VENTRICULAR ARRHYTHMIAS IN ATHLETES: DIAGNOSIS AND TREATMENT

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Total word count: 2981

Tables: 0

Figures: 3
ABSTRACT

Regular physical activity is associated to low mortality risk and sportsmen appear to the general public opinion as the healthiest individuals of the society. However, strenuous physical training has been associated to structural heart modifications and pathological conditions. Life threatening ventricular tachycardias (VT) and sudden cardiac death (SCD) are a rare but catastrophic event that always captures the interest of the media and of the scientific community. How can we prevent those events?

In the present manuscript, we review the pathophysiology and the treatment of the ventricular arrhythmias in the athletes and we describe the most common cardiomyopathies causing VTs in athletes. Athletes may present a spectrum of ventricular arrhythmias ranging from benign isolated PVCs to VF. Complex PVCs may prevent eligibility for sport competition; in absence of cardiac disease they can be successfully treated. Presence of a structural heart disease is the single factor that has the highest impact on patient’s prognosis; our best efforts should be paid to the athletes screening, risk stratification and, whenever possible, adequate treatment.

Key words: sport, athletes, sudden death, ventricular arrhythmias, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy.
CONDENSED ABSTRACT

In the present manuscript, we review the pathophysiology and the treatment of the ventricular arrhythmias in athletes. Presence of a structural heart disease is the factor with highest impact on prognosis; invasive treatment with implantable cardioverter defibrillator and/or catheter ablation may reduce the risk of sudden death.
Abbreviations:

AAD: Antiarrhythmic drug
ARVC: Arrhythmogenic right ventricular cardiomyopathy
CT: Computed tomography
HCM: Hypertrophic cardiomyopathy
ICD: Implantable cardioverter defibrillator
LVNC: Left ventricular non-compaction
MRI: Magnetic Resonance Imaging
PVC: Premature ventricular contraction
RVOT: Right ventricular outflow tract
SCD: Sudden cardiac death
VT: Ventricular tachycardia
INTRODUCTION

Physical exercise is associated with several cardiovascular benefits: it lowers blood pressure, improves insulin sensitivity, lipid levels and it also represents the cornerstone of cardiac rehabilitation in patients with coronary heart disease and heart failure. Individuals performing regular physical activity have a lower mortality risk, as compared to those reporting no physical, with a direct dose-response effect. However, strenuous training may lead to progressive adaptations known as "athlete’s heart". Life threatening ventricular tachycardia (VT) and sudden cardiac death (SCD) have been reported in athletes; they are a rare but catastrophic event. Prevalence varies by age, location, and data collection mode. To date, the most reliable data show a prevalence of 1 in 50000 in competitive athletes. Along with life threatening ventricular arrhythmias (VAs), athletes may experience low risk VAs. In the present manuscript, we review the pathophysiology and the treatment of the VAs in the athletes and we describe the most common cardiomyopathies causing VTs in athletes.

Premature ventricular beats in athletes

Premature ventricular contractions (PVCs) are abnormal heartbeats that originate from the ventricles and, in general population, they are a frequent finding with a good prognosis. Several studies evaluated the prevalence of PVCs in athletes; PVCs are frequently found in competitive athletes during pre-participation screening; endurance athletes engaged in iron man, marathon and cycling show a higher number of PVCs, as compared to general population. In the majority of cases, these arrhythmias are not associated with any underlying cardiac disease. In the presence of no more than two consecutive PVCs and in absence of structural heart disease, family history of SCD and frequent/polymorphic PVCs, the prognosis is usually favorable; current American Heart Association and American
College Cardiology Guidelines consider athletes with that condition as eligible for sport participation. Exercise test is helpful for predicting arrhythmia behavior during sport activity and for patients stratification; PVCs that disappear during exercise or recovery have a favorable prognosis and are considered as part of the so called “athlete's heart syndrome”; PVCs increasing in frequency during exercise are associated with risk of death. Very frequent PVCs (>10,000 per day), can progressively impair the left ventricular systolic function, leading to the PVC-induced cardiomyopathy; this condition is reversible if PVCs are promptly treated.

Possible therapeutic strategies include deconditioning, antiarrhythmic drugs and catheter ablation. Biffi et al. reported that 19 weeks of detraining may help to suppress PVCs and idiopathic VTs in athletes without underlying structural or electrical heart disease; longer periods (3 to 6 months) of abstinence from sport activity are associated with a prolonged suppression of ventricular ectopy. Long time deconditioning, however, is not the preferable treatment strategy for competitive athletes, who rely on a continuous training for maintaining their “professional” levels.

β-blockers, Calcium channel blockers, class IA and class III antiarrhythmic drugs (AADs) are effective in reducing PVC burden; they also have a role in the prevention of recurrent VTs in absence of structural heard disease. The antiarrhythmic drug treatment is challenging in athletes because β-blockers, that represent the first line therapy in non-athletes, are prohibited in the majority of sports by the World Anti-Doping Agency. Catheter ablation in nowadays a widespread and effective treatment for frequent PVCs. Ling et al. showed that patients randomized to catheter ablation of right ventricular outflow tract (RVOT) PVCs had a 1-year recurrence rate of 19.4%, accounting for a relative risk reduction of 78.1%, as compared to patients randomized to AADs (metoprolol or propafenone). In a retrospective study including 1185 patients who underwent catheter
ablation for idiopathic PVCs, 85% were free from the arrhythmia at 1.9 years follow-up; PVCs originating from RVOT were associated to a higher probability of clinical success without AADs, as compared to those originating from aortic cusps, epicardium, or papillary muscles. Procedures were hampered by a low (5.2%) complication rate, mostly related to vascular access. Based on different outcomes of PVC ablation, it is worth to evaluate the possible origin of the arrhythmia before considering catheter ablation for PVCs. Current European Society of Cardiology guidelines recommend catheter ablation of PVC originating from RVOT in symptomatic patients, in patients with a failure of anti-arrhythmic drug therapy (e.g. beta-blocker) and in patients with a decline in LV function due to RVOT-PVC burden (class IB). In patients with PVCs originating from left ventricular outflow tract, aortic cusp and epicardium, catheter ablation should be considered by experienced operators in patients not wanting long-term anti-arrhythmic drug therapy (like most athletes) and after failure of one or more sodium channel blockers (class IC agents).

Ventricular tachycardia in athletes without cardiomyopathy

VT is defined as the upset of three or more consecutive premature beats originating in the ventricles at more than 100 bpm. In the general population it is usually associated to the presence of a cardiomyopathy or a genetic heart disease. VTs in absence of underlying structural heart disease are classified as idiopathic VTs and represent about 10% of all VTs. They may originate from various heart structures, including the RVOT, the left ventricular outflow tract and the fascicles in left ventricle (fascicular VT).

As a general electrophysiological rule, the interplay of two factors is relevant for the development of the arrhythmias: the substrate and the trigger. In athletes, chronic increase of cardiac output and increased pulmonary arterial pressure can favor oxidative stress, myocardial cell damage and desmosome disruption. These events are probably the cause of
the transient rise in cardiac biomarkers such as troponin and brain natriuretic peptide and right ventricular dysfunction after endurance exercise 16.

Physical exercise is a known trigger for the onset of VTs. The real mechanism underlying the VAs is not fully understood, but there are several conditions that may have a possible role: the prevalence of the parasympathetic tone, that increases the dispersion of refractoriness; the shift in sympathetic tone during exercise, that stimulates beta-adrenergic receptors; the reduction of serum levels of electrolytes, lost during prolonged exercise; the extracellular acidosis, that alters the intracellular sensitivity to calcium; the intracellular accumulation of adenosine monophosphate associated to the reduction of intracellular calcium levels 17 18. All these components favor the onset of electrical instability that can finally end in ventricular fibrillation 19. The most frequent site of origin of VTs in extreme’s sport athletes is the RVOT20; the recording of multiple VT morphologies in the same patient is the exception and it should promptly rise the suspicion of scar-related tachycardia in the setting of a cardiomyopathy.

Possible treatment modalities for VTs in structurally normal hearts follow recommendations similar to those for PVCs regarding detraining, AADs and catheter ablation. In rare cases, SCD should be prevented with an implantable cardioverter defibrillator (ICD); these devices should be considered in patients with recurrent sustained VTs, who are receiving chronic optimal medical therapy. However, ICD implantation in athletes presents several limitations: they have a significant psychological and social impact (appropriate and inappropriate shocks, appearance, functional limitations); concerns regarding the leads integrity over the years in a young population are still a major issue. Exacerbation of symptoms, arrhythmias and ICD shocks are the important factors that should prohibit moderate and vigorous exercise in sports players with already implanted ICD and history of life threatening VTs.
Cardiomyopathies as a cause of ventricular arrhythmias in athletes

Cardiomyopathies are the most frequent causes of VTs in athletes younger than thirty years old; the major contribution is played by hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular non-compaction (LVNC)\textsuperscript{21}. Coronary arteries anomalies, chanellopathies (including Brugada syndrome and Long QT syndrome), along with commotio cordis, are increasingly recognized as a dramatic cause of sudden cardiac death in the athletes with a morphological normal heart\textsuperscript{7}.

**Hypertrophic cardiomyopathy**

HCM is the most common inherited cardiomyopathy worldwide, affecting 1 in 500 individuals. It is also the most prevalent cause of SCD in young athletes, accounting for 36% of SCD in a US National Registry\textsuperscript{22,23}.

The hallmark of HCM is an altered asymmetric or symmetric left ventricular hypertrophy that enters in differential diagnosis with the cardiac remodeling found in “athlete's heart”\textsuperscript{24}. Differential diagnosis between the two conditions, although hard to be achieved, is mandatory, since athlete's heart is a benign condition. Training, indeed, may cause left atrial, left and right ventricular enlargement with normal systolic and diastolic function; it can also cause an increase in left ventricular wall thickness beyond the cut-off of 13 mm; this is, however, a dynamic condition that gradually progresses and usually reverts with detraining. Clinical and echocardiographic criteria may help to distinguish athlete's heart from HCM (Figure 1).

Arrhythmias and SCD can be the first manifestation of HCM and they can occur during mild or vigorous exercise. The link between exertion and arrhythmias leading to SCD is very strong, being half of the SCDs in HCM patients exercise-related\textsuperscript{7}. Pre-participation screening program for sport eligibility was proven to reduce the incidence of SCD due HCM in
competitive sport players. Initial routine screening includes familiar history, physical examination and basal 12 leads electrocardiogram; second level non-invasive evaluation with transthoracic echocardiography, cardiac MRI and eventually genetic testing should be performed in presence of pathological findings at the first step; third level invasive tools, such as endocardial biopsy, should be confined only to selected cases. All sports players with diagnostic criteria for HCM should receive familiar counseling and SCD risk assessment. Exertional syncope, young age, extreme ventricular hypertrophy (> 20 mm), inducible ventricular tachycardia and a familiar history of SCD are the most important risk factors. Athletes with HCM are at risk of developing symptoms and cardiac arrest, even when considered at low-risk by European Society of Cardiology and American Heart Association algorithms; the incidence of event/symptoms is largely independent from continuation or interruption of regular exercise and sport programs.

The mechanism of SCD in HCM sports players is frequently related to polymorphic VTs or ventricular fibrillation, while monomorphic VTs are a rare cause. Monomorphic VTs can be found in each stage of the disease, being more frequent in the early than in the late stage, when left ventricular dilation and systolic dysfunction are manifest. Disorganized cellular architecture (myocardial disarrays), expanded interstitial collagen and presence of myocardial scar detected at delayed contrast enhanced MRI are associated to the induction of monomorphic VT, similarly to what happens for myocardial scar in ischemic heart disease. Presence of late gadolinium enhancement at cardiac MRI correlates with the risk of SCD.

ICDs are the only effective therapeutic options to prevent SCD; after estimation of individual risk profile, ICDs should be implanted in patients with risk of SCD at least moderate (4% at 5 years) according to the European Society of Cardiology Guidelines. Catheter ablation of monomorphic VT in HCM sports player is a promising therapeutic option, although only few cases were reported; the procedure can be successful both during the early and the
late phases of the disease. In the dilated phase of HCM, VT circuits are located in the septal basal segment or in the anterior and anterolateral segments, with a larger extent of fibrosis than in the early stage. Even when acutely effective, catheter ablation at the moment cannot be considered as an effective strategy for long-term SCD prevention.

**Arrhythmogenic right ventricular cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disorder, transmitted with autosomal dominant inheritance, that predominantly involves the right ventricle. It affects 1 on 5000 persons in the general population. ARVC is one of the major causes of VTs and SCD in athletes, being the first cause in Italy. This regional difference might be related to the high prevalence of the disease in Italy and the effectiveness of the National screening program in disqualification athletes with a diagnosis of HCM.

Genetic alterations were found in the genes encoding desmosomes, proteins that permit cell-to-cell adhesion, leading to myocyte disconnection and subsequent cell death. Progressive fibro-fatty replacement of the myocardium, right ventricular dilation and dysfunction are the hallmarks of the disease. Desmosomes physiologically interact with gap-junction and sodium channels to control myocyte excitability, thus forming a network called "connexome"; altered desmosomes led to a decrease in the content and distribution of gap junctions protein connexin 43 on the cellular membrane and a decrease of the amplitude and kinetics of the sodium current; these elements favors VT induction. Furthermore, the fibro-fatty substitution provides the electrophysiological substrate for scar-related arrhythmias with a re-entry mechanism, similarly to what happens for ischemic VTs.

The contribute of physical exercise to ARVC clinical manifestations has been acknowledged by several studies: physical exercise, which increases pressure, afterload, and wall stress to
a greater extent in the right than in the left ventricle, may aggravate desmosomes damage\textsuperscript{40}. ARVC patients with a history of athletic activity had reduced RV and LV function compared with ARVC non-athletes, with a linear relationship between amount of physical activity and reduced RV and LV function; similar results were shown in mutation positive family members \textsuperscript{41}. High levels of physical exercise are also reported to increase the risk of VA occurrence\textsuperscript{42}. In a population of 65 ARVC index patients and 45 mutation-positive family members, VAs occurred at younger age in athletes (36±13 years vs 50±16 years); a cut-off of 2.5 hours vigorous exercise/week for at least 6 years predicted exercise-induced VA occurrence with a sensitivity of 76% and specificity of 79%\textsuperscript{41}.

In ARVC patients, the basal electrocardiogram shows T-wave inversion in the right precordial leads from V1 to V4 (Figure 2). A wide spectrum of VAs has been associated to ARVC, ranging from PVCs to non-sustained or sustained left bundle branch block, and VT that can degenerate into ventricular fibrillation. The QRS axis during VT usually differs from the QRS axis typical of idiopathic RVOT VT (positive QRS complex in II, III and aVF leads) and many patients have multiple QRS morphologies (Figure 3). In the final stage of the disease, when scar and systolic dysfunction involve both ventricles, the morphology of VT can show left or right bundle branch block pattern. VAs are induced and exacerbated by adrenergic activation during strenuous exercise activity. The prognosis of ARVC strictly depends on ventricular dysfunction and the severity of arrhythmias: the most important prognostic predictors are aborted SCD due to VF and sustained VT.

In ARVC patients, competitive sports are prohibited\textsuperscript{21} and only low intensity exercise may be allowed. Amiodarone and beta-blockers are the recommended pharmacological therapy for prevention of VAs. Electrophysiological study can be used to assess VT/VF inducibility, but its role in the prognostic stratification is still controversial\textsuperscript{43,44}. In patients with ARVC and recurrent sustained VTs, catheter ablation is a valid therapeutic option. More than 70% of patients were VT-free during a follow-up of 56 months after the ablation and additional
15% of patients had only a single VT episode. A combined endo-epicardial approach was associated to an increased arrhythmia-free survival and lower long-term use of AADs, as compared to endocardial approach alone. ICD implantation is recommended in patients with a history of aborted SCD or hemodynamically poorly tolerated VTs. In any other cases, the ICD implantation should be considered following a risk stratification for SCD taking into account several variables, such as: symptoms and duration of the arrhythmic episodes, age of the subject, lifestyle, life expectancy, potential social impact, long term complications, response to antiarrhythmic drugs and their possible intolerance. In any case, prophylactic ICD implant should not be proposed to athletes with ARVC with the purpose of allowing participation in high-intensity sports competitions because the risk of device-related complications and exercise triggered arrhythmias are both relevant.

**Exercise-induced right ventricular arrhythmogenic cardiomyopathy**

Chronic and extreme physical exercise can lead to a form of cardiomyopathy similar to ARVC, but without genetic mutations, called “exercise-induced right ventricular arrhythmogenic cardiomyopathy”; it shares the same pathological mechanism with ARVC, by promoting myocardial desmosome damage due to augmented wall stress during intense exercise and creating VT re-entry circuits. It is characterized by the presence of fibrosis in the anterior and sub-epicardial portion of the right ventricular outflow tract in absence of fibro-fatty substitution. The absence of fatty infiltration may be a clue difference between exercise-induced remodeling and familial ARVC. The scar area is usually not recognized by normal diagnostic imaging tests [echocardiography, Magnetic Resonance Imaging (MRI) and computed tomography (CT)], but only with the electroanatomical mapping; the latter shows an area of unipolar pathological voltages <4,4 mV. The cardiomyopathy mainly affects endurance athletes who practice more than 10 hours/week of sport activity for several years (median 9405 MET-h/year). Cycling (72%), distance
running (6%), triathlon (6%) and kayaking (2%) were the sport activities most frequently associated to the disease. The incidence of exercise-induced ARVC was evaluated by La Gerche et al: among 47 athletes presenting with RV arrhythmias with origin other than RVOT, despite clinical definite ARVC diagnosis in 51% and suspected ARVC criteria according to Task Force Criteria in additional 36%, pathogenic desmosomal mutations were detected in 12.8% only.

Invasive EP study is useful to identify patients at risk of major arrhythmic events, showing sensitivity and specificity respectively of 62% and 74%. It is worth to point out that 20% of patients with a negative EP study developed major arrhythmias. Catheter ablation has been proposed, requiring an epicardial approach; it is reported to be potentially curative and associated with an excellent prognosis.

CONCLUSIONS

Athletes may present a spectrum of VAs ranging from benign isolated PVCs to VF. No more than two consecutive PVCs are usually associated to a benign prognosis. More complex PVCs may prevent eligibility for sport competition; in absence of cardiac disease, they can be successfully treated by catheter ablation. Best efforts should be payed to the identification of any underlying cardiac disease; presence of cardiomyopathies or inherited heart disease usually prevents eligibility for sport completion, requires careful risk stratification and adequate treatment.

SOURCE OF FUNDING: None declared
CONFLICT OF INTEREST: Dr. Della Bella is a consultant for St. Jude Medical and has received honoraria for lectures from Biosense Webster, St. Jude Medical and Biotronik.
REFERENCES


FIGURE LEGENDS

**Figure 1.** Differential diagnosis between Hypertrophic Cardiomyopathy and athlete’s heart.

**Figure 2.** Twelve leads ECG in a patient with Arrhythmogenic Right Ventricular Cardiomyopathy.

**Figure 3. Panel A:** ECG showing Ventricular tachycardia in a patient with Arrhythmogenic right ventricular Cardiomyopathy. **Panel B:** Electroanatomical mapping with CARTO system showing a low-voltage area in the peri-tricuspid area of the right ventricle.