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Is There a Role for Genes in Exercise-Induced Atrial Cardiomyopathy?

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In endurance athletes, prolonged high intensity exercise participation can have deleterious effects on the myocardium with subsequent structural and electrical remodelling. In a subset of athletes, there is a predilection for atrial involvement and the risk of atrial fibrillation (AF) is increased. The mechanisms underpinning exercise-induced atrial cardiomyopathy have yet to be fully elucidated and the contribution of an individual's genetic makeup is unknown. Some athletes may have rare genetic variants that are sufficient to cause AF irrespective of exercise exposure. In AF-causing variant carriers, the additional haemodynamic stress of exercise on atrial structure and function might accelerate or increase the severity of disease. Variants in genes that lack known links to AF may indirectly promote an arrhythmogenic substrate by affecting threshold levels for exercise-induced myocardial damage and remodelling responses, or by effects on AF-associated co-morbidities, sinus node function, and autonomic nervous system tone. Given the exquisite stress-sensitivity of the atria, mechanosensitive ion channels could plausibly have a key role in mediating exercise effects on atrial structure and function. Knowing an athlete's profile of genetic variants may be useful for AF risk stratification and have implications for clinical management. Pre-participation genetic testing may influence sports choices and facilitate AF prevention.

Keywords Exercise-induced atrial cardiomyopathy • Atrial fibrillation • Genes • Mechanosensitive ion channels

Introduction

Q4 The pleiotropic benefits of exercise to counter a range of human ailments, including cardiovascular disease, diabetes, obesity, cancer, osteoporosis, mental illness, and the ageing process itself, have been widely promulgated. However, there is also increasing awareness of the exercise paradox, namely, that while regular, moderate exercise is health-promoting, too much exercise can be harmful [1,2]. This does not necessarily apply to all types of exercise, and athletes who engage in high intensity endurance training have been identified as a subset at increased risk [3]. The hearts of these individuals are subjected to recurrent periods of sustained haemodynamic stress that can culminate in electrical, structural, and functional remodelling of the cardiac chambers [2]. This can give rise to a pro-arrhythmic state, and endurance athletes have been found to have an increased incidence of both atrial and ventricular arrhythmias [4]. Not all endurance athletes who are exposed to equivalent exercise "dose" will develop cardiac arrhythmias however, suggesting that other factors might be involved. One highly plausible and attractive explanation is that a person's genetic makeup might be a key determinant of arrhythmia susceptibility. In this review, we will focus on the effects of endurance exercise in the atrium. Three broad hypotheses will be presented for potential ways in which genetic variation might be involved in the pathogenesis of exercise-induced atrial cardiomyopathy and in atrial fibrillation (AF) risk. Q5

"Environmental" Effects of Endurance Exercise on Atrial Structure and Function

Exercise-induced atrial cardiomyopathy is most likely to occur in athletes who participate in endurance sports such as cycling,

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cross country skiing, triathlon running, and rowing, with the intensity and duration of training and competition being important factors [3–5]. These sports require sustained vigorous effort and increased stroke work that, over time, can have deleterious effects that include myocardial inflammation, ischaemia, oxidative stress, and cell death. These insults can trigger suites of adaptive changes that result in myocardial hypertrophy, fibrosis, chamber dilatation, electrical remodelling, and altered autonomic nervous system tone [6,7]. Collectively, these changes contribute to an atrial arrhythmogenic substrate and predispose to AF development. Once AF is established, further structural and electrical atrial remodelling occurs as a consequence of the arrhythmia itself and this sets up a vicious cycle in which ''AF begets AF'' [8,9]. In the context of the athlete's heart it is pertinent to keep in mind that a number of additional deleterious ''environmental'' factors might be in the mix, including performance-enhancing drugs, such as anabolic steroids, growth hormone and erythropoietin, and energy drink consumption [2,7]. Exercise-induced myocardial damage may also be accentuated by poor training habits, particularly with excessive training intensity, inadequate recovery after intense efforts, or persistence of training during illness such as viral infections [7]. Overall, it has been estimated that endurance athletes have a four- to fifteen-fold increased risk of AF when compared to the general population [7]. For any individual, however, it is difficult to predict whether AF will occur or not, based on exercise history alone.

Hypothesis 1: Rare Genetic Variants May Be a Primary Cause of AF

A subset of endurance athletes may carry rare genetic variants that are sufficient alone to cause AF. These individuals would be expected to manifest AF during their lifetimes, irrespective of exercise participation (Hypothesis 1; Figures 1 and 2). The index of suspicion for a primary genetic aetiology is higher in early-onset AF cases and in families in which AF appears to be inherited as a Mendelian trait. Over the past two decades, genetics studies in these patient cohorts have resulted in identification of numerous rare variants in at least 40 genes that are putatively causative of AF (reviewed in [10]). These genes mostly encode cardiac ion channels, with gain-of-function and loss-of-function variants identified that shorten or increase the length of the atrial action potential, respectively. The list of disease-associated genes now includes a number of cardiac transcription factors as well as genes that encode cardiomyocyte structural components [10]. Collectively, these discoveries suggest that rare variants in a wide range of genes may directly affect atrial structural and electrophysiological properties resulting in an arrhythmogenic substrate.

Hypothesis 2: AF-Related Genetic Variants and Exercise May Have Independent and Additive Effects

Given that the prevalence of AF in athletes is higher than in the general population, a strong alternative hypothesis is that having a genetic predisposition to atrial arrhythmia *and* having prolonged high intensity exercise exposure would have additive effects on the risk of AF development (Hypothesis 2; Figure 1). In this ''two-hit'' model, AF-related genetic variants and exercise would be predicted to have independent effects on the atrial substrate. In this setting, AF may occur at an earlier age or be relatively more severe than would be expected with either genetic variants or exercise exposure alone.

Genetic risk could be conferred by single rare variants that are sufficient to cause disease, or by combinations of commonly-occurring variants that affect disease susceptibility. The first genome-wide association study for AF identified a significant locus on chromosome 4q25 that has been robustly replicated [11]. Genome-wide association studies undertaken in tens of thousands of AF cases and control subjects by the AFGen consortium and others have now identified more than 30 distinct AF-associated loci [12,13]. Many of these loci are located in non-coding regions within introns or between genes and the mechanisms by which these genetic variants affect AF pathogenesis have yet to be fully elucidated. Although this type of study can show statistical associations between regions of the human genome and AF, there is significant overlap

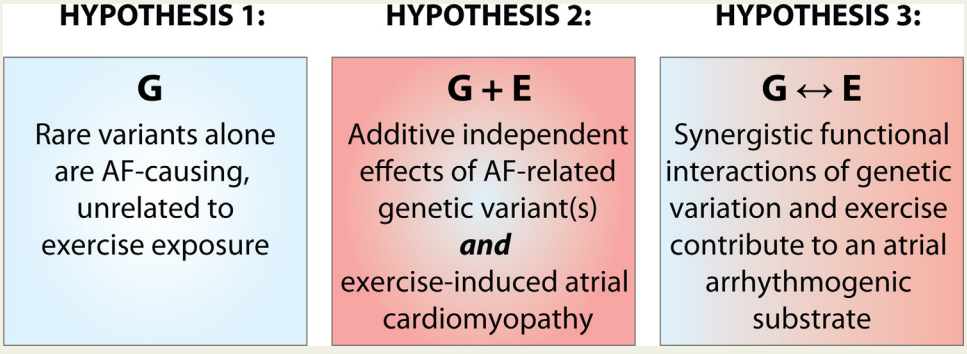

Figure 1 Hypotheses for potential roles of genetic variation (G) and exercise (E) as a cause of atrial fibrillation (AF) in endurance athletes.

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