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JCCM ISSN 2575-0143 JOURNAL OF CARDIOLOGY AND CARDIOVASCULAR MEDICINE

Literature Review

Atrial fibrillation in elite athletes. What is missing?

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Abstract

Although the beneficial effect of physical activity in the general population is well established, in elite athletes under vigorous physical activity, the effect on the electrical system of the heart is controversial. Indeed, several studies have shown an increased rate of atrial fibrillation among athletes, whereas others suggest that improved exercise capacity with training reduces atrial fibrillation recurrence. The pathophysiologic explanation of that discrepancy is missing, although several underlying mechanisms have been proposed. Taking into account the current knowledge, it seems that, although the beneficial effects of exercise are well recognized, there are conflicting data regarding the relation of the occurrence - the rate of atrial fibrillation to high-volume exercise and too long-term training. Its significance on the quality of life especially in highly trained athletes remains to be elucidated. Therefore, this short review will try to discuss this discrepancy and hopefully underlie the arising arguments.

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Submitted: October 10, 2022
Approved: October 26, 2022
Published: October 27, 2022

How to cite this article: Tsougos E, Giallafos E, Paraskevaidis I. Atrial fibrillation in elite athletes. What is missing? J Cardiol Cardiovasc Med. 2022; 7: 085-092.

DOI: 10.29328/journal.jccm.1001139

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Introduction

In the general population as well as in patients with cardiovascular disease, several reports strongly recommend physical activity in order to increase cardiorespiratory capacity and fitness [1,2]. In keeping with these studies, exercise training seems to improve endothelial dysfunction, attenuate atherosclerotic plaque vulnerability and ameliorate functional capacity and muscle strength [3,4]. Additionally, exercise tends to normalize several cardiovascular risk factors such as hypertension and cardio-metabolic disorders. Hence reducing morbidity and mortality [5-7]. Therefore, physical activity is highly recommended in a diseased and healthy population [8]. However, it is unclear whether the amount of exercise is associated with beneficial effects. Of note, it has been proposed that 15 min per day or 90 min per week of moderate-intensity exercise is beneficial [9], whereas marathon runners performing a prolonged vigorous activity show biochemical and echocardiographic evidence of cardiac dysfunction and injury [10]. Notably, although the beneficial effect of normal physical activity in the general population is well established, in elite athletes under vigorous physical activity the effect on the electrical system of the heart is controversial. Indeed, several studies suggest an increased rate of atrial fibrillation among athletes [11-13], as well as in the normal population caused by the high volume of exercise effort [14,15]. On the contrary, other studies suggest *'that both greater exercise capacity and increases in exercise capacity with exercise training reduce atrial fibrillation recurrence change* [16]. However, it is noteworthy that athletes performing rigorous training are dealing with a high workload that is much greater than that proposed for heart disease prevention [17,18]. The pathophysiologic explanation of this discrepancy is still missing, likely proposed causes include sympathetic/parasympathetic tone unbalance, left atrial and/or left ventricular dilatation, and hypertrophy [19-24].

Atrial fibrillation (AF) is a very common cardiac arrhythmia with the incidence in adults ranging between 0.5% - 15% with linear relation to age [25,26]. Its association with cardiovascular mortality is well established. Its etiology is multifactorial, including non-modifiable causes such as increased age, sex, and genetic factors, as well as modifiable ones such as hypertension, diabetes mellitus, heart failure, and coronary artery disease [27]. According to current knowledge, although the beneficial effects of exercise physical activity are well recognized, there are conflicting data regarding the relationship between the occurrence - the rate of atrial fibrillation and high volume or prolonged exercise. Its effect on the quality of life especially in highly trained athletes remains to be elucidated. Therefore, this short review will try to discuss this discrepancy and hopefully underlie the arising arguments.

Define an 'Athlete'

Until recently different definitions existed in an attempt to identify the truly-active athlete. This has led to confusion, complicating published results interpretation. In 2016 a working definition for an athlete was suggested for medical and health sciences research proposing four criteria: 1, training in sports aiming to improve his/her performance/ results; 2, actively participating in sports competitions; 3, formally registered in a local, regional, or national sports federation; 4, sports training and competition being the main activity (way of living) or focus of personal interest, devoting several hours in all or most of the days, exceeding the time allocated to other types of professional or leisure activities [28]. The latest European Society of Cardiology Guidelines on sports cardiology suggested that the definition of "athlete" has to depend on the degree of exercise. Thus, 3 categories were proposed according to to exercise volume; 'elite' athletes, who generally exercise ≥ 10 h/week 'competitive' athletes who exercise ≥ 6 h/week, and 'recreational' athletes who exercise ≥ 4 h/week. However, as the authors state, this distinction is arbitrary [29].

The lack of a clear definition and classification leads to confusion in the studies' results interpretation. Some studies enroll different subjects with different profiles and levels of competition or subjects that do not fulfill all the criteria of the 'athlete' definition. This highlights the need for a universally accepted definition of 'athlete'.

Pathophysiology - approach of adverse outcome in Athletes

During high-volume exercise, there is a cardiovascular and peripheral (skeletal muscle) adaptation characterized by the increase of pre- and after-load, heart rate and cardiac output, enlargement of cardiac chambers, and increase in catecholamine production and oxygen demand (Figure 1). This adaptation in some cases (e.g. marathon runners) could be rather harmful, as suggested by the increase in cardiac biomarkers such as troponin, CK-MB, and BNP. Furthermore, free radical production, inflammation, and immune and fibroblast cell activation lead to a fibrotic process in the myocardium, creating a potentially arrhythmogenic substrate associated with all sorts of arrhythmias and sudden cardiac death [18,30-32]. Interestingly, the exercise-related cardiac remodeling noticed in most professional athletes is not restored in all cases after cessation of competitive activity [30,33-38] highlighting the need for methods and markers to allow identification of those individuals. Moreover, a hypothesis of a yet unrecognized structural remodeling, promoting a scarring process [39,40], or even ion exchange alteration has been suggested. Findings from studies on cardiac MRI are conflicting; some have reported patchy myocardial scarring in 12% or even 50% of marathon athletes [30,36,41] suggesting probably a source of myocardial electrical instability, while others showed a similar amount of fibrosis between athletes and controls [42,43]. Interestingly, studies in a small group of trainees have shown that a high volume of exercise may lead to right ventricular dysfunction and to myocardial fibrosis [30,32], with unknown consequences [18,30,32,44,45]. In any case, given the lack of data the speculated term exercise-induced arrhythmogenic cardiomyopathy is on the table [46].

Atrial fibrillation and physical activity

In the general population, atrial fibrillation might be the result of either a trigger effect caused by atrial ectopy or cardiac substrate modulation due to hypertension, coronary artery disease, valvular heart disease, *myocarditis,* and heart failure. However, this is not the case in young highly trained persons. In this particular population, the underlying mechanism of atrial fibrillation is rather speculative. Some studies indicate no relationship between physical activity and atrial fibrillation

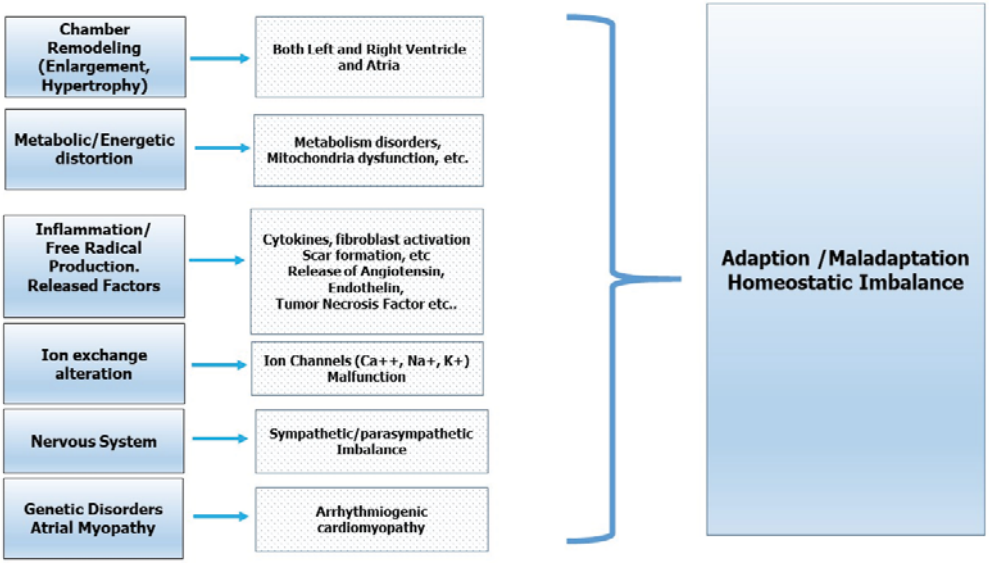

Figure 1: Presumed mechanism of Atrial Fibrillation in Athletes.

[8,47,48] whereas, others [49], suggest a close association between them. Keeping this discrepancy on the road there are published data that relate the time of exercise or the presumed AF treatment, with this superventricular arrhythmia [50,51]. On the other hand, there are reports with no relation between a high volume of exercise and risk for atrial fibrillation [52]. The latest guidelines on sports cardiology do not elaborate on the impact of atrial fibrillation and its relation to physical activity. Indeed, the authors underline their ignorance on this topic by stating that *'The threshold lifetime sports activity for increasing the risk of developing AF is unknown. It is also unknown whether ongoing participation in vigorous exercise at the same intensity after successful AF ablation is associated with a higher risk of AF recurrence'* [29]. Thus, the etiology of AF in highly trained people has to be elucidated, although several mechanisms Figure 1, such as cardiac chamber remodeling, genetic predisposition, sympathetic/parasympathetic tone imbalance, fibrosis, and inflammation have been suggested. 18,20,23,24 Certain inherited gene defects might, under the presence of environmental factors like aging, obesity, systemic inflammation, arterial hypertension, and/or diabetes mellitus, promote chamber remodeling, alter the atrial electrophysiological properties, and finally establish atrial fibrillation [52A,52B]. Elite athlete's remodeling can be caused by long-term high volume exercise which may trigger arrhythmogenesis [13,31,34,36,53,55-57], due to several factors including atrial wall fibrosis, a potential source of re-entry circuits [23,57]. Additionally, the injured myocardium in active highly trained athletes such as marathon runners may have created a very subtle substrate; cardiac fibrosis, or even Ca++, K+, Na+ channel alteration/dysregulation, that is a source and a consequence of electrical instability.

Another suggested trigger mechanism for atrial fibrillation is increased nervous system activity which is common in highly trained people. However, the increased activity is countered by the functional sympatholysis [58-61] which creates a local rather than a global effect making the increased sympathetic activity as a trigger for atrial fibrillation less likely. Although parasympathetic activity might be a potential mechanism since triggers localized reentry, it seems that this is not the case unless there is an ectopic activity on pulmonary veins that is activated by the increased vagal tone that promotes a shortening of the atrial refractory period [11,23]. Thus, the sympathetic/parasympathetic ratio activity is less likely to be the main cause of atrial fibrillation induction [62].

Interestingly, it seems that long-term rigorous training may lead to left atrial remodeling which might be the source of atrial fibrillation [13,41,63,64]. Indeed, this has been proposed in an experimental model by showing an increased atrial fibrillation susceptibility due probably to a fibrosis process [41].

Atria and physical activity

Although in the general population there are convincing data showing the close relation between left atrial remodeling and atrial fibrillation, in the case of the highly trained population there are conflicting data. Indeed, several studies in athletes have suggested an association between left atrial remodeling and atrial fibrillation [23,65-69], whereas others doubt this concept by stating that *'LA enlargement represents an innocent consequence of chronic and intensive exercise conditioning'* [70]. Accordingly, it has been shown that although the left atrial is enlarged in athletes, its function remains normal or even is improved [71,72]. Moreover, no relationship between left atrial enlargement and electrophysiologic remodeling has been clearly demonstrated [71,73]. Several pathophysiological changes occur in both atria occur during exercise. The heart is forced to augment the stroke volume in order to satisfy the metabolic needs of the body. The increased negative left ventricular early diastolic pressure leads to a larger downslope motion of both mitral and tricuspid annulus resulting in an increased atrial reservoir phase. [74-76]. Additionally, the atrial contraction phase is increased due to the high atrial pressure [77] along with the shortening of the conduit phase. Although the physiologic adaptation of both atria is well proven, it remains a fact that low to median exercise is beneficial whereas in highly trained athletes it could be detrimental. However, the latest is not the case for all highly trained athletes. Therefore, there must be a differentiation in both adaptive and maladaptive processes [78]. In fact, the capacity of the organism to overcome myocyte hypertrophy, inflammation, fibrosis, free radical production, released factors such as angiotensin, tumor growth factor, endothelin, etc [79-85], as well as the energetic and metabolic disturbances/maladaptation [86-88] is crucial and therefore we have to pay attention on this particular and very elegant topic (Figure 1). However, mechanisms related to energy and cellular metabolism are highly complicated and dependent on many intrinsic and extrinsic factors including specific high-energy food intake or even anabolic capture substances. For instance, an elite athlete's performance is influenced by diet habit status during different religious beliefs (Christian fasting state, Ramadan for Muslims) which interfere with circadian rhythm. These mechanisms have a synergistic effect on the Autonomic Nervous System disturbance and promote the induction and/or persistence of AF [88A,88B].

Understanding the ambiguity

Several explanations might be proposed in order to justify our poor understanding. For instance, the existing variety of definitions of training as demonstrated by several studies that took into account both the amount [89-95] and the long-term physical activity must be taken into account. The U-shape relation between atrial fibrillation and the volume of exercise might be a reason [8,9,53,91,96], along with the lack of this relation in women [91]. Studies with a more homogeneous population as far as sex, the volume of exercise load, and duration of exercise shall be designed in order to reach a more reasonable conclusion. Moreover, many studies

have enrolled veteran athletes which might have affected the results and consequently the conclusions. Several reports suffer from statistical heterogeneity suggesting conclusions of questionable significance. We do need to conduct studies methodologically and properly designed. Is it reasonable to enroll 'athletes' of different sex, age, type, frequency and volume of exercise, daily duration of exercise, or even weekly or annual duration? Is the sample size powered enough to give such conclusions? Are all the enrolled 'athletes' under the same regimen of their day-life habits? [15,50,56,96]. Of note, in an attempt to overpass these limitations a systematic review and meta-analysis have been recently published, but as the authors admit, their review is limited by the strict methodological criteria that they applied; excluding a high number of studies, indicating thus the need for performing larger and more accurately designed studies [98]. Surprisingly, there is also a lack of concrete data concerning the occurrence of atrial fibrillation. According to a study that comprise highly trained athletes [70], the occurrence - rate of atrial fibrillation is only 0.2-0.3% whereas others found a much higher incidence [14,15,53,56,70,96,99-107], reaching even 31%.

Although the distinction between physiological and abnormal response is more or less clear [78], it must be taken into account the capability of new well-designed studies to predict those who are prone to overpass the homeostatic balance.

In conclusion, atrial fibrillation is an arrhythmia that is present in a variable percentage of highly trained individuals with unknown so far etiology. The cause and the pathophysiologic background of this arrhythmogenic event remain to be elucidated. The scientific community should take into account the raised discrepancies and conduct a properly designed study. Importantly, we have to focus on those highly trained individuals who have the profile/characteristics to present not only this particular arrhythmia but any cardiac harmful event.

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