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Exercise restrictions for patients with inherited cardiac conditions: Current guidelines, challenges and limitations

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ABSTRACT

Inherited primary arrhythmia syndromes are a clinically heterogeneous group of relatively uncommon but important inherited cardiac conditions that are associated with an increased risk of sudden cardiac death (SCD) in the setting of a structurally normal heart. These include long-QT syndrome (LQTS), Short-QT syndrome (SQTS), Brugada syndrome (BrS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). The cardiomyopathies represent the other major group of inherited cardiac conditions associated with SCD, of which hypertrophic cardiomyopathy (HCM) is the most common. Exercise is a known trigger of ventricular arrhythmias in many of these conditions, however marked genetic and clinical heterogeneity within individual diseases means that certain patients are at a much greater risk of lethal ventricular arrhythmias during exercise than others. For instance, LQTS type 1 (LQT1) and CPVT patients are at particular risk during exertion, whilst in patients with other genetic variants of LQTS, BrS and SQTS, alternative triggers are more significant precipitants. Many channelopathy (principally Brugada, CPVT) & cardiomyopathy (mainly HCM) patients receive primary or secondary prevention therapy with an implantable cardiac defibrillator (ICD). Exercising with an ICD *in situ* carries a range of additional risks including inappropriate shocks and lead complications. This review will focus on the risk of exercise-induced SCD in patients with inherited cardiac conditions, the current clinical guidelines in this area and the special consideration of patients with an ICD.

1. Introduction

Physical activity has a number of important health benefits, from primary and secondary prevention of chronic diseases including coronary heart disease [2] and type II diabetes mellitus [3], to reducing the risk of developing depression and anxiety [4] (Fig. 1). Exercise, a specific form of physical activity, is generally planned, repetitive and carried out with the aim of improving fitness and health, whilst physical activity more broadly includes daily activities such as housework and activity for means of transportation. Physical inactivity is a global pandemic, with recent data suggesting that eliminating this problem would remove between 6% and 10% of major non-communicable diseases including coronary heart disease, type 2 diabetes mellitus, breast and colon cancers [5].

Despite the overwhelming beneficial effects of exercise for people of all ages, including those with chronic medical conditions, there is a small subset of individuals in which exercise carries with it a significant risk of sudden cardiac death (SCD), which must be weighed carefully against the advantages previously discussed. There is a well-described association between a number of inherited cardiac conditions and an increased risk of SCD during high-intensity exercise. These include cardiomyopathies such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), as well as inherited primary arrhythmia disorders, particularly long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Data from the United States demonstrates that such conditions account for at least 40% of SCD in young athletes [6,7].

This review will focus on the risk of exercise-induced SCD in patients with inherited cardiac conditions and the difficulties currently faced with advising such patients about exercise limitations in the clinic. An emphasis will be given to the channelopathies and the two most frequent cardiomyopathies leading to SCD in sports: HCM and ARVC.

2. Inherited primary arrhythmia syndromes and exercise

The understanding of inherited primary arrhythmia syndromes has been revolutionised over the last 20 years by the discovery of multiple mutations in ion channel genes & structural cardiac proteins of the sarcomere (in HCM) & desmosome (in ARVC) [8]. In 2013 a consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes was released, focusing chiefly on

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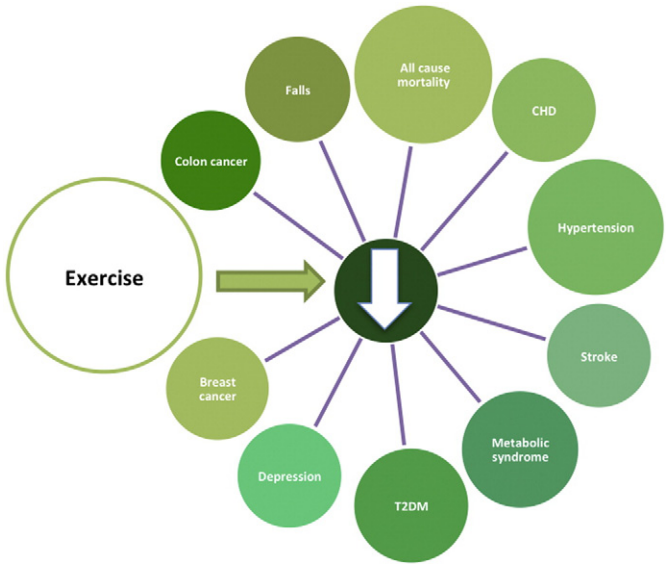

Fig. 1. Benefits of exercise. Exercise has a wide range of beneficial effects. These include reducing all cause mortality and a reduction in risk of developing a range of physical and psychological disorders including coronary heart disease (CHD), type 2 diabetes mellitus (T2DM) and depression.

pharmacological therapy and ICD implantation recommendations [9]. These are a clinically diverse group, and risk stratification depends on a number of factors including the clinical features, family history and genotype.

The evidence for increased risk of SCD during exercise is the strongest for young athletes participating in competitive sport. Data from a 21-year prospective cohort study of all young people in the Veneto Region of Italy showed sports participation in athletes affected by cardiovascular conditions predisposing to life threatening arrhythmias triggered SCD, with an estimated relative risk (RR) of SCD of 2.8 in athletes compared with non-athletes ($p < 0.001$) [10]. However, the results of this study are contested, as the outcomes are dependent upon the duration of observation. Indeed, in an Israeli study evaluating events pre- and post the legislation on athletic ECG screening, prior to mandatory screening the incidence was 2.54 events per 100,000 athlete-years, while it was 2.66 events per 100,000 athlete-years in the decade following legislation ($p = 0.88$) [11].

A study from the United States found that male joggers were at a 7-fold increased risk of SCD compared to those participating in less strenuous activities [12]. Importantly, the risk for SCD appears to be greater still for those who sporadically engage in high activity exercise compared to those with habitual high levels of activity [13]. Despite a large number of congruent findings, the most recent study, a large 3-year nationwide prospective study in Denmark, failed to identify a significant difference in SCD rates between non-competitive and competitive athletes [14].

Whilst primary inherited arrhythmia syndromes are relatively rare, there is an argument that screening for genetic heart disease that predisposes to SCD during exercise may be beneficial, particularly in young athletes [15]. Currently there is little evidence that convincingly demonstrates that this would be a beneficial approach, with a recent report by the Belgian Health Care Knowledge Centre concluding that there is no strong evidence that screening young athletes will reduce the risk of SCD, it is unlikely to be cost-effective and could potentially be harmful [16]. This is also supported by an Israeli study of historical cases published in the lay press in the observational analysis highlighted above [11].

A distinction is often made in the literature between those engaged in competitive or recreational sport. It can be argued however that many recreational activities are undertaken with equally high intensity, and the form and intensity of activity are perhaps more useful variables to consider. The most commonly employed method of quantifying the physical intensity of particular activities is to use the metabolic equivalent value (METS). Typically the higher the intensity, the higher the MET value and the greater the associated risk of cardiac arrest or SCD. Intensity of exercise is also important when investigating the beneficial effects of physical activity in the whole population, with data from a recent study in Copenhagen suggesting that moderate exercise is preferential to both inactivity and strenuous jogging, with a U-shaped association observed between jogging intensity and all-cause mortality [17].

Another important factor to consider however is age. With increasing age, the cardiovascular benefits of regular exercise begin to become more significant, whilst in younger patients the inability to participate in the exercise of their choice can have a profound psycho-social impact and significantly impair quality of life.

2.1. Long-QT syndrome

LQTS is a disorder of myocardial repolarisation characterised by QT interval prolongation on the ECG (Fig. 2), syncope or cardiac arrest and is a leading cause of SCD in young people [18]. *KCNQ1* (LQT1), *KCNH2* (LQT2) and *SCN5A* (LQT3) are the most commonly mutated LQTS genes, accounting for approximately 90% of all genotype-positive cases [20]. The prevalence of LQTS was estimated to be approximately 1:2000 in Caucasians in the largest prospective study to date, carried out in 18 Italian maternity hospitals [19], however precise data regarding the true prevalence worldwide is lacking. Patients under 40 years old with untreated LQTS have approximately a 0.28%–0.96% per year risk of SCD or cardiac arrest, which varies between gender and genotype [21].

The mainstay of therapy in LQTS is beta-adrenergic blockade, which reduces both syncope and SCD [23]. Alternative therapies include left cardiac sympathetic denervation, cardiac pacing, implantable cardiac defibrillator, and adjunct therapies including potassium, mexilitene, flecainide and nicorandil. In addition, a recent study into the use of automated external defibrillators (AEDs) in children with LQTS showed that, in selected patients, carrying an AED could be a useful lifesaving and cost-effective alternative to having an ICD [24]. Although currently untested, this approach may also have utility in young adults involved in sports who do not qualify for an ICD. Lifestyle modification, including avoidance of drugs which can prolong the QT interval, as well as recommendations regarding physical activity and exercise is advised for all patients diagnosed with LQTS [23].

In patients with LQTS, corrected QT interval (QTc) dynamics are known to vary depending on genotype during exposure to different triggers [25]. Patients with LQT1 are at particular risk during sympathetic activation, whilst patients with LQT 2 or 3 are more likely to have cardiac events during rest or sleep, with a limited apparent role for exercise [26,27]. Swimming is a relatively genotype specific trigger for arrhythmias and SCD in LQT1 [29], whilst auditory stimulation has been shown to be an important trigger in Type 2 LQTS particularly in mutations affecting the ion channel pore [30]. Differentiating between genotype is therefore a crucial factor to consider when advising patients about exercise in the clinic.

2.2. Short QT syndrome

SQTS, first described in 2000 [31], is a rare familial disorder characterised by abnormally short cardiac repolarization. Initially SQTS was defined as a QTc interval ≤ 340 ms, however the diagnostic criteria is not established and the natural history of the disease is poorly understood, given that only approximately 200 SQTS patients have been reported in the literature to date [32]. It is thought to be most commonly caused by autosomal dominant mutations in potassium and calcium channel subunit genes [33–35], and is associated with malignant atrial and ventricular arrhythmias and SCD. In the largest SQTS cohort to date, the annual risk of cardiac arrest was approximately 1%, and most often