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Review

Exercise and Inherited Arrhythmias

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ABSTRACT

Sudden cardiac death (SCD) in an apparently healthy individual is a tragedy that prompts a series of investigations to identify the cause of death and to prevent SCD in potentially at-risk family members. Several inherited channelopathies and cardiomyopathies, including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular cardiomyopathy (CPVT), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) are associated with exercise-related SCD. Exercise restriction has been a historical mainstay of therapy for these conditions. Syncope and cardiac arrest occur during exercise in LQTS and CPVT because of ventricular arrhythmias, which are managed with β-blockade and exercise restriction. Exercise may provoke hemodynamic or ischemic changes in HCM, leading to ventricular arrhythmias. ARVC is a disease of the desmosome, whose underlying disease process is accelerated by exercise. On this basis, expert consensus has erred on the side of caution, recommending rigorous exercise restriction for all inherited arrhythmias. With time, as familiarity with inherited arrhythmia con-

RÉSUMÉ

La mort subite d'origine cardiaque chez une personne apparemment en bonne santé est un événement tragique qui impose de procéder à une série d'évaluations afin d'en déterminer la cause et de la prévenir chez les membres de la famille pouvant être à risque. Plusieurs canalopathies et cardiomyopathies héréditaires, notamment le syndrome du QT long (SQTL), la tachycardie ventriculaire polymorphe catécholaminergique, la cardiomyopathie hypertrophique (CMH) et la cardiomyopathie arythmogène du ventricule droit, sont associées à la mort subite d'origine cardiaque liée à l'exercice. Jusqu'ici, la restriction de l'exercice a toujours constitué la pierre angulaire de la prise en charge de ces affections. En présence de SQTL congénital ou de tachycardie ventriculaire polymorphe catécholaminergique, une syncope et un arrêt cardiaque peuvent survenir durant l'exercice à cause d'arythmies ventriculaires, qui sont prises en charge par l'administration d'un bêtabloquant et la restriction de l'exercice. En présence d'une CMH, l'exercice peut entraîner des modifications hémodynamiques ou ischémiques et ainsi provoquer des arythmies ventriculaires. La car-

Sudden cardiac death (SCD) of an apparently healthy individual is a tragedy and, particularly when it occurs during exercise, can send shock waves through a community. Systematic investigation of cardiac arrest survivors and SCD victims' families will identify evidence of an underlying inherited arrhythmia syndrome in a significant proportion, thus providing a diagnosis and preventing further SCD in potentially at-risk family members.[1] Unaffected individuals can generally be reassured with expectant follow-up.[1-4] The majority of sudden deaths occur during sleep or at rest.[5] In exercise-related SCD, the most common inherited causes are long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Ongoing advances in our understanding of inherited arrhythmia syndromes provide increasing opportunities to identify at-risk individuals and to recommend medical and lifestyle interventions to decrease the risk of events and potentially slow disease progression. However, guidelines based on expert consensus have recommended strict exercise restrictions based on very little quantitative evidence.[6] The benefits of exercise are innumerable and extend beyond the cardiovascular field. In this review, we discuss recommendations and restrictions for patients with conditions in which exercise may have an adverse effect, including LQTS and CPVT. Recent literature has also identified a potential link between exercise and arrhythmic events in Brugada syndrome (BrS).[7] The early repolarization electrocardiographic pattern, although commonly seen in athletes, is not associated with any increased risk of SCD in this population. Inherited

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ditions has increased and patients with milder forms of disease are diagnosed, practitioners have questioned the historical rigorous restrictions advocated for all. This change has been driven by the fact that these are often children and young adults who wish to lead active lives. Recent evidence suggests a lower risk of exercise-related arrhythmias in treated patients than was previously assumed, including those with previous symptoms managed with an implantable cardioverter-defibrillator. In this review, we emphasize shared decision making, monitored medical therapy, individual and team awareness of precautions and emergency response measures, and a more permissive approach to recreational and competitive exercise.

diomyopathie arythmogène du ventricule droit est une maladie du desmosome dont le processus morbide sous-jacent est accéléré par l'exercice. Par conséquent, les experts s'entendent couramment pour dire que la prudence est de rigueur et recommandent une restriction stricte de l'exercice pour tous les types d'arythmies héréditaires. Or, avec le temps, une meilleure connaissance des arythmies héréditaires et le diagnostic de formes plus légères de la maladie ont fait en sorte que les praticiens remettent maintenant en question la recommandation de strictes restrictions dans tous les cas. Ce changement est motivé par le fait que les patients sont souvent des enfants ou de jeunes adultes qui désirent mener une vie active. De récentes données probantes semblent indiquer une diminution du risque d'arythmie liée à l'exercice plus importante que celle présumée antérieurement chez les patients traités, notamment ceux ayant déjà présenté des symptômes maîtrisés par un défibrillateur cardioverteur implantable. Dans le présent article, nous mettons l'accent sur la prise de décision partagée, la surveillance du traitement médical, la sensibilisation du patient et de l'équipe aux précautions et aux mesures à prendre en cas d'urgence, et l'adoption d'une approche plus permissive à l'égard de l'exercice tant en contexte récréatif que compétitif.

cardiomyopathies, including HCM and ARVC, are covered in this review but are discussed in greater detail separately in this issue of the *Canadian Journal of Cardiology*. Additional arrhythmia syndromes including short QT syndrome, idiopathic ventricular fibrillation, familial conduction disease, and dilated cardiomyopathy are discussed because of the lack of recognized risk associated with exercise in these diseases.

Long QT Syndrome

LQTS is an inherited ion channelopathy characterized by adrenergically triggered polymorphic ventricular tachycardia (VT).[8] The underlying genetic mutations lead to ion channel dysfunction, which can be exacerbated by the stress of adrenergic states.[8] Individuals with LQTS can have changes in potassium, sodium, and calcium currents during exercise that can put them at risk for the development of torsade de pointes.[9] In patients with LQTS type 1 (LQT1), loss of function mutations in the I_{Ks} potassium channel result in failed QT shortening during peak exercise. Patients with LQTS type 2 (LQT2) typically show failed QT shortening in early exercise, with subsequent QT prolongation in late recovery, resulting from mutations in the I_{Kr} potassium channel.

Early data demonstrated an increased frequency of cardiac events during exercise in patients with LQT1, with the majority of patients experiencing events during high-adrenergic situations (ie, swimming) rather than sleep (62% vs 3%).[10] Patients with LQT1 also have greater sensitivity to sympathetic stimulation, with specific mutations further increasing the arrhythmia risk.[11] In untreated patients, LQTS-related cardiac events occurred in 55%, and aborted cardiac arrest or SCD occurred in 15% of patients with LQT1 with transmembrane mutations.[11] Thus, guidelines have historically advocated for an aggressive restriction from competitive sports, with the exception of low-intensity sports (eg, billiards, curling, golf).[12]

Recent evidence suggests a much lower rate of exercise-related cardiac events, particularly in treated patients. In a series of high-risk athletes with previously symptomatic LQTS and implantable cardioverter defibrillator (ICD) implantation, the rate of cardiac events was low (1.6% over 5.1 $\pm$ 2.9 years), with no deaths despite ongoing participation in competitive sports.[13] Studies have also demonstrated a pronounced reduction in exercise-triggered events with medical therapy in patients with LQT1 and LQT2.[14,15] Therefore, previous exercise recommendations may be excessively restrictive, and recent guidelines have become more lenient, allowing for competitive sports in selected treated patients with symptomatic LQTS.[16] The goals for treatment with respect to use of medical therapy are outlined further on, particularly with respect to proof of β-blockade through surveillance exercise testing.

Catecholaminergic Polymorphic Ventricular Tachycardia

In CPVT, disease-causing mutations destabilize calcium handling in the sarcoplasmic reticulum, which can lead to delayed afterdepolarizations, triggered activity, and VT in response to adrenergic stimulation.[17] Patients with CPVT often present with symptoms during their first decade of life, with adrenergically driven polymorphic or bidirectional VT. The genes linked to CPVT include the cardiac ryanodine receptor (*RyR2*) and calsequestrin-2 (*CASQ2*). Thirty percent of affected individuals with untreated CPVT will experience cardiac arrest, and 80% will experience a syncopal event in their lifetimes.[18]

Studies have historically demonstrated a strong association between arrhythmic events and exercise or catecholamine stimulation.[19] In a cohort of patients with CPVT, the rate of SCD was high (24% after 6.8 $\pm$ 4.9 years), with medical therapy only moderately successful in controlling symptoms. Thus, guidelines have recommended strict restrictions on physical activity (ie, strenuous exercise, competitive sports) and avoidance of stressful environments for patients with CPVT.[6,16] Of interest, exercise testing often provokes ventricular arrhythmias at intermediate heart rates (100-120 bpm), which are then suppressed by more rapid sinus tachycardia at higher workloads.[20] Anecdotally, spontaneous events are often reported