**FÈDÈRATION INTERNATIONALE DE MÈDECINE DU SPORT /
THE INTERNATIONAL FEDERATION OF SPORTS MEDICINE**

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Recommendations for Medical Evaluation and Sports Participation in Athletes with a Family History of Sudden Cardiac Death

A statement for health professionals from the Scientific Commission of the International Federation of Sports Medicine (FIMS)

The sudden and unexpected cardiac death of a young athlete is a rare but dramatic and devastating event that strikes the core of our sensibilities and raises a number of important questions, including the feasibility of a strategy to prevent these catastrophes. The incidence of sudden death in young athletes is very low, estimated to be in a range of one out of 100,00 to 300,000 individuals per year. As proven by autopsy studies, an underlying cardiovascular disease (usually asymptomatic and undiagnosed during life) is responsible for most of these tragic events.

Inevitably, the question arises whether the risk for sudden cardiac death could be minimized by identifying those subjects at risk through a cardiovascular preparticipation evaluation and by restricting subjects at-risk from participating in competitive athletic activities. However, the most effective screening strategy for identifying these at-risk individuals is still uncertain. In addition, due to the enormous number of athletes and the rarity of the phenomenon, such screening procedures are unlikely to be cost-effective.

FIMS supports the concept that physicians and health professionals working in the area of sport and physical exercise should do as much as possible to identify life-threatening diseases in athletes, with the aim to reduce the cardiovascular risk associated with sport participation. Although detection of some of the conditions known to cause sudden cardiac death in athletes is difficult, it is wise to have a structured approach to the evaluation of the athletes with a family history of sudden cardiac death. In this perspective, the Scientific Commission of FIMS was prompted to establish recommendations intended to promote awareness for this compelling problem and to contribute to reducing the incidence of sudden death, especially in those individuals with increased risk.

Therefore, this position statement provides the clinician with recommendations for medical evaluation and participation in athletic activities for candidates who have a family history of sudden death from cardiac disease. The following recommendations should specifically be addressed to those

athletes with family evidence of one of the following diseases: hypertrophic cardiomyopathy (HCM); arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC); Brugada syndrome; long QT syndrome (LQTS); pre-excitation syndrome (WPW); Marfan syndrome; mitral valve prolapse (MVP); congenital coronary artery anomalies; premature coronary atherosclerosis; and undiagnosed sudden death in the family.

Any athlete suspected of having a family history of one of the diseases listed above should be carefully evaluated to determine whether he/she also has the suspected disease. Once evaluations are done, the recommendations for athletic activity produced by the 26th Bethesda Conference should be applied, based on the classification of sports as presented in Table 1 (1).

HYPERTROPHIC CARDIOMYOPATHY (HCM)

HCM is a primary and usually familial cardiac disease for which several disease-causing mutations in genes encoding proteins of the sarcomere have been identified. HCM presents heterogeneous morphologic alterations and clinical course. The characteristic of this disorder is a hypertrophied and non-dilated left ventricle, in the absence of other conditions that could produce the magnitude of hypertrophy present.

The following information was considered regarding this disease:

1. HCM is the most common structural cardiac abnormality associated with sudden death in young athletes.

2. Certain genetic mutations, such as Arg403Gln and cardiac troponin T mutations, are associated with a particularly adverse prognosis.

3. Occurrence of sudden death in the family is a marker of high risk for all affected members.

4. The risk for sudden death increases in youth until the third decade. After that age, the likelihood of sudden death decreases.

5. Morphologic features of HCM may not be present (and identifiable by echocardiography) until adolescence, and diagnosis may not be certain in children. The probability of correct diagnosis increases in advanced youth and adult age.

6. Genetic analysis of families where the gene mutation(s) is identified may diagnose with certainty the affected family members.

7. The prognostic value of genetic mutations in young asymptomatic carriers with mild (or absent) phenotypic expression of the disease is still uncertain, however.

Recommendations for diagnostic evaluation

1. Candidates with relatives (parents, siblings, grandparents, uncles, aunts, and cousins) who have been diagnosed with HCM should undergo a cardiovascular examination that includes at least a 12-lead ECG and 2D-echocardiography.

2. When these diagnostic tests suggest the diagnosis of HCM, a comprehensive cardiac evaluation (including exercise stress test, 24-hour ECG Holter monitoring) is recommended.

3. Genetic analysis is recommended when the mutation(s) responsible for the familial HCM is known.

Recommendations for participation in athletic activities

1. Candidates with unequivocal diagnosis of HCM who are < 35 years of age should avoid strenuous training and athletic competition. They should not participate in any competitive athletic activities, with the possible exception of the low-intensity physical activities (Class IA). Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competition increase the risk of sudden death in these patients.

2. Candidates with unequivocal diagnosis of HCM who are > 35 year of age and have no risk factors (e.g., family history of sudden death, syncope, sustained or non-sustained ventricular tachycardia, marked left ventricular hypertrophy, left ventricular outflow gradient >50 mmHg, exercise-induced ischemia or hypotension, and carriers of certain high-risk genes) may reasonably be considered at low risk for sudden cardiac death. In selected subjects, participation in mild to moderate athletic activities (Classes IA, IB, and IIA) may be allowed, as long as periodic evaluations are done at least once a year.

3. Candidates with HCM diagnosed among relatives, but who do not have evidence of HCM based on a 12-lead ECG and 2D-echocardiography, should be restricted from competitive athletic activities during adolescence until full body growth is reached. When familial genetic mutation is known, genetic testing is recommended to exclude the presence of the disease. In the absence of this analysis, presence of HCM should be periodically (yearly) checked until complete body growth is reached. After that, candidates who do not show evidence of HCM may participate in sport activities without restrictions, with the recommendation of periodic follow-up and testing.

4. If genetic analysis excludes the familial mutation responsible for HCM, the candidate should not

be restricted from athletic activities.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC) OR DYSPLASIA

ARVC is a primary cardiac disease, characterized by a progressive myocardial atrophy and fibro-fatty replacement. ARVC especially affects the right ventricle and is associated with ominous ventricular arrhythmia with risk of cardiac arrest.

The following information was considered regarding this disease:

1. The incidence of ARVC as a cause of sudden death in athletes is not completely defined and may be greater in certain geographical areas, such as the North-East of Italy.

2. Familial occurrence of this disease is found less consistently than with other diseases (such as HCM).

3. Although evidence is limited, there is agreement that exercise and sport participation may precipitate ventricular tachyarrhythmias leading to cardiac arrest.

4. Echocardiography and radionuclide right ventriculography may detect morphological and functional changes consistent with the disease, but may not be diagnostic when ARVC has only a limited extension. At present, MRI represents the most sensitive noninvasive diagnostic testing to identify (or raise suspicion of) this disease.

5. For diagnostic purposes, attention should be also paid to 12-lead ECG changes, such as T-wave inversion in precordial leads V1 to V3 (in subjects < 15 years) and greater QT-interval dispersion (> 50 msec) in right precordial leads. Premature ventricular contractions with left bundle branch block morphology and vertical axis also support the presence of the disease.

6. About half of the subjects with ARVC may be symptomatic (with syncope and/or palpitations) before the occurrence of sudden death.

Recommendations for diagnostic evaluation

1. Candidates with diagnosis of ARVC among family members should undergo a cardiac evaluation that includes, at least, 12-lead ECG and 2D-echocardiography. In addition, Holter monitoring, exercise testing, QT-interval dispersion and signal-average ECG are highly recommended.

2. If these diagnostic tests cannot clarify the diagnosis and a doubt persists for the presence of ARVC, MRI scan or right ventricular angiography are recommended.

Recommendations for athletic activity

1. Candidates with unequivocal diagnosis of ARVC should be restricted from athletic activities, regardless of the presence of symptoms or ventricular arrhythmia. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competition increase the risk of sudden death in these patients.

2. When the diagnosis of ARVC is equivocal in the candidate, but the disease is present among relatives, efforts should be made to exclude ARVC by using imaging techniques (MRI) or right ventricular angiography and endomyocardial biopsy. If the disease cannot be excluded with certainty, the candidate should be restricted from sports activities.

3. When the diagnosis of ARVC has been reasonably excluded, the candidate can participate in athletic activities without restrictions. However, he/she should be encouraged to pass periodic (yearly) cardiac evaluations.

BRUGADA SYNDROME

This syndrome defines a primary and familial cardiac disease that is characterized by a 12-lead ECG pattern of right bundle branch block and ST-segment elevation in precordial leads V1 to V3. It is usually associated with rapid polymorphic ventricular arrhythmia leading to sudden death.

Recommendations for diagnostic evaluation

1. Candidates with Brugada syndrome among family members should undergo a cardiac evaluation that minimally includes a 12-lead ECG, Holter monitoring and/or exercise testing. The typical 12-lead ECG pattern of the syndrome may not be so evident under basal conditions and can be unmasked by intravenous administration of antiarrhythmic drugs (ajmaline, flecaineide). There is also an ongoing effort to use genetic analyses to diagnose Brugada syndrome.

Recommendations for athletic activity

1. Candidates with diagnosed Brugada syndrome should be restricted from athletic activities, regardless of the presence of symptoms or ventricular arrhythmia. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competitions increase the risk of sudden death in these patients.

2. If genetic and non-invasive diagnostic testing exclude the presence of the familial mutation responsible for the Brugada syndrome, the candidate should not be restricted from athletic activities.

However, he/she should be encouraged to pass periodic (yearly) cardiac evaluations.

LONG QT SYNDROME (LQTS)

Congenital LQTS is predominantly a hereditary disorder, usually transmitted in an autosomal dominant manner. In a smaller number of affected subjects, transmission is autosomal recessive and associated with sensorineural deafness. This disorder is associated with torsade de pointes, usually precipitated by emotional circumstances and/or physical activity, and presents clinically with syncope and sudden death.

The following information was considered regarding this condition:

1. LQTS is a relatively rare cause of sudden death in young individuals, including athletes, and usually occurs in subjects with a history of recurrent syncope.

2. Sudden death has been found in family members and carriers of LQTS who do not show long QT intervals on their resting 12-lead ECG.

3. There is an ongoing effort to use genetic analyses to diagnose LQTS. There are families in which it is possible to characterize genetic alterations and to identify family members who are asymptomatic carriers. In the near future, major breakthroughs are anticipated that may enable a widespread use of genetic diagnosis of carriers.

Recommendations for diagnostic evaluation

Candidates who have family members with diagnosis of LQTS should undergo:

1. Resting 12-lead ECG with special consideration of QT-interval and the morphology of T-waves (alternans, notched T, bifid T-waves). In addition, 24-hour Holter monitoring and exercise testing should be performed with attention to arrhythmia, QT-interval and T-wave morphology changes at various hours of the day and night, or during exercise.

2. Genetic testing should be performed (if available) to identify family members who are asymptomatic carriers of the disease.

Recommendations for athletic activity

1. Candidates who have evidence of LQTS, including those recognized as asymptomatic carriers, should be restricted from athletic activities, regardless of the presence of symptoms or ventricular arrhythmia.

2. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competition increase the risk of sudden death.

3. In the absence of results from a genetic analysis, candidates in whom diagnosis of LQTS could not be excluded on the basis of usual diagnostic testing should be restricted from athletic activities.

PREEXCITATION SYNDROME (WPW)

The syndrome initially described by Wolff, Parkinson, and White identifies individuals who are prone to paroxysmal tachycardia and who have a 12-lead ECG showing a shortened PR interval with slurred upstroke of the QRS complex (delta wave).

The following information was considered regarding this pathologic condition:

1. Although relatives of candidates with WPW may have a higher incidence of WPW, this disease does not show autosomal dominant or recessive inheritance.

2. The incidence of sudden death in asymptomatic WPW is very low and in the range of <1 per 1000 patients / year. However, sudden death may be the first clinical presentation in these subjects and may occur also in adult or mature age.

3. The vast majority of WPW patients are diagnosed by the resting 12-lead ECG pattern. However, it is not so uncommon that the preexcitation pattern may be present only occasionally in the resting 12-lead ECG, due to changes in the accessory pathway refractoriness.

Recommendations for diagnostic evaluation for individuals with suspected WPW

1. Candidates with first-degree relatives who have WPW should undergo a 12-lead ECG.

2. If there is evidence of pre-excitation in the 12-lead ECG, an assessment of risk for ventricular fibrillation (responsible for sudden cardiac death) should be recommended. The risk stratification may be reliably based on transesophageal or intracavity electrophysiological (EP) studies that attempt to identify the shortest RR interval during induced atrial fibrillation (high risk when < 200 msec at rest or < 200 msec during exercise), the presence of multiple accessory pathways and enhanced atrial irritability.

Recommendations for athletic activity

1. Candidates with no evidence of WPW should not be restricted from athletic activities.

2. Candidates with WPW who are judged at low risk on the basis of an EP study should not be restricted from athletic activities, with the exception of those activities performed in an at-risk environment (such as scuba diving, climbing, etc.).

3. Candidates with WPW who are judged at high risk on the basis of an EP study should be restricted to only mild athletic activities (class IA). In these cases, radiofrequency catheter ablation of the accessory pathway should be considered and recommended prior to participation in high-intensity athletic activity.

4. Candidates with WPW and a history of syncope or documented atrial flutter/fibrillation are considered at high risk and should not participate in any competitive athletic activity, until they undergo successful ablation of the accessory pathway.

5. Candidates who have undergone successful accessory pathway ablation, who are asymptomatic and who wish to participate in high-intensity athletic activity should undergo repeated electrophysiologic evaluation to confirm the efficacy of ablation and absence of inducible arrhythmia.

MARFAN SYNDROME

Marfan syndrome is an inherited autosomal disorder affecting the connective tissue, presenting clinically with musculoskeletal, ocular, cardiac and great-vessel abnormalities.

The following information was considered regarding this syndrome:

1. Death occurs from acute aortic dissection into a hemithorax or into the pericardium. Exercise and athletic activity increase the risk of acute dissection.

2. Most cases of death due to aortic dissection in young people occur in patients with Marfan syndrome or isolated aortic anuloectasia.

Recommendations for diagnostic evaluation

1. Candidates from a family with a definite diagnosis of Marfan syndrome should undergo a comprehensive musculoskeletal, ocular and cardiac evaluation (including 2D-echocardiogram). Genetic testing exploring the mutation of gene-encoding fibrillin 1 associated with this disease (if available) is recommended in these candidates in order to exclude the presence of genetic defects with only a limited phenotypic expression.

2. If only musculoskeletal features (arachnodactyly, tall stature, pectus excavatum, kyphoscoliosis, i.e., a Marfanoid habitus) are present, also in the apparent absence of the disease among relatives, the same diagnostic testing (including echocardiography) should be done to exclude the occurrence of sporadic forms of the disease.

3. When results derived from the non-invasive diagnostic tests

cited above are equivocal, genetic testing is necessary to exclude the mutation of gene-encoding fibrillin 1 associated with this disease.

Recommendations for athletic activity

1. If there is no evidence for Marfan syndrome, candidates should not be restricted from athletic activities.

2. Candidates with unequivocal diagnosis of Marfan syndrome should be restricted from all athletic activities, with the possible exception of the mild (class IA) activities. In that case, echocardiographic measurement of aortic root dimension should be repeated every six months. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competition increase the risk of aortic dilatation and dissection.

3. Candidates with only Marfanoid habitus but no evidence of the disease should not be restricted from athletic activities. They should be encouraged to pass periodic (yearly) evaluations, including 2D-echocardiography.

MITRAL VALVE PROLAPSE (MVP)

MVP is characterized by the myxomatous degeneration of the valve collageneous layer, with a wide spectrum of morphological and clinical presentation.

The following information was considered regarding this condition:

1. MVP is very common in the general and in the athlete population, with a prevalence of 3-5%. Sometimes MVP has a familial incidence, either as a primary valve disorder or as part of a generalized connective tissue abnormality.

2. Although MVP is usually a benign condition, in a very few instances MVP has been reported as the only cardiac abnormality in young subjects who have died suddenly. Risk factors for sudden death in patients with MVP are considered to be: 1) family history of sudden death; 2) recurrent syncopal episodes; 3) prolonged QT interval; 4) marked morphological alterations of the mitral valve and moderate to severe mitral regurgitation; 5) complex ventricular arrhythmia (frequent, polymorphic PVCs and repeated NSVT runs); and 6) embolic events.

Recommendations for diagnostic evaluation

1. Candidates with relatives having a proven diagnosis of MVP should be screened by auscultation and echocardiography.

2. When a candidate is diagnosed with MVP, a thorough family and personal history, echocardiography, 24-hour

Holter monitoring and maximal exercise testing should be done.

Recommendations for athletic activity

1. No restrictions apply to candidates with evidence of uncomplicated MVP.

2. Candidates with MVP associated with any of the complications cited above should be restricted to low-intensity sports only (Class IA). High-intensive athletic activities should be avoided based on the likelihood that intense athletic training and competition increase the risk of valve degeneration, worsen the mitral regurgitation and enhance the risk of sudden death in these patients.

CONGENITAL CORONARY ARTERY ANOMALIES

Congenital coronary anomalies present a spectrum of different conditions, including: 1) origin from the wrong aortic sinus (most commonly, both right and left coronary arteries arising from either the right sinus or the left sinus); 2) left coronary artery origin from pulmonary trunk; 3) high takeoff of coronary arteries; or 4) stenosis of coronary ostia attributable to valvelike ridge. In the case of coronary artery origin from the wrong aortic sinus, the mechanism leading to myocardial ischemia and sudden death is related to the compression of the abnormal coronary vessel between the exercise-induced dilated ascending aorta and pulmonary trunk. Another postulated mechanism is the slit-like opening of the abnormal ostium that is further narrowed during exercise.

The following information was considered regarding this condition:

1. Sudden death may be the first clinical manifestation of this pathologic condition in young and adult individuals, and is usually precipitated by exercise.

2. Chest pain is usually absent in these subjects, about 25% of whom may experience prodromal symptoms in the form of palpitations and/or syncope due to ventricular arrhythmia during effort.

3. The mechanisms of ischemia are difficult to reproduce in the clinical setting and exercise ECG testing is usually negative in these individuals.

Recommendations for diagnostic evaluation

1. Candidates with a relative having a proven diagnosis of congenital coronary artery anomaly should be evaluated by a selective echocardiographic study of the aortic root with visualization of the origin and proximal course of coronary arteries. Additional investigation includes 12-lead ECG, exercise ECG and 24-hour ECG Holter monitoring.

2. If this pathologic condition is suspected from noninvasive testing, coronary angiography should be performed.

Recommendations for athletic activity

1. Candidates diagnosed with congenital coronary anomaly should be restricted from athletic activities, regardless of the presence of symptoms or ventricular arrhythmia. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competition increase the risk of myocardial ischemia leading to sudden death in these patients.

PREMATURE CORONARY ATHEROSCLEROSIS

Multivessel atherosclerotic coronary artery disease, usually associated with postinfarction scars, is the most common pathologic finding in adult and elderly athletes who die suddenly during exercise.

The following information was considered regarding this condition:

1. Coronary atherosclerosis is the most common reason for myocardial ischemia beyond the age of 30 years.

2. Ischemic heart disease is the dominant cause of exercise-related sudden death in adults and senior athletes.

Recommendations for diagnostic evaluation

1. If a first-degree relative of the candidate is known to have suffered premature coronary disease (under the age of 30), the profile of risk factors for coronary atherosclerosis, including blood lipids, should be evaluated.

2. If one or more risk factors are present, a maximal exercise test should be performed.

3. An exercise test should also be performed in any male candidate above the age of 35 years (45 years if a woman) with a family history of ischemic heart disease or sudden death.

4. If the exercise ECG gives equivocal evidence of myocardial ischemia, nuclear scintigraphy is recommended.

Recommendations for athletic activity

1. As long as there is no evidence of coronary disease, candidates should not be restricted from athletic activities.

2. For candidates with risk factors for atherosclerotic coronary artery disease, a strategy for reducing the risk profile should be undertaken. Candidates with familial dyslipidemia who are being treated with HMG CoA reductase inhibitors should be observed for muscle damage.

3. If there is evidence for ischemic heart disease, candidates should be restricted from competitive athletic activities. Candidates should not participate in competitive athletic activities, based on the likelihood that intense athletic training and competitions increase the risk of myocardial ischemia leading to sudden death. However, regular recreational and leisure physical activity should be recommended.

UNDIAGNOSED SUDDEN DEATH IN THE FAMILY

This definition indicates the absence of a structural cardiac abnormality identified at pathologic examination being responsible for sudden cardiac death. The cause of sudden death in young athletes remains unclear in about 5 to 10%.

Recommendations for diagnostic evaluation

1. In candidates with a family history of sudden death of unknown etiology, it is important to exclude the presence of all the pathologic cardiac conditions cited above that are potentially responsible for sudden death. For this purpose, any existing information on the circumstances of death, as well as from the autopsy (if one was performed should be obtained.

2. If such information cannot be obtained, comprehensive cardiovascular testing should be undertaken to exclude the structural cardiac diseases that can lead to sudden death. These diagnostic tests include (but are not limited to) a 12-lead ECG, 2D-echocardiography and exercise testing. The Holter monitoring, signal-averaged ECG, MRI (or invasive testing) should also be considered according to the specific clinical suspicion.

Recommendations for athletic activity

1. Only when there is a reasonably clinical certainty that the candidate does not have a structural cardiac disease at risk for sudden death, should the candidate be permitted to participate in athletic activity without restrictions.

2. Depending on the diagnosis, candidates with other cardiac conditions should be advised accordingly.

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