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EDITORIAL COMMENT

Long QT Syndrome

A Preventable Cause of Exercise-Induced Sudden Cardiac Death*

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Exercise-induced sudden cardiac death (SCD) in the athlete is a tragic event that dramatically affects the media and medical communities, raising the issue of which prevention strategies might have avoided such a fatality.[1] The physically active military population shares with athletes both intense physical exercise and mental stress, which are associated with vigorous sport activity, and shows a comparable incidence of exercise-induced SCD.[2]

The mechanism for SCD associated with physical exertion is abrupt, adrenergic-dependent ventricular fibrillation (VF) that occurs as a consequence of an underlying clinically silent cardiovascular disorder.[3] The cause of exercise-induced SCD reflects the age of participants: although atherosclerotic coronary artery disease accounts for the vast majority of fatal events in middle-aged/senior individuals, in the younger population (aged ≤35 years), there is a broad spectrum of pathologic substrates consisting of genetic cardiomyopathies (mostly hypertrophic and arrhythmogenic cardiomyopathy), congenital anomalies of coronary arteries, myocarditis (either acute myocardial inflammation or postinflammatory myocardial scar), and valvular diseases, including mitral valve prolapse.[1,3,4]

A sizeable proportion of exercise-related SCDs are categorized as "idiopathic" because no structural heart disease is found at autopsy. Harmon et al[5] demonstrated that the most common finding at autopsy was autopsy-negative SCD, accounting for 25% of fatalities among U.S. National Collegiate Athletic Association athletes. Likewise, Smallman et al[6] reported that the cause of death was not identified at postmortem investigation in 31% of young individuals with SCD among active component U.S. military. There is compelling evidence that most of these autopsy-negative SCDs are caused by an arrhythmic syndrome—namely, either inherited cardiac ion channel defects, including long QT syndrome, or idiopathic VF, which account for a primarily electrical ventricular instability.

Twelve-lead electrocardiogram (ECG) offers the potential to raise clinical suspicion or detect at a presymptomatic stage those lethal conditions that manifest with ECG abnormalities. Outcome studies on the long-running Italian experience demonstrated that systematic preparticipation ECG screening successfully identified young athletes with at-risk cardiovascular abnormalities, thus protecting them from sport-related SCD. A long-term study (1982-2004) in the Veneto region of Italy reported a 90% reduction in the SCD rate among screened athletes, mostly because of fewer fatalities from cardiomyopathies that were diagnosed by screening.[3] A more recent Italian investigation (2009-2019) showed that serial (annual) preparticipation cardiovascular evaluations increased the power of the screening program to detect young athletes with conditions putting them at risk of SCD—either genetic with a late-onset phenotype or acquired—and, most importantly, was associated with a low risk of cardiac arrest (0.6 per 100,000 athletes per year) over long-term follow-up.[7] In that study, among 69 athletes diagnosed with a

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cardiovascular condition at risk of SCD, 14 (20%) had ion channel diseases, including long QT syndrome (LQTS) (n = 13) and Brugada syndrome (n = 1), which were identified because of typical ECG abnormalities and/or positive family history. These findings indicate that early detection by preparticipation ECG screening and appropriate management of cardiomyopathies and channelopathies causing risk of SCD in the young athletic population is lifesaving.

In this issue of *JACC: Case Reports*, Chung et al[8] report the case of a U.S. marine who experienced aborted SCD while engaged in underwater diving exercises. She successfully recovered after prompt cardiopulmonary resuscitation with immediate external defibrillation. On basal ECG, there was a prolongation of the QTc interval of 502 ms in the absence of any acquired causes for QT prolongation. There was a notably positive family history for SCD and LQTS. Molecular genetic testing confirmed the diagnosis of LQTS1 by the identification of a pathogenic variant of the *KCNQ1* gene.

The reported case[8] is emblematic of the common scenario of exercise-induced SCD, which occurs in apparently healthy and physically active individuals as the first manifestation of a clinically silent cardiovascular abnormality. In the present case, the cause of the malignant ventricular arrhythmia leading to cardiac arrest was LQTS, that is, a genetic cardiac ion channel disease characterized by the ECG pattern of QT interval prolongation associated with an increased propensity to life-threatening ventricular arrhythmias (torsades de pointes and VF in the absence of structural heart disease).[9] The disease is caused by variants of genes mainly encoding subunits of cardiac potassium channels (LQT1 and LQT2 genotypes) and sodium channel (LQT3 genotype), and gene-specific risk stratification and management are currently available in clinical practice. The LQT1 genotype, which was identified in the present case, is characterized by a pathogenic variant on the *KCNQ1* gene that encodes the α-subunit of the potassium channel responsible for the slow potassium current (I_{Ks}) and represents the most common genetic defect of LQTS (30%-35% of cases). The "loss-of-function" genetic defect results in a prolongation of the repolarization of myocardial cells with electrical heterogeneity, which represents the arrhythmia substrate. In this form of LQTS, exercise is the most important trigger of malignant arrhythmia. In patients with LQT1, beta-adrenergic stimulation results in the abnormal reduction of repolarizing currents caused by defective I_{Ks} channels with paradoxical tachycardia-related prolongation of QT intervals. The lack of appropriate adaptation of repolarization in relation to the catecholamine release during exercise results in lengthening of action potential duration which, in turn, may predispose to early after-depolarizations, leading to torsades de pointes by triggered activity.[9] In this regard, the occurrence of cardiac arrest of the present marine soldier during underwater diving exercises is consistent with the notion that swimming is a relatively genotype-specific arrhythmogenic trigger for type 1 long QT syndrome.[9] The combination of exertion and face immersion in cold water in individuals with a genetically determined reduction of I_{Ks} (LQT1) may cause an abnormal prolongation of the QT interval and increased dispersion of refractoriness, which act as a trigger of premature ventricular beats, which may induce torsades de pointes and VF.

As stressed by Chung et al,[8] the reported case calls attention to the potential lifesaving role of systematic ECG screening for the early detection of potentially lethal diseases in the physically active military population, which is exposed to the risk of exercise-induced arrhythmic cardiac arrest, similar to competitive athletes. In Italy, military applicants undergo the same cardiovascular screening protocol of competitive athletes, which includes familial and medical history, physical examination, and standard ECG.[10] In the United States, the current protocol is limited to personal (but no family) history and physical examination, without ECG, which was removed from the official U.S. military accession screening policy in 2002.[2] Abnormal physical examination findings and premonitory symptoms are present in a large minority of individuals who experience SCD. Searching for a family history positive for cardiovascular disease or SCD is proven to increase the screening sensitivity.[7] The addition of ECG substantially enhances the power of screening for the early detection of causes of SCD like LQTS, which manifests with typical ECG abnormalities. Concerns regarding the implementation of preparticipation ECG screening relate predominantly to the high number of false positive findings, which result in additional, expensive investigations or even unnecessary limitation (or disqualification) of physical activity. The prevalence of false positive results depends largely on the criteria used to define an ECG result as abnormal. Recently, important advances have been made in the interpretation of ECG findings in athletes, and modern criteria have been proposed to improve the ability to distinguish physiologic from pathologic ECG changes and to

increase the specificity while maintaining the screening sensitivity.[11]

In conclusion, the case reported by Chung et al[8] highlights the importance of ECG screening of the military population to identify clinically silent cardiovascular diseases at risk of SCD during exertion, like LQTS. Future research should focus on the impact of systematic application of modern criteria for ECG interpretation to reduce the false positive rates and increase the cost-effectiveness of screening programs of military recruits.

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