

Review

Atrial fibrillation in highly trained endurance athletes – Description of a syndrome



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ABSTRACT

Atrial fibrillation (AF) is the most common heart arrhythmia, the risk of which typically increases with age. This condition is commonly associated with major cardiovascular diseases and structural heart damage, while it is rarely observed in healthy young people. However, increasing evidence indicates that paroxysmal AF can also onset in young or middle-aged and otherwise healthy endurance athletes (e.g., cyclists, runners and cross-country skiers). Here we review the topic of AF associated with strenuous endurance exercise (SEE), for example cycling, running and cross-country skiing, especially at a competitive level, and we propose the definition of a new syndrome based on the accumulating data in the literature: SEE-related AF under the acronym of 'PAFIYAMA' ('paroxysmal AF in young and middle-aged athletes'). Special emphasis is given to the proper differentiation of PAFIYAMA from 'classical AF' regarding pathophysiology, diagnosis and medical management.

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1. Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia [1–3], the risk of which increases with age (affecting ~9% of people aged ≥65 years). This condition is usually associated with major cardiovascular diseases as well as with structural heart damage. Its prevalence ranges from 0.5% in young patients (i.e., those aged <40 years) to >5% in patients aged 65 years and older [4,5]. The prevalence of AF is usually higher in men than age-matched women [6,7]. Low-to-moderate intensity endurance exercise (e.g., brisk walking) prevents the onset of AF [8–13]. This type of exercise might also reduce AF-related symptoms, as well as mortality and morbidity in affected people [14,15]. By contrast, long-term practice of strenuous endurance exercise (SEE, e.g., cycling, marathon running, cross country skiing) has been associated with an increased risk of developing AF, particularly paroxysmal AF, in otherwise healthy young or middle-aged adults [16–30]. Subjects engaged in

long-term SEE are more often prescribed flecainide than sedentary people [31], probably due to underlying AF. Nevertheless, the reported prevalence of AF among athletes is quite variable, ranging from 0.3% to 12.8%, which reflects methodological biases such as differences between studies in subjects' age, training status or sports specialty [32]. Another caveat in this field of research emerges from the fact that the vast majority of studies have been conducted in men only. Although regular physical activity is associated with a lower risk of AF in women [33,34], little is known about the prevalence of AF among female endurance athletes. In a Swedish cohort, repeated participation in a 90-km cross-country ski race was associated with increased AF risk in men, but not in women [22], and exercise-induced hypertension in men might be a factor [35]. However, a recent study in a Norwegian cohort suggested that prolonged SEE might also cause AF in women, wherein those performing SEE for ≥40 years had an increased risk of self-reported AF of borderline significance compared to sedentary counterparts [36].

There is a growing debate on the question of whether SEE-associated AF is medically comparable to that occurring in the elderly and whether or not it should be treated alike [37–39]. In accord with Turangam et al. [40], although AF is the most common tachyarrhythmia in both

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endurance athletes and the general (non-athletic) population, there are likely differences in the etiology and clinical presentation of the two conditions, and the treatment approach might also differ. In this review, we discuss the mechanisms, clinical features, and treatment options of the AF that develops in previously healthy endurance athletes. Due to its unique characteristics, we propose it is considered as a 'new syndrome'.

2. Etiology of SEE-associated AF

Although the pathophysiological mechanisms responsible for the onset of AF in athletes remain to be clearly elucidated, below we review the main potential substrates and triggers for the onset of this condition (see also Fig. 1 for a summary):

2.1. LA remodeling

A clear association between increased left atrial (LA) size induced by SEE and AF has not been consistently reported [26], but dilation/extension of the less-muscular chambers of the atria, for example such as that potentially induced by long-term exposure to SEE and higher arterial blood pressure during exercise [35] with insufficient time for recovery between exercise bouts, might lead to microtrauma, inflammation and fibrosis, which are potential substrates for arrhythmias [41]. LA enlargement and atrial wall stretching might increase proportionally with lifetime training hours [42] or within competition level. Notably, Pelliccia et al. observed that ~20% of competitive athletes exhibited an LA diameter > 40 mm [26]. In those athletes with increased LA size [26], this structural heart change is conventionally regarded as a physiologic, non-pathological adaptation [26,43–47].

The LA volume, as well as the indexed ratio of end-systolic LA volume to end-diastolic volume, can also increase with SEE, for example in triathletes [48] or in former elite endurance athletes who are still active in Masters categories (marathoners, cyclists) [49]. Mont et al. observed that LA anteroposterior, longitudinal and transverse diameters and volumes increase with SEE [46], although physiological changes in atrial function were not assessed. D'Ascenzi et al. reported an improved LA function of top-level endurance athletes compared with controls, coupled with a LA reservoir within the normal range and a reduced LA active contribution to resting left ventricle (LV) diastolic filling in the former [50]. Brugger et al. observed that LA anatomy and electrical remodeling did not negatively affect atrial mechanical function in endurance runners [51]. Notably, filling pressures did not differ between athletes and controls in the aforementioned studies, and remained

stable in response to training in the former, which suggests that atrial dilatation in athletes occurs due to volume rather than pressure overload. In contrast to elderly people, endurance athletes suffer from both repeated pressure and volume overload during long exercise sessions; this pathophysiologic condition might play a key role. The notion that LA function is not negatively affected by SEE has been confirmed in female competitive athletes after 4 months of training [52]. New techniques to directly evaluate LA performance might lead to new insight on LA function [53].

Micro-RNAs (miRNAs) are small noncoding genome regions that regulate a myriad of cell processes and body functions including cardiac function under physiological and pathological conditions, for example they help reconstruct ion channels by regulating gene expression in cardiomyocytes during the process of arrhythmia. Some miRNAs are important mediators of pro-arrhythmogenic remodeling (i.e., those implicated in electrical and structural remodeling, atrial fibrosis, and calcium homeostasis such as miR-1, miR-26a, miR-29b, miR-30a and miR-133a), and have hence been proposed as potential biomarkers of AF [54]. Clauss et al. analyzed the blood levels of miRNAs after a marathon run [55]. Trained ('elite') runners showed more pronounced changes in several miRNAs compared with baseline values than less trained ('non-elite') runners. Notably, miR-1 and miR-133a levels increased significantly after the race in elite runners compared with their less trained peers, whereas miR-26a decreased only in the former. In addition, these authors linked two cardiac tissue-specific miRNAs associated with myocardial ischemia-induced arrhythmia, miR-1 and miR-133a, to LA diameter in the elite runners. Both markers were up-regulated and correlated with LA diameter 24 h after a marathon in the latter but not in those ('non-elite') with a lower training background. The authors speculated that the level of miRNA expression may explain, at least in part, the discrepancy between 'beneficial moderate exercise' and 'potentially harmful SEE', and that circulating miRNAs could serve as biomarkers of pro-arrhythmogenic signaling leading to atrial enlargement after long-term SEE.

On the other hand, the investigation of possible gender-specific differences in SEE-related AF might help to gain more insight into the pathophysiology of this type of arrhythmia. In this regard, although biatrial enlargement has also been demonstrated in female endurance athletes [52], it seems that female veteran endurance athletes have less pronounced atrial remodeling, lower sympathetic tone, balanced autonomic function, and lower blood pressure than their male counterparts [56].

2.2. LA fibrosis

LA fibrosis might play a key role in the generation of supraventricular arrhythmias [50]. Although development and progression of atrial fibrosis is considered the hallmark of structural remodeling in AF and therefore a substrate for AF perpetuation [57], this phenomenon has only been observed in two studies with SEE-exposed animals (Wistar rats) [58,59]. Sixteen weeks of SEE increased the expression of fibrosis biomarkers in rodents' atria and ventricles compared with a control group. The SEE-induced fibrotic changes were reversed after an 8-week exercise cessation period [58]. Another study showed that a 16-week SEE intervention increased atrial fibrosis in rats, a phenomenon that remained unchanged after detraining [59].

Indirect evidence of SEE-induced atrial fibrosis in humans comes from a study by Lindsey et al., which included 45 veteran endurance athletes [60]. When compared with sedentary controls, these individuals displayed higher levels of three biomarkers of cardiac fibrosis, plasma carboxyterminal propeptide of collagen type I (PICP), carboxyterminal telopeptide of collagen type I (CITP), and tissue inhibitor of matrix metalloproteinase type I (TIMP-1) [60]. However, there was no assessment of actual atrial fibrosis. D'Ascenzi et al. assessed LA fibrosis using echocardiography and cardiac magnetic resonance imaging (cMRI), concluding that myocardial stiffness

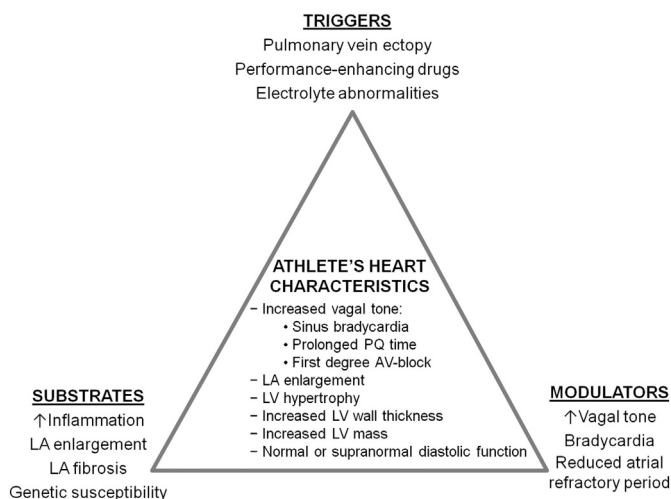


Fig. 1. Possible etiopathogenic causes (substrates, triggers and modulators) involved in the onset of paroxysmal AF in SEE practitioners. Extracted from Mont et al. [86].

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