

# Prevalence, mechanism and management of atrial fibrillation in athletes<sup>1</sup>

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## Summary

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice with an estimated prevalence of 0.4% to 1% in the general population [1], increasing with age to 8% in those older than 80 years [2]. The recognised risk factors for developing AF include age, structural heart disease, hypertension, diabetes mellitus and hyperthyroidism [3]. However, the mechanisms underlying the onset and maintenance of AF in patients younger than 60 years in whom no cardiovascular disease or any other known causal factor is present are yet to be clarified. This condition is termed lone AF [4], and may be responsible for as many as 30% of patients with paroxysmal AF seeking medical attention [5, 6].

It is well known that regular exercise is beneficial to health and reduces the risks of cardiovascular diseases [7, 8]. However, recent studies suggest that long-term endurance exercise may increase the incidence of AF [9–16].

This review article is intended to analyse the possible links between AF and endurance sport practice, the pathophysiological mechanisms responsible for this association and the recommended therapeutic options.

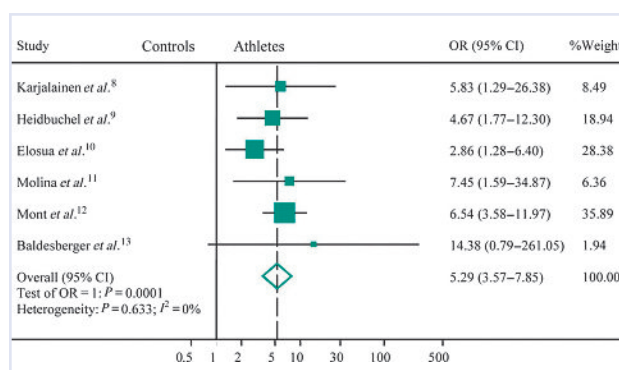
*Key words:* endurance sport; athletes; atrial fibrillation

## Atrial fibrillation and endurance sport

In recent years, an association has been demonstrated between endurance sport practice and AF or atrial flutter (fig. 1). In 1998, Karjalainen et al. [9] evaluated the presence of AF in 228 veteran male orienteering racers (cross-country runners) and compared this with AF prevalence in a matched control group. Lone AF (LAF) was diagnosed in 12 orienteering racers (5.3%) vs 2 control subjects (0.9%). A retrospective analysis of our

**Figure 1**

Meta-analysis of AF risk in athletes compared with controls. From: Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? *Europace*. 2009;11:1156–9. © Oxford University Press, Oxford, UK. Reprint with permission.)



group including 1160 consecutive patients showed that the proportion of regular sport practice (defined as a high-intensity sport practice of at least three hours a week) among men with LAF was much higher than among men from the general population (63 vs 15%) [10]. An age-matched case-control study of the same population of LAF patients found that the risk of developing LAF was five times greater (OR 5.06 [1.35–19]) in those currently practicing an endurance sport [11], and this association was observed at more than 1500 lifetime hours of sport practice. In a further study, our group analysed the incidence of LAF among marathon runners. The study included 183 individuals who ran the Barcelona Marathon in 1992 and 290 sedentary healthy individuals. After ten years of follow-up, the incidence of LAF was higher among marathon runners compared to sedentary men (annual incidence: 0.43/100 for runners, 0.11/100 for sedentary men) [15].

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Heidbuchel et al. [13] evaluated the influence of sport activity on the risk of AF after the ablation of atrial flutter. Of 137 patients with atrial flutter undergoing ablation of the right atrial isthmus, 31 (23%) regularly participated in endurance sports. A history of competitive sport practice was associated with a higher postablation risk of developing AF (multivariate HR 1.81 [1.10–2.98,  $p = 0.02$ ]), and ongoing practice of an endurance sport after the ablation also increased the risk of AF (multivariate HR 1.68 [0.92–3.06],  $p = 0.08$ ).

Baldesberger et al. [12] published similar data in a study of 62 professional cyclists who completed the Tour de Suisse professional cycling race at least once during the years 1955–1975. These athletes were compared with a control group of 62 male golfers who had never performed high endurance training. Individuals were matched for age, weight, hypertension and cardiac medication. Paroxysmal or persistent AF or atrial flutter was reported more often in the cyclists.

Additionally, recently, Aizer et al. [17] investigated the relation of vigorous exercise to AF risk in a large cohort of healthy male physicians. The authors compared four exercising groups with increasing levels of endurance with a non-exercising group as reference. The multivariate analysis at three-year follow-up showed that there was an increased risk of AF in the most exercising group. The increase in risk decreased with increasing age. In men >50 years of age, no significant association was found. However, the risk remained statistically significantly higher in men <50 years of age and joggers.

In contrast with these previous studies, Pelliccia et al. [18] reported that LAF was uncommon among competitive athletes and the incidence was similar to that observed in the general population. However, it should be noted that this study was performed among young athletes at the height of their activity, while previous studies supporting the association have included middle-aged individuals, after many years of sport practice. On the other hand, in the Cardiovascular Health Study [19], the incidence of AF in older adults (>65 years old) was lower with moderate-intensity exercise. However, this was not true with high-intensity exercise.

In summary, most of the available data support the significant association between excessive sport practice and the occurrence of lone AF. However, the underlying mechanisms are a matter of debate.

Finally, it should be mentioned that most of the previous studies have been performed in men, whereas the risk for women has not been well investigated.

### Pathophysiology of AF in endurance athletes

The pathophysiological mechanisms underlying the increased risk of AF in individuals who practice an

endurance sport remain unclear. Several mechanisms may be acting together. It is well accepted that arrhythmias depend on triggers, substrates and modulators and these factors might be present in relation to physical activity.

### Triggers: role of atrial ectopy

Pulmonary vein ectopy has been shown to be the trigger in most episodes of paroxysmal AF [20]. Both atrial and ventricular ectopy have been shown to be increased as a consequence of physical activity [12, 21]. Therefore, increased atrial ectopy, acting upon an appropriate substrate, might explain the increased risk for AF associated with sport practice. However, although an increase in ventricular ectopy and VT runs in former professional cyclists was reported by Baldesberger et al. [12], they did not find an increased incidence of atrial ectopy. Therefore, there is no currently available data to confirm the role of atrial ectopy as AF trigger in athletes.

### Influence of the autonomic nervous system

The role of the cardiac autonomic nervous system (ANS) in the initiation and maintenance of AF has been actively investigated [22–25]. Coumel [26] studied the influence of autonomic innervations in the appearance of AF and atrial flutter and originally described “vagal AF”. The symptoms of “vagal AF” described by Coumel include: (1.) predominantly affects males between 30 and 50 years of age, (2.) usually occurs at night and rarely occurs between breakfast and lunch when the sympathetic tone is high, (3.) rarely occurs during exercise or emotional stress, (4.) is frequently triggered during relaxation after stress and (5.) is often preceded by bradycardia lasting from seconds to hours. However, he did not establish a relationship between these episodes of AF and sport practice.

In addition, experimental animal models have demonstrated that atrial fibrillation can be induced by acetylcholine [27] and that increasing vagal tone shortens the atrial refractory period, which, combined with atrial stimulation, induces AF [28].

High vagal tone manifesting as sinus bradycardia and asymptomatic AV conduction delay in well-trained athletes has been known for decades. According to the GIRAFA study [14], vagal AF is the rule rather than the exception in patients with lone AF (70% of consecutive patients with lone AF had vagal AF). Therefore, the increased vagal tone induced by endurance sport practice could facilitate the appearance of AF. Further studies with a systematic inquiry into AF origin are needed.

### Exercise and structural changes in the atrium

Long-term endurance sport practice has been proposed as being responsible for structural changes in the atrium (e.g., enlargement, fibrosis) that may create a

favourable substrate for the disease, similar to hypertension or structural heart disease as a consequence of chronic volume and pressure overload. A small study by Frustaci et al. [29] analysed the structural changes in the atria of patients with lone AF. Inflammatory lymphomonuclear infiltrates, compatible with myocarditis, were found in 66% of the patients, a non-inflammatory cardiomyopathic process in 17% and patchy fibrosis in the remaining 17%.

Recent experimental data from our group showed that endurance exercise may induce fibrosis in a rat model of chronic exercise, particularly at the atrial and right ventricular level [30]. In this study, an increase in mRNA and protein expression of a series of fibrotic markers in the RV and in both atria was showed at 16 weeks of training. Additionally, Lindsay and Dunn [31] showed an increase in humoral markers of fibrosis in veteran athletes compared to sedentary subjects. Athletes showed an increase in three collagen markers – plasma PICP, C1P, and TIMP-1 – when compared with sedentary controls, suggesting that long-term sport practice may provoke fibrosis as part of the hypertrophic process in veteran athletes.

More recently, Breuckmann et al. [32] compared the myocardial distribution of late gadolinium enhancement (LGE) with delayed-enhancement cardiac MR imaging in nonprofessional male marathon runners and in asymptomatic control subjects and found a higher prevalence of LGE in runners than in age-matched control subjects (12% vs 4%;  $p = 0.077$ ). Similarly, Wilson et al. [33] observed a high prevalence (50%) of myocardial fibrosis in healthy, asymptomatic, veteran, male life-long athletes, compared to zero cases in age-matched veteran controls and young athletes.

Additionally, previous studies have found that excessive training may lead to tissue injury, which activates circulating monocytes, producing large quantities of IL-1 $\beta$  and/or IL-6 and/or TNF- $\alpha$  and systemic inflammation [34].

However, there are no studies in the literature that confirm an association between AF, inflammation and exercise.

Recent studies suggest that structural remodelling is often present in the atrium of elite athletes. Pelliccia et al. [17] described the remodelling induced by exercise in elite sport athletes. Their study showed that those involved in regular endurance practice have a larger atrium than the sedentary controls. Furthermore, a significant proportion (20%) had enlarged atria according to established normal values.

GIRAFa study data [14] found that patients with LAF had a larger atrium than the controls, and patients with a first episode of AF had the same atrial size compared to those suffering recurrences, which might mean that structural changes were present before onset of AF.

In addition, experimental studies of our group [30] observed a left atrial dilatation, LV hypertrophy and dilatation, and diastolic dysfunction at 16 weeks of training, findings which are consistent with the features of the athlete's heart described in humans.

The reversibility of arrhythmogenic remodelling has also been assessed. Clinical studies have reported regression of the morphological changes characteristic of the athlete's heart after long-term detraining [35]. Our group evaluated whether a period of rest could allow reversion of the profibrotic changes induced by endurance training in our model of endurance exercise in rats [30]. After eight weeks of detraining, the abnormal cardiac remodelling parameters resulting from intense exercise training regressed to control levels.

More studies are needed to ascertain the mechanisms that participate in the promotion and reversal of the remodelling associated with long-term exercise and detraining, respectively.

### Clinical characteristics of sport-related atrial fibrillation

Whereas AF is an unusual finding in athletes below 35 years old, it becomes more common after 45 years of age. The typical clinical profile of sport-related AF is a veteran male athlete in his forties or fifties, who has been involved in regular endurance sport practice since his youth and is currently involved in regular endurance high-intensity sport practice.

The AF is usually paroxysmal with crisis, initially very occasional and self-limited, but typically becomes more frequent and prolonged over the years as AF becomes persistent. The AF crisis frequently coexists with common atrial flutter in many patients. Characteristically, AF episodes occur at night or after meals. Since the AF crisis rarely occurs during exercise, the patient is reluctant to accept a relationship between the arrhythmia and sport practice.

### Management of AF in athletes

Furlanello et al. [35] described a good response to sport abstinence in top level athletes with AF. Hoogsteen J et al. [36] showed that 11–30% athletes experienced reduction of attacks of AF by reducing sport activity. Our observations agree with these findings, so our first approach in these patients is to recommend limiting physical activity. However, these patients are very dependent on physical activity and it is difficult for them to reduce their endurance sport practice.

After all of the potential contributing factors have been eliminated (i.e., medical conditions such as hyperthyroidism, pericarditis, Wolff-Parkinson-White syndrome, hypertrophic cardiomyopathy or long QT syndrome; substances such as cocaine, caffeine, anabolic steroids and sympathomimetics in cold medicines), the

Study Group on Sports Cardiology of the European Association for Cardiovascular Prevention and Rehabilitation [37] recommends that athletes in an early stage of paroxysmal AF should discontinue training for two months to stabilise sinus rhythm. The degree of improvement during this resting period determines if athletes can resume their training.

In athletes without other cardiac disorders, the recommendation for sport participation also depends on the ventricular rate during AF. If there is a history of high ventricular rate or haemodynamic instability during AF, the athletes should be instructed to stop exercising if palpitation or related symptoms occur. Such patients may need medications that slow the ventricular rate, ideally at doses that do not cause sinus bradycardia at rest or chronotropic incompetence during exercise. In these patients, we prescribe AV-node slowing agents despite moderate bradycardia during sinus rhythm. A close follow-up including ECG-Holter monitoring to rule out severe bradycardia is usually performed.

Task Force 7 of the 36th Bethesda Conference [38] recommends that athletes with asymptomatic AF in the absence of structural heart disease can be permitted to participate in any competitive sport, provided they maintain a ventricular rate that increases and slows appropriately and is comparable to that of a normal sinus response in relation to the level of activity, while receiving no therapy or therapy with AV nodal-blocking drugs. Asymptomatic athletes who have AF episodes lasting 5 to 15 seconds with no increase in duration during exercise can participate in all sports.

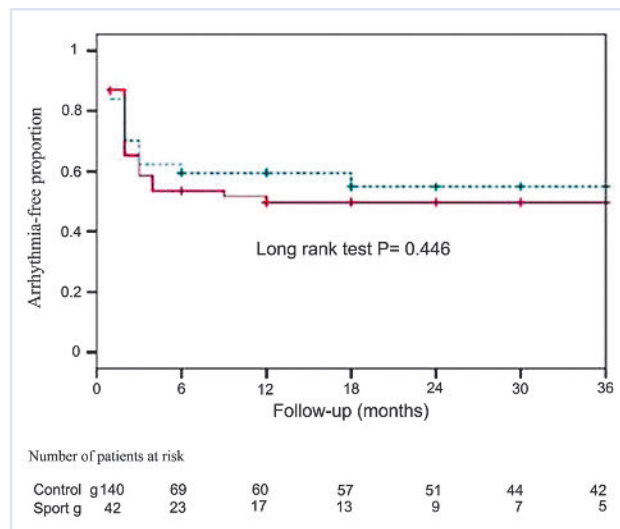
The possible long-term role of medications (ACE inhibitors, angiotensin inhibitors, calcium antagonists or beta-blockers) in preventing cardiac hypertrophy remains to be elucidated, although angiotensin inhibitors do seem to play a role in improving the results of cardioversion or AF ablation [39, 40]. Particular caution should be exercised with the monotherapeutic use of class 1 antiarrhythmic drugs in AF patients. These drugs may prevent AF recurrences, but can also convert AF into slow atrial flutter, which may conduct one-to-one to the ventricles during situations of high sympathetic tone [41, 42]. Class 1 drugs can be initiated for the prevention of AF episodes after adequate ventricular rate control during exercise has been assured.

When therapy with class 1 drugs is indicated in athletes, a combination with diltiazem or prophylactic ablation of the flutter circuit must be considered. The “hybrid” therapy of class 1 drugs and the ablation of flutter may obviate the need for maintenance therapy with bradycardic agents [43, 44].

In most athletes with paroxysmal AF we use class 1 drugs as the “pill-in-the pocket” approach [45]. These patients are always instructed to refrain from sports as long as the arrhythmia persists and until at least one half-life of the antiarrhythmic drug has passed.

**Figure 2**

Kaplan-Meier curves for long-term freedom from recurrent arrhythmias after a single ablation procedure in lone AF athletes group (dashed line) and control group (solid line). From: Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, et al. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. *Europace*. 2010;12(1):30–6. © Oxford University Press, Oxford, UK. Reprint with permission.



On the other hand, circumferential pulmonary vein ablation (CPVA) is an effective and safe treatment of AF, with success rates ranging from 40% to 85% in the general population [46]. In athletes, a study by Furlanello et al. [47] described a 90%-success after a mean of two ablation procedures in 20 athletes without major complications.

A recent study by our group [48] compared the effectiveness of CPVA between a population of endurance athletes with lone AF and other patients with AF. Athletes were defined as those who performed regular endurance sport activity (cycling, jogging, swimming, soccer, rowing, etc.) for at least three hours per week for at least the 10 years immediately preceding the arrhythmia diagnosis. The mean age of endurance athletes with lone AF was 48.5 years and 93% were male. In all the patients CPVA was performed due to symptomatic and drug-refractory AF. We did not find differences in CPVA effectiveness between the two groups (fig. 2). Furthermore, endurance sport practice was not a predictor of the ablation outcome.

Anticoagulation may be necessary in competitive and leisure time athletes with unsuccessful rhythm control or with rate control treatment, depending on the presence of classic risk factors for thromboembolic events [49]. Anticoagulation therapy excludes these individuals from sports with a risk of bodily collision or trauma [37].

In summary, endurance sport cessation associated with drug therapy seems to us the best suitable approach as an initial therapy, particularly in nonprofessional, veteran athletes. However, based on the excel-

lent results of AF ablation in this group of patients, we offer them an early ablation management, which is also offered to patients reluctant to take drugs.

## Conclusions

Long-term endurance sport practice has been demonstrated to increase the risk for AF, probably due to the underlying role of cardiac autonomic nervous system and left atrial structural changes (dilatation, inflammation and fibrosis). Further studies are needed to clarify the mechanism of AF in endurance sport practice and to look for a threshold limit for the intensity and duration of physical activity that may avoid the development of AF, without limiting the cardiovascular benefits of exercise.

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