms. An annual follow-up of these patients is recommended.

Table 5. Exercise and sports participation recommendations for patients with NCCM

Recommendation	Class	Level
Competitive exercise/sport may be considered, if desired (with the exception of those for whom syncope could involve harm or death) for patients with left ventricular non-compaction cardiomyopathy who are asymptomatic, who have a left ventricular ejection fraction ≥50% and who did not have frequent or complex ventricular arrhythmias during ambulatory Holter monitoring or ergometry.	IIb	C
High- or very high-intensity exercise, including competitive sports, may be considered for patients with positive genotype/negative phenotype for left ventricular non-compaction cardiomyopathy (with the exception of laminin A/C or filamin C carriers).	IIb	C
High-intensity exercise or competitive sports are not recommended in patients with any of the following: Symptoms; left ventricular ejection fraction <40% or frequent or complex ventricular arrhythmias during ambulatory Holter monitoring or ergometry.	III	C

Source: own source based on Pelliccia *et al.*, 2021, https://goo.su/m705a.

There is no specific scientific evidence regarding the safety and efficacy of cardiac rehabilitation programs in patients with NCCM. Nonetheless, patients with left ventricular dysfunction should undergo a cardiac rehabilitation program, following recommendations similar to those available for patients with dilated cardiomyopathy.

Myocarditis

Myocarditis is a non-ischemic inflammatory pathology of the myocardium that can lead to ventricular dysfunction, heart failure, arrhythmias, and even sudden death (**Caforio** *et al.*, 2013). When this

inflammation also involves the pericardium, it is called myopericarditis.

The main etiology of myocarditis is viral in the developed world (enterovirus, parvovirus B-19, and human Herpesvirus type 6, SARS-CoV-2), although there are other etiologies, both infectious and non-infectious, such as inflammatory, toxic, or reactive (Lampejo et al., 2021), as shown in Table 6.

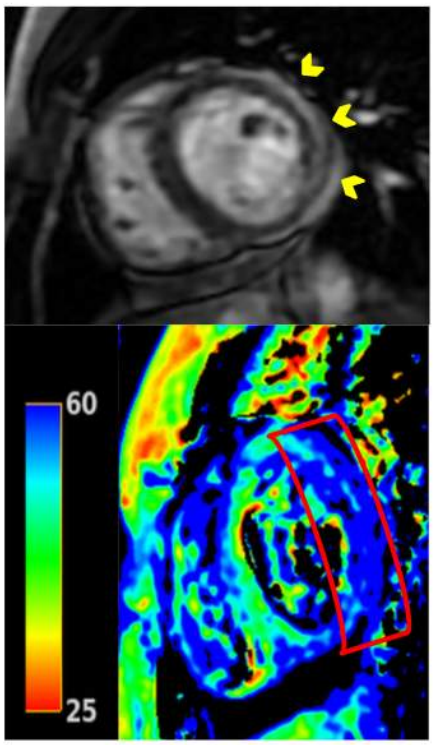
Table 6. Main causes of myocarditis

1. Infectious causes
Viral: Adenovirus, enterovirus (including *coxsackievirus*), parvovirus B19, influenza, SARS-coV and HIV-1.
Bacterial: Mycoplasma *pneumoniase*, spirochetes (including *Treponema pallidum* and *Borrelia burgdorferi*), *Staphylococcus spp* and *Streptococcus spp.*
Fungal: *Aspergillus spp.* and *Candida spp.*
Protozoal: *Plasmodium spp.* and *Toxoplasma spp.*
Helminths: *Schistosoma spp.* and *Toxocara spp.*
Rickettsial: *Rickettsia rickettsiae* and *Coxiella burnetii*.
2. Non-infectious causes
Hypersensitivity/Allergies: Antibiotics, anticonvulsants, and vaccines.
Systemic inflammatory disorders: Sarcoidosis, systemic lupus erythematosus, thyrotoxicosis, diabetes *mellitus*, inflammatory bowel disease, and granulomatosis with polyangiitis.
Toxic myocarditis: Stings/bites, amphetamines, cocaine, catecholamines, radiotherapy, chemotherapy, and immunotherapy with checkpoint inhibitors.
Post-transplant reaction: Such as post-cardiac transplantation or post-hematopoietic progenitor transplantation.
Autoreactive: Post-giant cell and lymphocytic myocarditis.

Source: own source based on Lampejo, *et al.*, 2021, https://goo.su/JJcT.

In recent years, special attention has been paid to myocarditis associated with COVID-19 and its vaccine. Recent meta-analyses (**Castiello** *et al.*, 2022) indicate that the incidence of COVID-19 myocarditis is difficult to estimate, probably exceeding 22 cases per 100,000 inhabitants, although it must be differentiated from myocardial damage (defined by troponin elevation) in the context of COVID-19 infection, the incidence of which is significantly higher (19-28 % of patients diagnosed with COVID). The diagnosis, treatment, and prognosis of these patients do not seem to differ from other types of viral myocarditis, although there are still no long-term studies to validate these data. With respect to vaccine-associated myocarditis, its incidence is much lower: 41 cases per million in U.S. series (**Morgan** *et al.*, 2022), being somewhat more frequent in young males (Figure 5). It is postulated that it may be related to testosterone and its role in modulating the immune response in myocarditis (**Marshall** *et al.*, 2021). Short-term management and prognosis do not seem to differ from other types of myocarditis, and long-term studies are needed to validate these hypotheses.

Figure 5. MRI. 21-year-old amateur male athlete, admitted for chest pain and low-grade fever, after administration of second dose of COVID-19 vaccine



Source: own source.

The MRI shows the presence of lateral late enhancement (upper image with yellow arrows), as well as increased T2 values (red rectangle) in the same place, diagnostic findings of myocarditis. Given the presence of active inflammation, it was recommended to avoid moderate-to-high intensity exercise in the next 6 months before a new reevaluation.

The clinical presentation of myocarditis is highly variable, and may be preceded by previous infection symptoms (rhinitis, diarrhea); dyspnea, chest pain, and general discomfort usually appear, although myocarditis can develop in a more severe and rapidly progressing manner (fulminant myocarditis) in the form of acute heart failure, cardiogenic shock, or sudden death. 50% of patients recover LVEF within 30 days, while ventricular dysfunction persists in 25% of them, and the remaining 25% of patients may experience progress to the fulminant phase (**Grn** *et al*., 2012).

For diagnosis, apart from the previously mentioned symptomatology, it is important to perform the following studies.

- **Laboratory tests:** These will show elevated troponins as a result of myocardial damage, as well as B-type natriuretic peptide (BNP), if associated with heart failure and acute phase reactants due to underlying inflammation. It is also important to request a toxicological test (cocaine, amphetamines), a thyroid profile, an autoimmune profile, and to evaluate parameters of involvement of other organs, mainly renal and hepatic.

- **ECG:** Not very sensitive; low voltages can be seen if associated with pericardial effusion, supraventricular or ventricular arrhythmias, left bundle branch block

and repolarization alterations, which may resemble an acute coronary syndrome.

- **Echocardiogram:** Generally, thickened myocardial walls (both of the LV and the RV) will be observed due to inflammation and edema. They are usually associated with a lesser or greater degree of ventricular dysfunction and/or segmental abnormalities, which can change (**Caforio** *et al.*, 2013). Pericardial effusion is possible if there is associated pericarditis.

- **CMR:** It has excellent sensitivity in detecting hyperemia and edema, aided by T1/T2 mapping and extracellular volume (ECV) (**Radenkovic** *et al.*, 2017). The existence of late gadolinium enhancement (LGE), which usually has a non-ischemic pattern, as well as its extension, is of vital importance, since it worsens the prognosis of these patients. A LGE >10% increases the probability of major medium- to long-term cardiovascular events by 79% (**Gati** *et al.*, 2018).

- **Endomyocardial biopsy:** It is the gold standard diagnostic technique, in addition to allowing, in a large proportion of cases, to ascertain the etiology of myocarditis (such as giant cell endocarditis, which also involves specific treatment, or combined use with polymerase chain reaction to identify specific microbiological agents in the sample) (**Cooper** *et al.,*

2009) and prognostic stratification of the most severe forms (**Anzini** *et al.*, 2013).

In sport, myocarditis is known to be the cause of about 4% of SCD (Finocchiaro et al., 2016), due to the exaggerated inflammatory response that can lead to lethal arrhythmias. Consequently, as long as such inflammatory response persists, athletes with myocarditis should refrain from any moderate-to-high intensity physical exercise (regardless of age, sex, or degree of LV systolic dysfunction), for 3-6 months, according to both American Heart Association (AHA) and ESC recommendations (**Maron** *et al.*, 2004; **Pelliccia** *et al.*, 2019). However, after this time, a complete recovery of the pro-inflammatory state must be verified before resuming the sporting activity:

- **Laboratory tests:** They must show a normalization of myocardial damage markers and inflammatory parameters.
- **Stress test and 48-hr Holter monitoring:** They must show minimal presence of exercise-induced arrhythmias.
- **Echocardiogram:** It must show a normalization of LVEF and absence of segmental abnormalities.

- **MRI:** It should be repeated after 6 months, if there was edema or LGE in the acute phase. Patients with a LGE >20% or persistent LV dysfunction should refrain from competitive or moderate/high intensity exercise (**Gati** *et al*., 2018), and only low-intensity exercise is allowed (40% of VO2 peak or 55% of maximal HR). In patients with persistent left ventricular dysfunction, the recommendations would be the ones for patients with heart failure with reduced LVEF.

Finally, it is important to remember that patients who have suffered myocarditis are at risk of recurrence, especially those with acute phase LGE, due to a higher rate of major cardiovascular events. For this reason, patients who have suffered myocarditis should be reevaluated annually (Pelliccia et al., 2021), according to the following recommendations (Table 7).

Table 7. Exercise and sports participation recommendations for patients with myocarditis

Recommendation	Class	Level
Comprehensive evaluation with imaging tests, ergometry and Holter monitoring is recommended after recovery from acute myocarditis to assess the risk of sudden cardiac death with exercise.	I	B
Resuming all types of competitive sports after 3-6 months should be recommended for patients who have had acute myocarditis and are symptom-free, with normal troponins and markers of inflammation, left ventricular ejection fraction assessed by transthoracic echocardiography and normal nuclear magnetic resonance, without evidence of inflammation or fibrosis on cardiac MRI, with good functional capacity, and absence of frequent or complex ventricular arrhythmias on ambulatory Holter monitoring or ergometry.	IIa	C
Recreational or competitive sports practice is not recommended for patients with a probable or confirmed diagnosis of myocarditis while inflammation is present.	III	C
Moderate-to-high intensity exercise is not recommended for a period of 3-6 months after having suffered acute myocarditis.	III	B
Recreational exercise or high-intensity competitive sports are not recommended for patients with residual myocardial scar and persistent left ventricular dysfunction.	III	C

Source: own source based on Pelliccia *et al.*, 2021, https://goo.su/m705a.

Pericarditis

Pericarditis is a pathology characterized by inflammation of the pericardium, which may or may not be preceded by upper respiratory or gastrointestinal symptoms (Imazio et al., 2015). As in myocarditis, viruses are the main etiology in the developed world (Adler et al., 2015), although there are other possible causes, as described in Table 8.

Table 8. Main causes of pericarditis

1) Infectious causes
Viral: Enterovirus *(coxsackievirus, echovirus*), herpesvirus, adenovirus, parvovirus B19.
Bacterial: *Mycobacterium tuberculosis, Coxiella burnetii, Borrelia burgdorferi, Pneumococcus spp., Meningococccus spp., Gonococcus spp., Streptococcus spp., Ataphylococcus spp., Haemophilus spp., Chlamydia spp., Mycoplasma spp., Legionella spp., Leptospira spp., Listeria spp., Providencia stuartii.*
Fungal: *Hisroplasma spp., Aspergillus spp., Blastomyces spp., Candida spp.*
Parasitic: *Echinococcus spp., Toxoplasma spp.*
2. Non-infectious causes
Autoimmune: Systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, scleroderma, systemic vasculitis, sarcoidosis, familial Mediterranean fever, inflammatory bowel disease, Still's syndrome.
Neoplastic: Primary tumors (rare, with pericardial mesothelioma being the most frequent) or metastatic tumors (frequent; the most frequent are lung, breast and lymphoma).
Metabolic: Uremia, myxedema, anorexia nervosa.
Traumatic/iatrogenic: By direct trauma (trauma, esophageal perforation), indirect trauma (non-penetrating thoracic damage, radiation) or late presentation trauma (post-infarction, post-pericardiotomy, post-radiofrequency ablation or pacemaker implantation).
Drug-related: Systemic lupus erythematosus (SLE)-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin), antineoplastic drugs (doxorubicin, cytosine arabinoside, T-fluorouracil, cyclophosphamide, penicillins, cyclophosphamide, thiazides, cyclosporine, bromocriptine, tumor necrosis factor [TNF] inhibitors).
Other causes: Amyloidosis, aortic dissection, pulmonary arterial hypertension, chronic heart failure, pericardial agenesis.

Source: own source based on Adler *et al.*, 2015, https://goo.su/dMIEDAu.

The form of presentation can be acute (<4-6 weeks), incessant (between 6 weeks and 3 months without remission), chronic (>3 months), and recurrent (recurrence after a first episode) (**Adler** *et al.*, 2015). The key feature is chest pain, typically with deep inspiration, worsening when lying down and improving when leaning forward.

For the diagnosis of acute pericarditis, according to the latest ESC pericarditis guidelines, 2 out of 4 of the following criteria are required (Adler et al., 2015): Typical pericarditic chest pain, pericardial friction rub, presence or worsening of pericardial effusion on the echocardiogram, and concave ST elevation or PR depression on the ECG. The existence of analytical inflammation or analytical inflammation detected by imaging techniques are criteria to support the diagnosis.

A CMR should be considered only in cases with diagnostic uncertainties or elevated troponin levels in the analysis, which would indicate myocardial damage.

The high-risk criteria, and therefore the need for hospitalization, according to the ESC guidelines, include: Persistent fever >38 °C, subacute course of severe pericardial effusion (>2 cm) or tamponade, and lack of response to treatment with nonsteroidal anti-

inflammatory drugs (NSAIDs) after 7 days. Other minor criteria to consider are the presence of myopericarditis, immunosuppressed individuals under anticoagulant therapy, or associated with rib trauma. The pharmacological treatment is based on the combination of anti-inflammatory medications (preferably NSAIDs) and colchicine in low doses, with a tapering regimen (**Imazio** *et al*., 2010).

Pericarditis, in general, is associated with a good prognosis and, in addition to what has been commented in myocarditis, it is necessary to stop practicing sports until the inflammatory phase is resolved, usually between 30 days and 3 months, depending on the severity of the condition (**Pelliccia** *et al.*, 2018), since the absence of rest is associated with a significant increase in recurrence. Prior to resuming sports practice, a reevaluation with laboratory tests, ECG, and echocardiogram is required (Table 9).

Table 9. Exercise and sports participation recommendations for patients with pericarditis

Recommendation	Class	Level
Resuming exercise, including competitive sports, is recommended between 30 days and 3 months after complete recovery from acute pericarditis, depending on clinical severity.	I	C
Recreational or competitive sports practice is not recommended for patients with a probable or confirmed diagnosis of pericarditis while inflammation is active, regardless of age, sex, or degree of left ventricular systolic dysfunction.	III	C
Participation in moderate-to-high intensity exercise, including competitive sports, is not recommended for patients with constrictive pericarditis.	III	C

Source: own source based on Pelliccia *et al.*, 2021, https://goo.su/m705a.

Patients with pericardial effusion, even if they are asymptomatic, should rest until resolution of the effusion. Those with progression to pericardial constriction should refrain from practicing competitive or moderate-to-high intensity exercise. Finally, those with myopericarditis should follow the same recommendations previously discussed for myocarditis.

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