Syncope in the young athlete: Assessment of prognosis in subjects with hypertrophic cardiomyopathy

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Abstract Syncope is a common but concerning event in young athletes. Although mostly due to benign reflex causes, syncope may be arrhythmic and precede sudden cardiac death. Efforts must therefore be made to distinguish post-exertional syncope from syncope during exercise, which can be an ominous sign of a possible underlying heart disease, such as hypertrophic cardiomyopathy. Prevention requires cooperation between physician and athlete, in order to identify individuals at risk and to protect them from sudden death. Solving this diagnostic dilemma may lead to recommendations for athletes to be cleared to play or disqualified from competitive sports, and presents challenging and controversial decisions to the health care provider that can prove difficult to implement. Although exercise contributes to physical and psychological well-being, there are insufficient data to indicate whether an athlete with hypertrophic cardiomyopathy diagnosed after a syncopal episode can safely resume competitive physical activity. The purpose of this study was to review the literature on syncope in young athletes and its relationship to individuals with hypertrophic cardiomyopathy, in order to enable accurate assessment of prognosis and the possibility of resuming competitive sports.

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Keywords
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Sincope no jovem atleta: uma avaliação do prognóstico em doentes com cardiomiopatia hipertrófica

Resumo A sincope nos jovens atletas é um acontecimento comum e preocupante. Embora os mecanismos benignos reflexos predominem, a sincope pode ter causa arrítmica e preceder a morte súbita cardíaca. Como tal, devem ser feitos esforços para distinguir sincope pós-exercício físico da sincope observada durante o exercício físico, o que pode ser uma constatação ameaçadora de uma possível doença cardíaca subjacente, tal como a cardiomiopatia hipertrófica. A prevenção e estratificação por parte do médico e do atleta são tarefas importantes, que

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Introduction

Syncope is a sudden and transient loss of consciousness (TLoC) accompanied by loss of postural tone, due to transient global cerebral hypoperfusion.\textsuperscript{1-4} It is characterized by rapid onset and spontaneous complete recovery without neurological sequelae, although feelings of fatigue may be present.\textsuperscript{1-4} Episodes are typically brief – no longer than 20 s in reflex syncope – but can last up to several minutes in some individuals.\textsuperscript{1,2} In contrast to true syncope, presyncope may be described as a feeling of lightheadedness that precedes or almost results in collapse, without loss of consciousness.\textsuperscript{2,7}

In general, athletes are defined as those who participate in sports requiring intense systematic training and regular competition against others in an organized team or individual sport.\textsuperscript{6,9} Young competitive athletes (aged <35 years) are widely regarded as a special subgroup of healthy individuals with a unique lifestyle, who are seemingly invulnerable and capable of extraordinary physical achievement.\textsuperscript{9,10}

Although the long-term overall benefit of regular exercise has been shown to reduce mortality due to cardiovascular events, the risk of an acute event is transiently increased during and immediately after acute, particularly vigorous, exercise.\textsuperscript{6,8,11}

Athletes with syncope represent a unique challenge for the physician, as the potential causes range from benign neurally mediated episodes to underlying heart disease such as hypertrophic cardiomyopathy (HCM), which may be a harbinger of sudden cardiac death (SCD).\textsuperscript{1,8,11-17} Irrespective of age, sudden death during competitive or recreational exercise is a devastating event that has a significant impact on both lay and medical communities, owing to its high profile and the awareness that its causes are clinically identifiable and tractable.\textsuperscript{10,18} Thus, the major goals in the management of syncope are the early detection of malignant variants, avoidance of SCD, and the prevention of recurrent syncopal episodes, in order to improve patients’ quality of life.\textsuperscript{5,6,19}

In fact, due to the unique structure and pressures of organized athletic competition or to their unwillingness to consider the importance of warning symptoms like presyncope or syncope, athletes with heart disease may not always correctly judge when it is prudent to cease participation in sports.\textsuperscript{6,9} Young healthy individuals who report a TLoC during exercise require a focused and thorough assessment to identify potentially lethal cardiac disorders.\textsuperscript{7,12,14}

The purpose of this study was to review the literature on syncope in young athletes and its relationship to patients with HCM, in order to enable accurate assessment of prognosis and the possibility of resuming competitive sports.

Methods

MEDLINE was searched for relevant Portuguese- and English-language human studies published between January 1, 2005 and October 1, 2015, using the search terms (“athletes”[MeSH Terms] OR “athletes”[All Fields]) AND (“syncope”[MeSH Terms] OR “syncope”[All Fields]) OR (“cardiomyopathy, hypertrophic”[MeSH Terms] OR (“cardiomyopathy”[All Fields] AND “hypertrophic”[All Fields])) OR (“hypertrophic cardiomyopathy”[All Fields] OR (“hypertrophic”[All Fields] AND “cardiomyopathy”[All Fields])). A total of 278 matches were found.

After screening of titles and abstracts for an initial assessment of eligibility, the full text of potentially relevant articles was obtained and reviewed for final decisions on inclusion.

Recent publications (until March 31, 2016) and citations from the initial selection were added to the search results. The final study included 56 papers.

Epidemiology

Previous studies consistently show that syncope accounts for up to 3% of all hospital emergency visits and 1-6% of hospital admissions.\textsuperscript{20,21} However, the percentage of patients presenting with syncope at emergency departments who are hospitalized varies significantly.\textsuperscript{19}

The prevalence of syncope in the general population is high, up to 40%.\textsuperscript{2} Its incidence is estimated at 6.2/1000 person-years, increasing with age but with a peak of first fains in patients aged 10-30 years.\textsuperscript{3,12,22}

In the Framingham study, in a population of 7814 individuals over a 26-year follow-up, the incidence of syncope was similar between men and women, but almost double in participants with a history of cardiovascular disease.\textsuperscript{1} The risk of recurrence was particularly high among participants with
cardiac syncope, and this was associated with increased risk of premature death and cardiovascular events. However, most syncope in young individuals is neurally mediated, also known as reflex or vasovagal syncope. Nevertheless, little is known about its incidence in athletes. Colivicchi et al. reported a cohort of 7568 athletes undergoing preparticipation screening, of whom 474 (6.2%) reported at least one syncope in the preceding five years. Most of these (86.7%) were reported as unrelated to exercise and occurring during ordinary daily activities, 12% were post-exertional and usually occurred soon after cessation of exercise, and only 1.3% of cases were during exercise (with diagnoses of HCM, right ventricular outflow tract tachycardia and exercise-induced neurally mediated syncope). On follow-up, both subjects with HCM and right ventricular outflow tract tachycardia were permanently disqualified from competitive sports activity. Those with a prior history of syncope had a recurrence of 20.3 per 1000 subject-years, whereas those without a prior history of syncope had an incidence of 2.2 per 1000 subject-years. All recurrence episodes were consistent with benign syncope.

In order to estimate the absolute number of sudden deaths in US competitive athletes, Maron et al. assembled a large registry of 1866 athletes, between eight and 39 years old, who died suddenly (or survived cardiac arrest) over a 27-year follow-up period. Sudden deaths were predominantly due to cardiovascular disease (56%), with HCM as the most common underlying organic heart disease (36%).

In 2003, Corrado and colleagues published a 21-year prospective cohort study of all young people of the Veneto region of Italy. They demonstrated that the higher risk of SCD in young competitive athletes was strongly related to underlying cardiovascular disorders such as arrhythmogenic right ventricular cardiomyopathy and congenital coronary artery anomalies but not HCM; they had previously reported that HCM was successfully screened by preparticipation assessment and affected athletes were disqualified.

Pathophysiology

There are multiple mechanisms that may lead to TLoC. They are classified as traumatic forms, such as concussion, or non-traumatic forms, such as syncope, epileptic seizures, psychogenic and other rare miscellaneous causes.

There may be a prodromal period, mainly in neurally mediated syncope and secondary to orthostatic hypotension, in which various symptoms (e.g. lightheadedness, diaphoresis, chest pain, palpitations, nausea, weakness and visual blurring) warn that syncope is imminent. However, TLoC usually occurs without warning, particularly when cardiac syncope is the cause.

Although syncope is almost always benign in young athletes and rarely reaches the attention of a clinician, it may be the first symptom of several cardiac diseases, including HCM, arrhythmogenic right ventricular cardiomyopathy and anomalous coronary artery origin, all of which have been recognized as causes of SCD in this population.

HCM is a heterogeneous disease, attributed to mutations in genes that encode sarcomere proteins, and with autosomal dominant inheritance in most cases. It is characterized by widespread and bizarre myocardial hypertrophy associated with diffuse fibrosis and no identifiable cause such as hypertension or congenital heart disease.

Even in the absence of the typical risk factors associated with HCM, extrapolation of risk level from non-athletes to highly trained competitive athletes is tenuous due to the unstable electrophysiologic substrate and its propensity for potentially lethal ventricular arrhythmias during the physiological stresses inherent to exercise (e.g., catecholamine surge and disturbances in blood volume, electrolytes and hydration).

Although the basic causes of syncope in HCM can be broadly divided into primary hemodynamic mechanisms (such as reflex syncope) and arrhythmias, in most cases it results from a combination of factors which influence the circulatory balance.

Prognosis

Over the last few years, due to better diagnostic procedures, there has been increasing recognition of the impact that prolonged training has on cardiac remodeling. Known as athlete’s heart, this physiological modification to exercise is generally regarded as a cardiovascular adaptation to systematic training characterized by a benign increase in cardiac mass, with specific circulatory and cardiac morphological alterations, and leading to electrocardiographic and echocardiographic changes. Differentiation between athlete’s heart and a pathological condition with the potential for SCD such as HCM is not easy, but is essential to avoid inappropriate disqualification from sport.

Syncope during exercise

It is important to note that exercise-induced neurally mediated syncope typically occurs in subjects without heart disease. Exercise-induced neurally mediated syncope is in fact syncope that occurs after exercise or during pauses in play (e.g. time outs or shooting foul shots) and is unlikely to occur during exertion. Syncope or presyncope occurring during exertion is more likely to be life-threatening than that occurring at rest.

With regard to prognosis, in patients with structural heart disease the occurrence of syncope during effort almost invariably predicts a cardiac cause of syncope. As in the non-athlete, subjects with no organic heart disease are at low risk of SCD. By contrast, the presence of a major cardiac condition is highly predictive of sudden death. Syncope itself is not a risk factor for poor outcomes, which are rather associated with the severity of the underlying disease.

Only ventricular arrhythmias associated with structurally normal hearts are curable (the cure rate with radiofrequency ablation is approximately 90%). Therefore, in patients with structural heart disease radiofrequency ablation cannot be relied upon to protect against SCD.

It is important to emphasize that, until a diagnosis is established or pathological causes excluded, athletes with exercise-induced syncope should be excluded from further sports participation, even in the presence of a free-standing automated external defibrillator.
According to the 2015 American Heart Association/American College of Cardiology (AHA/ACC)\textsuperscript{26} and the 2005 European Society of Cardiology (ESC)\textsuperscript{33} guidelines, all athletes with a diagnosis of HCM should abstain from moderate and high-intensity competition, but not from low-intensity, low-static sports (class IA) such as golf, bowling or cricket. This recommendation is independent of age, gender, symptoms, extent of hypertrophy, left ventricular outflow obstruction, late gadolinium enhancement on cardiovascular magnetic resonance and previous major therapeutic interventions, such as surgical myectomy or alcohol ablation,\textsuperscript{26,33} since it is based on the premise that in some cardiomyopathies, including HCM, competitive sports and vigorous exercise can increase the likelihood of SCD by promoting disease progression or exacerbating the arrhythmogenic myocardium over time.\textsuperscript{34-37}

Frequently, disqualification from competition leads to significant psychological effects and may also have considerable financial consequences for patients participating, or planning to participate, at a professional level.\textsuperscript{34}

Several factors, such as habitual moderate-intensity exercise, may reduce the risks of sports participation.\textsuperscript{35,38,39} In the Physician’s Health Study, although bouts of strenuous exercise were associated with a transient increase in the risk of SCD, habitual vigorous exertion, enough “to work up a sweat”, attenuated this hazard.\textsuperscript{40} Therefore, the “weekend athlete” phenomenon of sporadic high-intensity activity should be discouraged, and patients wishing to exercise vigorously should do so regularly.\textsuperscript{38,39}

The participation of elementary and high-school students in physical education classes creates a dilemma for parents, teachers and physicians.\textsuperscript{35,41} Together, they should undertake a reasonable analysis of physical education class requirements, and participation in school gym classes should be individualized as much as possible.\textsuperscript{41} It is also important to assure appropriate hydration during physical activity, especially in patients with outflow tract obstruction and/or small and hyperdynamic left ventricular chambers.\textsuperscript{35}

Several therapeutic strategies have been developed for patients with HCM, including drugs, surgery, alcohol septal ablation, and placement of a pacemaker or implantable cardioverter-defibrillator (ICD).\textsuperscript{31} ICDs are highly effective and probably the only way to restore normal rhythm and prevent SCD.\textsuperscript{43}

**Genotype positive-phenotype negative hypertrophic cardiomyopathy**

The evidence on which to base the decision whether to disqualify individuals who have only preclinical signs of HCM from playing competitive sports, especially in the absence of symptoms or family history of SCD, is the subject of debate.\textsuperscript{26} Although family genetic screening for HCM is widely implemented in clinical practice, its natural history and the clinical significance of genetic findings remain little understood.\textsuperscript{35,41,44} As a consequence, physicians face the problem of establishing protocols for sports participation by athletes who are genotype positive-phenotype negative for HCM.\textsuperscript{35,41} Based on the level of current knowledge, if detailed assessment of the patient remains normal, exclusion from competitive sports, particularly those with high cardiac demand, is recommended by the ESC but not by the AHA/ACC.\textsuperscript{26,33} The ESC is more selective in restricting these borderline athletes to recreational and non-competitive sport activities.\textsuperscript{33,41} This recommendation is based on the assumption that, in the majority of gene carriers, systematic intense physical activity can trigger cellular mechanisms leading to the HCM phenotype (i.e., left ventricular hypertrophy) and clinical complications such as ventricular arrhythmias.\textsuperscript{33,35,41}

With these theoretical risks in mind, both the ESC and AHA/ACC guidelines suggest similar prudent recommendations for athletes with preclinical HCM, including regular follow-up and close monitoring, especially if there is a family history of HCM or SCD.\textsuperscript{26,33}

Thus, in order to take into account the comfort level of the athlete with regard to continuing to compete with an uncertain level of risk, physician and athlete should have a fully informed discussion about the risks and benefits of a particular sporting activity.\textsuperscript{32,41}

**Myocardial bridging**

Myocardial bridging (MB), in which a segment of a major epicardial coronary artery runs intramurally through the myocardium, is a relatively common morphological component of HCM, often observed in angiographic series.\textsuperscript{45-47}

During systolic contraction, the surrounding myocardium compresses the coronary artery lumen and impedes blood flow.\textsuperscript{45} However, despite the high prevalence of MB in HCM, data on its contribution to the well-documented risk of exercise-related cardiac events in HCM are sparse and its impact on outcomes remains the subject of debate.\textsuperscript{45-47}

According to the AHA/ACC guidelines, athletes with MB and evidence of myocardial ischemia or prior myocardial infarction should be restricted to low to moderate intensity competitive sports. Otherwise, they may participate in all competitive sports.\textsuperscript{48}

In a recent study of individuals with HCM, Tian et al. concluded that the presence of MB was not a predictor for adverse clinical outcomes, since it was not evidently associated with increased risk for all-cause death, cardiovascular death, SCD and deterioration of heart failure.\textsuperscript{49} This is due to the unique hemodynamic features of the coronary arterial system, in which forward flow occurs predominantly in diastole and compression occurs during systole; the extent of obstruction is influenced by anatomical features of MB (such as length and location) and by the shape of coronary narrowing.\textsuperscript{46,49} Coronary artery compression caused by MB may show elliptical narrowing, whose effects on coronary flow are less significant than concentric narrowing, which is typical of coronary heart disease.\textsuperscript{46} Nevertheless, pathologic studies suggest that vessels more deeply embedded in the myocardium (2-3 mm) are most vulnerable to exercise-induced ischemia.\textsuperscript{48,49}

Therefore, deciding on a case-by-case basis appears to be a reasonable approach to the athlete with suspected MB, and management can include stepwise escalation of therapy with periodic exercise stress testing to assess efficacy.\textsuperscript{45,49}
Implantable cardioverter-defibrillator therapy in young athletes

Some athletes view their ICD as a universally protective device that enables them to exercise at higher intensities than advised. Although an athlete’s desire to perform high-intensity sports should not be taken as an indication for the use of a prophylactic ICD, given its effectiveness, healthcare providers will increasingly be faced with medical and ethical challenges regarding sports participation of HCM patients with ICDs.

However, the unique physiological milieu and extreme conditions of competitive sports mean that the reliability of ICDs in such settings is unpredictable and probably suboptimal. The risks of competitive sports include not only a greater frequency of ventricular arrhythmias, but also higher defibrillation thresholds secondary to exercise-related metabolic changes and hence potential failure of a shock to convert a life-threatening arrhythmia, inappropriate shocks, damage to the device and danger of injury due to TLOC following an arrhythmia or a shock, potentially threatening the athlete and other participants.

According to the 2005 American College of Cardiology 36th Bethesda Conference (BC36), the placement of an ICD in an HCM patient does not change the competitive sports recommendations, i.e., that restriction from participation in contact and most non-contact sports is advisable. This recommendation is being reassessed by the AHA/ACC on the basis of recent data. Furthermore, athletes with ICDs, if they have a history of ventricular flutter or ventricular fibrillation, may only engage in class IA sports after a period of three months without episodes requiring device therapy. When appropriate or inappropriate ICD interventions occur, a six-week period refraining from sports should be considered to assess the effect of changes in ICD programming.

Whether the presence of an ICD should preclude competitive sports participation is controversial. At the heart of this dilemma is a lack of clinical or experimental evidence of the natural history of athletes with an ICD participating in competitive sports. If an ICD shock can effectively terminate an arrhythmia during sports without adverse sequelae, the decision becomes one of quality of life. According to the AHA/ACC, athletes with ICDs, participation in class IA sports is reasonable after a period of three months without episodes of ventricular flutter or ventricular fibrillation requiring device therapy (no information is given about the presence of underlying structural heart disease).

In 2003, in a group of 132 ICD recipients with HCM, Begley et al. observed that 88% of appropriate ICD discharges occurred during sedentary or mild to moderate activity. In eight patients (12%) shocks were delivered during strenuous competitive sports (50% of these during basketball or soccer games) and all were successful.

A survey of Heart Rhythm Society (HRS) members caring for patients with an ICD (614 respondents), physician recommendations for sports participation for patients with ICD varied extensively, and most respondents individualized instructions based on the underlying condition. Only 10% recommended avoidance of all sports more vigorous than golf or bowling. Most (76%) recommended avoidance of contact sports, with about half advising against competitive sports or those with a particular likelihood of injury, for instance rock climbing or bungee jumping. Overall, 70% of patients with ICDs participated in vigorous and even competitive sports, with basketball, running and skiing being the most cited. Although shocks were common during sports (40% reported patients receiving ICD shocks), most commonly running and basketball, significant adverse outcomes of the arrhythmias and/or shocks received were very rare: 5% of practitioners reported damage to an ICD system attributed to repetitive-motion activities, like weight-lifting and golf; 1% reported known injury to a patient; and less than 1% reported failure of shocks to terminate the arrhythmia.

Although this recommendation should be made with caution, especially in athletes with arrhythmias sensitive to exercise, teaching patients how to adjust their level of exertion by monitoring their target heart rate on a wrist device, being aware of impending cardiac symptoms and deliberately ending physical activity, will decrease shocks due to potentially lethal arrhythmias.

Regarding contact sports, some have advocated patching of the ICD implantation site because of the risk of trauma to the subcutaneously implanted device.

Although there are ample theoretical reasons to ban athletes with ICDs from sports, there is no solid evidence that sports competition is dangerous for all these patients, and some are participating in sports, regardless of the guidelines and physicians’ recommendations. Based on this fact, the ICD Sports Safety Registry, an observational prospective registry, was established to follow individuals with an ICD who have made the decision to participate in sports. There were 49 shocks in 37 participants (10% of the study population) during competition or practice, 39 shocks in 29 participants (8%) during other physical activity, and 33 shocks in 24 participants (6%) at rest. Ultimately, the ICD terminated all episodes, despite the occurrence of both inappropriate and appropriate shocks.

Finally, just as an ICD should probably not lead to a blanket restriction against sports participation, the presence of an ICD does not mean that every patient can safely participate. In fact, in patients with catecholaminergic polymorphic ventricular tachycardia, ICD therapy may have a proarrhythmic effect.

Physical injuries

A second potential difficulty with resuming competitive sports activity in athletes with HCM is the risk of traumatic injury due to presyncope or falls related to an arrhythmia or the ICD shock itself. Trauma secondary to syncope is usually seen in arrhythmic events and rarely in reflex syncope, in which episodes are preceded by prodromes and individuals often slump to the floor and thus are able to break their fall with their arms. As expected, traumatic injuries are worse in syncopeal episodes occurring in a standing position compared with those occurring while sitting or lying.

In the HRS survey, physical injuries were rare and significant traumatic injuries were extremely rare. Of nine
specific ICD shock-related injuries reported, six were minor; major injuries included two head injuries due to falls, one during running and one on a treadmill, and a neck injury during hunting. In another trial, the Antiarrhythmics Versus Implantable Defibrillators trial, although ICD interventions while driving occurred in 8% of the participants, most had resumed driving and the accident rate was lower than in the general driving population.56

In conclusion, because there is latency between arrhythmia onset and ICD intervention to terminate it and so a risk of TLoC, these patients should avoid extreme weather conditions or extreme sports, such as diving, hang-gliding, free weight lifting, piloting and rock climbing.36,41,42 Furthermore, some practitioners recommend wearing a lifejacket when swimming in open water.18

Discussion and conclusion

Syncope may be the final common symptom for a number of clinical conditions, as its potential causes range from frequent and benign conditions to rare life-threatening diseases such as HCM.1,8,11–17

In competitive athletes with HCM, striking a balance between the risks and benefits of competitive sports activity (including its intensity, duration and environmental conditions), and implementing lifestyle recommendations, are highly problematic endeavors and should depend on the physician-patient relationship.26,35 The presence of a syncope specialist ("the right physician"), adequate equipment ("the right place") and optimal organization ("the right time") may be necessary to individualize exercise instructions.5,41 Indeed, if sports do in fact carry the risks that have been speculated, a young athlete with HCM judged to be "low risk" may nevertheless be at unacceptably high risk by virtue of involvement in high-intensity competitive sports, and it is crucial to be aware of future serious problems.53

In light of the current availability of high-resolution non-invasive imaging techniques capable of assessing patterns of MB and the recent debate regarding the significance of MB, consideration of this anomaly as an SCD marker for young HCM patients would greatly impact risk stratification.49

More guidance is needed in helping these individuals and their families to make informed decisions concerning participation in sports, but there should be some degree of flexibility and individual responsibility.6,33 Although ICD shocks can decrease quality of life, if the risk of shock failure is no higher during sports and sports are safer than hypothesized, reducing restrictions may in fact improve patients' quality of life.33,52,53 This is an exciting possibility that awaits controlled and evidence-based studies.

Although the current guidelines were updated in November 2015, they do not differ significantly from those in BC#36. Besides they are a reasonable starting point, at present this may lead to defensive and restrictive practices.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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