REVIEW

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Endurance Exercise and Atrial Fibrillation – A State of the Art Review

Ausdauersport und Vorhofflimmern – Eine aktuelle Übersicht

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Summary

› **Increasing physical activity** has convincingly shown to reduce the risk of atrial fibrillation (AF). However, decades of repetitive bouts of prolonged and vigorous endurance exercise have recently emerged as a risk factor for AF in middle-aged male athletes.

› **The pathophysiology** underlying this relation poses a puzzling question with multiple hypothesized mechanisms, which probably in combination create the necessary substrate and trigger for AF onset. Adaptive atrial changes secondary to long-standing endurance training as part of the "athlete's heart" add special considerations as they build a grey zone of diagnostic uncertainty with atrial changes seen in individuals with AF. Evolving functional diagnostic modalities may re-shape this diagnostic grey zone and facilitate diagnostic workup.

› **Initiating management of AF** requires documentation of an AF episode, which can be challenging in athletes as it usually occurs intermittent. New wearable devices hold promise to facilitate early documentation and follow-up, but their diagnostic reliability still has to be established, especially during exercise. When counseling competitive athletes and highly active people regarding treatment options of AF, special considerations should be taken into account to reduce risk associated with AF but also sustain the numerous health benefits of regular exercise and the lifestyle of being a competitive endurance athlete.

› **This narrative, state of the art review** aims to describe the association between AF and endurance athletes including current findings and mechanistic concepts and thereby giving an update on a highly relevant clinical topic in sports medicine.

KEY WORDS:
Arrhythmia, Physical Activity, Master Athlete, Athlete's Heart, Prolonged Exercise

Zusammenfassung

› **Eine Steigerung der körperlichen Aktivität** steht in enger Verbindung mit der Reduktion des Risikos für Vorhofflimmern (VHF). Eine Vielzahl an Publikationen deutete in den letzten Jahren jedoch darauf hin, dass lange und intensive Ausdauerbelastungen über mehre Jahrzehnte das Risiko für Vorhofflimmern bei Männern im mittleren Lebensabschnitt erhöhen.

› **Die dieser Assoziation** zugrundeliegende Pathophysiologie ist nicht abschließend geklärt und unterschiedliche Mechanismen werden diskutiert, welche vermutlich in Kombination das notwendige Substrat und den Auslöser für VHF bilden. Vermeintlich adaptive Anpassungen der Vorhöfe auf Grund von mehrjährigem Ausdauertraining als Zeichen eines „Sportlerherzens" bildet einen diagnostischen Graubereich und ähneln Vorhofveränderungen bei Vorhofflimmerpatienten. Zunehmend können neue Funktionsmessungen die Differentialdiagnostik in diesem Graubereich verbessern.

› **Voraussetzung für eine VHF-Therapie** ist die Dokumentation einer VHF-Episode und kann auch bei Sportlern eine Herausforderung darstellen, da diese häufig nur intermittierend vorkommt. Neue tragbare Sensoren ermöglichen durch ein durchgehendes Monitoring eine frühe Dokumentation und die Möglichkeit von engmaschigen Kontrolluntersuchungen, jedoch ist deren Zuverlässigkeit noch nicht ausreichend untersucht, insbesondere während sportlicher Belastung. Bei der Beratung von leistungsorientierten Sportlern bezüglich Behandlungsoptionen bei VHF sollten spezielle Überlegungen nicht nur das mit VHF verbundene Risiko für Komplikationen und Folgeerkrankungen reduzieren, sondern auch die zahlreichen gesundheitlichen Vorteile von regelmäßigem Sport aber auch den gesundheitsfördernden Lebensstil von leistungsorientierten Ausdauerathleten in Betracht ziehen.

› **Diese Übersichtsarbeit** beschreibt die Assoziation zwischen VHF und Ausdauersportlern, schließt rezente Erkenntnisse und mechanistische Konzepte ein und gibt dabei eine aktuelle Übersicht über ein für die sportmedizinische Praxis relevantes Thema.

SCHLÜSSELWÖRTER:
Arrhythmie, körperliche Aktivität, Masterathlete, Sportlerherz, Ultrabelastung

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Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia and a common cause for stroke and heart failure (21). Increasing physical activity has convincingly shown to reduce the risk of AF in the general population (28). However, a growing body of literature supports a U-shaped relation between lifetime-accumulated high-intensity endurance training and AF in middle-aged men (1). The pathophysiology underlying this relation is incompletely understood with multiple hypothesized mechanisms, which probably in combination create the necessary substrate and trigger for AF onset. Initiating management of AF requires documentation of an AF episode, which can be challenging in athletes as it usually occurs intermittent. New wearable devices hold promise to facilitate early documentation and follow-up, but their reliability still

has to be established, especially during exercise. When counseling competitive athletes and highly active people regarding treatment options of AF, special considerations should be taken into account to reduce risk associated with AF but also sustain the numerous health benefits of regular endurance exercise and the lifestyle of being a competitive endurance athlete.

Epidemiology and Exercise Dose/Risk Relationship of Atrial Fibrillation in Endurance Athletes

Landmark studies with regard to AF incidence derived from Swedish participants (mean age 37 years) of the Vasaloppet cross-country skiing event (distances from 30-90 km). In comparison to the original study published in 2012 (3), in an updated version the sample size was extended (from 52,755 to 208,654), a control group was added and a gender specific analysis was performed (38). After a median follow up of 9 years the AF incidence (per 10,000) was 121 in skiers and 173 in non-skiers. But after adjusting for diseases related to AF, that are diabetes mellitus, hypertension, hyperthyroidism, and ischemic heart disease, a higher incidence of AF in participants with a high number of completed races and better performances was observed compared to non-skiers. AF increased stroke risk in both skiers and non-skiers, but skiers diagnosed with AF still had a lower incidence of stroke (hazard ratio: 0.81 [95%CI 0.65-1.01]) and almost half of the mortality (hazard ratio: 0.65 [95%CI 0.56-0.74]) compared with non-skiers with AF. Another controlled study with former professional cyclists with smaller heterogeneity in performance and longer follow up (median of 35 years after stopping their professional career) than the Vasaloppet study showed an AF prevalence of 10% in this cohort which was considerably higher than the control population consisting of age-matched golfers (4). Finally, in a prospective study with 115 patients with lone AF, that is AF in the absence of other cardiovascular diseases, and age-matched healthy controls, a history of high volume of vigorous lifetime endurance training was associated with increased risk for lone AF (7).

In summary and with regard to the well-established protective effect of low to moderate exercise volume and intensity as well as high cardiorespiratory fitness in reducing the risk for AF in both sexes (15), a U-shaped relation between lifetime-accumulated high-intensity endurance training and AF risk can be drawn for male middle-aged endurance athletes as illustrated in Figure 1. Different cutoffs for the ascending flank of the U-curve have been proposed in male athletes, starting from 5 h/week of vigorous intensity exercise at 30 years of age (12) and an accumulated sport practice of above 1500 h (14). However, exercise/AF-risk dose-response curve shows a high inter-individual variability and thus establishing an upper limit of 'safe' endurance training is elusive.

Based on the abovementioned evidence, current guidelines for the management of AF advocate that athletes should be counselled that long-lasting intense sports participation can promote AF (1). Still, although lifetime-accumulated hours of vigorous activity seem to be a predictor for exercise-induced AF, several further factors should be taken into account: the overall risk of exercise-related AF is low and competitive endurance exercise at the highest level has numerous health benefits and reduces overall mortality (23).

Gender Difference

Endurance exercise has a gender-specific association with AF risk, as women performing intense exercise were found to have 28% lower risk of AF compared to individuals with a sedentary lifestyle (25). It remains unclear why intense physical activity does not increase the AF risk women. Hypotheses that might explain this gender difference include (29): fewer comorbidities, shorter duration of exposure to vigorous exercise, lower sympathetic resting tone, lower blood pressure, gender-specific differences in autonomic response to exercise, impact of sex hormones released in response to exercise, less pronounced atrial structural remodeling. The relation between high-intensity endurance training and AF risk for female endurance athletes is illustrated in Figure 1.

Pathophysiology of Atrial Fibrillation in Endurance Athletes

Atrial Enlargement

In the general population, there is a well-established relationship between increased LA size and the incidence of AF (27), with arterial hypertension being the most important risk factor for atrial dilatation and AF. Endurance activities demand the generation and maintenance of high cardiac output, imposing a volume challenge that triggers an adaptive response, that is enlargement of all cardiac chambers. Consequently, endurance athletes have load-dependent larger LA dimensions compared with sedentary controls when evaluated by either LA diameter or LA volume indexed for body surface area (13, 36). Of note, no confirmatory study using a longitudinal design has proven the prognostic implication of atrial enlargement towards increased risk of AF in athletes. However, recently a retrospective, observational study in young elite Spanish athletes suggests that LA remodeling towards sphericity (that is, greater enlargement of the anteroposterior relative to the longitudinal diameter) might be associated with an increased AF risk (6). Mechanistic hypotheses that describe the relation between LA size with increased risk of AF postulate that i) atrial enlargement is directly related to mechanical wall stress, according to Laplace's law. This holds especially true for the atria, as they have thinner myocardial wall compared to the ventricles; ii) hidden hypertension or hypertension during exercise bouts may further exacerbate this increase in atrial wall stress (22); iii) an increase in atrial mass, which may facilitate conduction heterogeneities and re-entrant electrical activity and thus AF (47). Whether enlarged athlete's atria undergo the same pathophysiologic changes is currently unknown. Thus, although it is tempting to assume that LA dilatation imposes the same prognostic implications among endurance athletes and non-athletes, this hypothesis is not supported by sufficient evidence so far.

Atrial Inflammation and Fibrosis

Although regular physical activity has been demonstrated to exert anti-inflammatory effects, acute bouts of vigorous and prolonged exercise transiently increase neutrophil count, induce the release of pro-inflammatory cytokines and provoke transient increase of cardiac biomarkers (30, 37). Tissue fibrosis results from an accumulation of fibrillar collagen deposits, occurring most commonly as a reparative process. Atrial fibrosis in athletes was first reported after heavy training in an animal model (16) and is hypothesized to be the consequence of increased atrial stretch and inflammation that only incompletely recover between bouts (17). Recently, a late gadolinium enhancement magnetic resonance imaging report provided direct evidence of a 6% increase in left atrial fibrosis in endurance athletes compared to healthy controls (34). Still, confirmatory evidence for exercise-induced fibrosis in athletes and/or that increased wall stretch contribute to myocardial fibrosis is lacking. ›

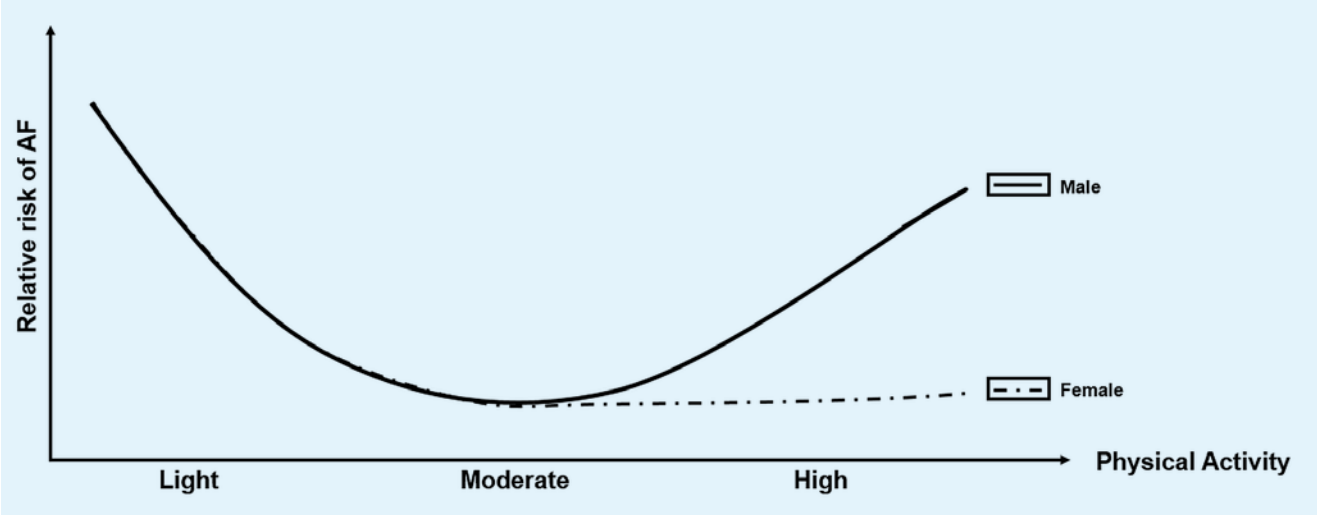

Figure 1

U-shaped relationship between endurance exercise dose and the relative risk of developing AF. While light-to-moderate endurance exercise decreases AF risk, this benefit may be lost or even reverted with higher loads.

Atrial Function

Until recently, atrial function was not getting much scientific attention as the atria were thought to be passive transport chambers only. But current literature indicates that the atria actively modulate ventricular filling and thus contribute to global cardiac performance via three repetitive functional phases (5). Recent advances in echocardiographic imaging such as speckle tracking echocardiography enabled a more independent insight into atrial function by visualizing and calculating each of the three phases separately. As increased atrial function has been shown to be a pre-requisite for an adequate cardiac output during endurance exercise (45) one could speculate that a compromised atrial function during or following endurance exercise coincides with an increased risk of AF. This, however, could not be observed in middle-aged male endurance athletes even after a 5-h laboratory triathlon (37). Still, master endurance athletes with documented paroxysmal AF, that is the first manifestation of AF, have decreased LA reservoir- as well as contractile function compared to endurance athletes without documented AF (20). Notably, in that study, LA strain assessment was more robust than the assessment of LA volumes and ECG parameters for differentiating between master endurance athletes with AF and healthy controls. Thus, functional assessment of the LA holds promise to identify endurance athletes at risk of developing AF due to maladaptive remodeling, especially in the diagnostic work-up of athletes with structural LA changes.

Autonomic Characteristics

Autonomic tone imbalance is an increasingly recognized factor governing AF initiation and maintenance. Regular physical activity promotes chronic cardiac parasympathetic enhancement at rest in animal models (16) and in athletes (44) suggesting that chronically elevated parasympathetic tone at rest plays an important role in exercise-induced AF (42). Moderate to intense exercise bouts promote a transient activation of the sympathetic tone and retrieval of the parasympathetic tone, in order to rapidly increase cardiac output and peripheral oxygen supply. After physical activity is stopped, parasympathetic tone rapidly increases, followed by a delayed and slow retrieval of the sympathetic tone (24). Of note, simultaneous activation of the parasympathetic and sympathetic tone synergistically shortens atrial refractory period and promotes calcium overload. This combination, which might occur during recovery after physical activity, evolves as particularly arrhythmogenic in the pulmonary veins (32). Of note, sinus bradycardia itself, independent of the autonomic tone balance, may also contribute to AF incidence, likely because of increased spatial refractoriness heterogeneity. In addition to changes in the autonomic tone balance, experimental and clinical data in recent years suggest that intrinsic training-induced electrophysiological remodeling of the sinus node could contribute to sinus bradycardia and subsequently AF in endurance athletes (10).

In general, athletes with AF usually present arrhythmic relapses in predominantly vagal situations (e.g. post-prandial, at night or immediately after exercise bouts (27)). However, some athletes may present with AF during physical activity (46), commonly associated with a decrease in exercise performance and symptoms as palpitations.

Premature Atrial Beats

Premature atrial beats are an independent predictor of AF and are associated with an up to three-fold increased risk of new onset AF in the general population (35). They exhibit their role as a trigger for AF (43) especially when they originate from atrial muscles surrounding the pulmonary veins (8). However, it is currently unknown whether athletes show an increased premature atrial beat burden in comparison to non-athletes. A recent study did not find any difference in the premature atrial beat burden between middle-aged athletes and controls, regardless of a history of paroxysmal AF (9), neither was there a relationship with hours of training per week or cumulative years of sports activity.

Finally, also genetic susceptibility has to be listed as possible contributor in the pathophysiology of AF since there is evolving evidence for a genetic component of AF in the general population (31). All abovementioned currently hypothesized determinants are depicted in Figure 2.

Diagnosis of Atrial Fibrillation in Endurance Athletes

Clinical Presentation

AF in endurance athletes without classic risk factors is usually asymptomatic at rest or presents with unspecific symptoms as easy fatigability, whereas endurance athletes with exercise-induced paroxysmal AF usually present with more specific symptoms as palpitations, shortness of breath or chest discomfort (46).

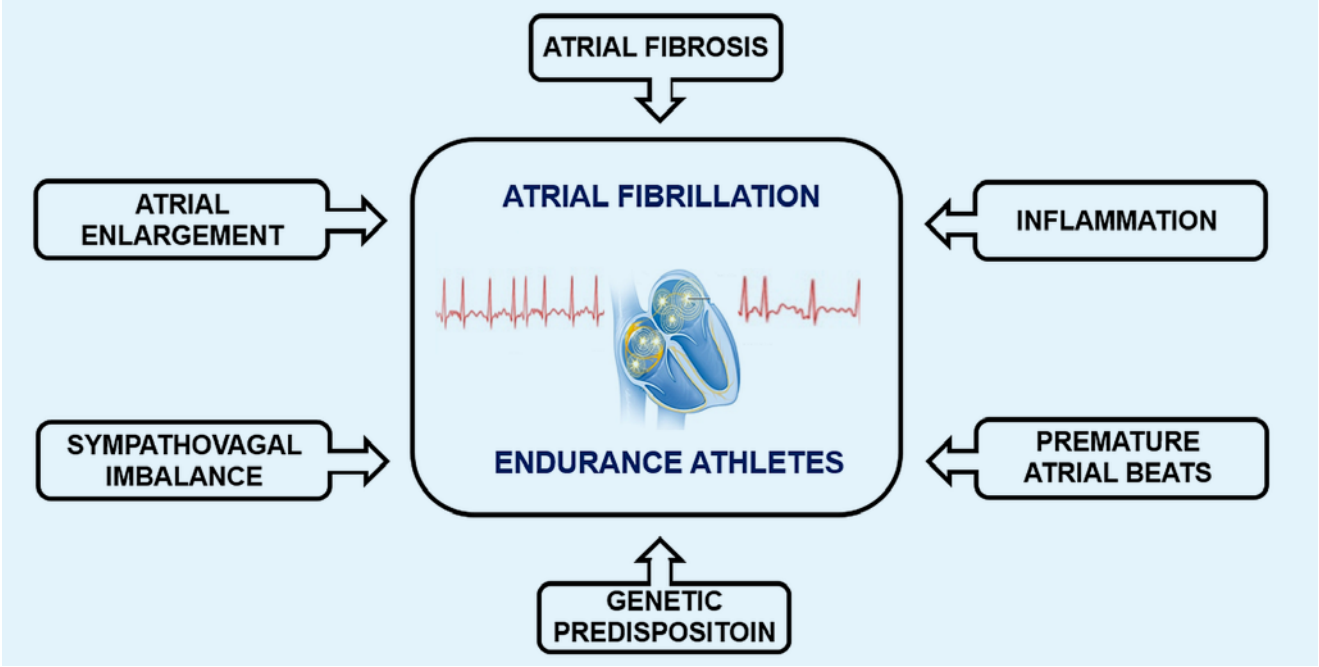

Figure 2

Schematic representation of the potential mechanisms underlying endurance exercise-induced atrial fibrillation.

Resting-, Stress- and Holter-ECG

An electrocardiographic (ECG) recording displaying the typical characteristics of AF is required to diagnose AF, that includes i) absence of p waves, ii) irregular atrial activity and iii) irregular QRS rhythm if atrio-ventricular conduction is preserved (that is, in the absence of complete AV block).

The most appropriate method to record AF depends on the type, duration and specificity of symptoms: Twelve-lead ECG may be useful in athletes complaining of frequent and continuous symptoms that allow them to seek medical attention. Longer recording periods may be needed in athletes reporting intermittent, short duration symptoms during daily life that preclude them from obtaining a conventional 12-lead ECG recording. Several recording methods are available, from continuous (e.g., Holter) to external loop recorders, typically lasting from 24 hours to 1 month. These may also be used to screen for AF in athletes with unspecific symptoms who are deemed to be at high risk of AF (e.g., high burden of atrial premature beats). Implantable loop recorders are rarely indicated to screen for AF in athletes. Alternatively, a stress test mimicking the type, intensity and duration of the physical effort might trigger and diagnose AF. Also, in those athletes with permanent AF who are willing to remain competitive after antiarrhythmic drugs have been initiated, stress tests may provide additional information on exercise capacity, hemodynamic behavior and peak heart rate (HR).

Novel Wearable Devices

For the last decades, endurance athletes have been recording their HR at rest and during sports to monitor their recovery and exercise intensity using chest strap-based HR watches. Recently, technological advances vastly extended the amount of physiologic data that miniaturized sensors may provide, not only to control training but also to monitor cardiac health. These days, commercially available chest straps provide additional information on RR intervals and even record single channel ECGs from which information about arrhythmias as AF can be derived. Chest strap-based HR monitors are increasingly replaced by optical sensors, built in smartwatches, which detect pulsatile signals using photoplethysmography. These approaches have already shown their utility in not only documenting but also automatically differentiating AF from sinus rhythm with high accuracy using machine learning-based algorithms (33). Still, noisy electrode readings due to motion artefacts are still an issue, especially in optical-based devices. However, it is expected that accuracy will continue to improve, and also overcome additional challenges like security of individual data. Nevertheless, although currently photoplethysmography and other techniques based on RR irregularity may be valuable screening tools, an ECG is currently still required to reach a definitive AF diagnosis (21). Overall, increased usage of medical wearables among endurance athletes seems to be a natural progression and technological progress will allow further miniaturization and even wearable, implantable, or ingestible devices for detecting AF. Thus, these devices will help to identify endurance athletes at increased risk or even diagnose unrecognized AF.

Treatment and Prognosis of Atrial Fibrillation in Endurance Athletes

Current therapeutic strategies in athletes with AF require a detailed evaluation of the affected athlete and an individualized approach heavily relying into shared-decision.

Initial decision should be targeted at evaluation of the need for anticoagulation to prevent thromboembolic complications. As for the general population (1), the indication for anticoagulation in athletes with AF should be based on the CHA2DS2-VASc score. In the absence of absolute contraindications, men with ≥1 point and women with ≥2 points might be considered for anticoagulation, preferably with non-vitamin K oral anticoagulants; men adding ≥2 points and women adding ≥ 3 points should receive anticoagulants (1). Athletes with AF are usually middle-aged men not accruing other cardiovascular risk factors, and thus long-term anticoagulation is usually not required. Nevertheless, short-term peri-procedural anticoagulation may be required during cardioversion or AF ablation. In case the athlete requires long-term anticoagulation, it is recommended to avoid sports with direct ›

bodily contact or prone to trauma (18). However, in selected cases a personalized pharmacokinetic/pharmacodynamic approach using new oral anticoagulants may allow sports participation when plasma drug concentration is minimal (26).

Notably, whether brief episodes of AF detected during longer-term monitoring by wearable devices carry similar risks as brief AF episodes during routine resting or Holter ECG is currently unknown. Indeed, a study from a large registry suggests that patients with brief episodes of AF detected by pacemakers or defibrillators may not have an increased risk of stroke or other adverse cardiovascular events (39). Two ongoing trials (NOAH-AFNET 6 and ARTESiA) are testing the potential benefit of oral anticoagulants in these patients.

AF commonly impairs physical activity performance and should be specifically inquired in competitive athletes. Most athletes will prefer rhythm control, which aims to achieve and maintain sinus rhythm. Ablation procedures targeting pulmonary veins are a cornerstone of the modern therapeutic arsenal for AF patients. In athletes, AF ablation is typically effective and safe, allows return to training and competition, and may be considered as a first-line approach (1). Pharmacological approaches are based on the pill-in-the-pocket strategy (2) or the use of AV node blocking drugs, as beta-blockers and calcium channel blockers (21). Considering that AV node blocking drugs affect exercise capacity, some small studies suggest that calcium channel blockers improve heart rate control (40) affect exercise capacity to a lesser extent (41) in comparison to beta-blockers.

Data supporting a potential therapeutic effect of reducing physical activity load is scarce and relies on a very low level of evidence based on conflicting retrospective studies (11, 19) and animal models (16). Economic dependence on sport may further jeopardize its applicability in professional athletes.

Independent of the strategy selected, it is advisable to perform an exercise test after therapy has been established, particularly if symptoms during physical effort were the referring symptom, to test the appearance of AF, hemodynamic behavior and peak HR.

Outlook

Taking into account the rising number of athletes participating in ultra-endurance events, endurance sport-associated AF is likely to become increasingly prevalent in near future. Current data are still insufficient to adopt specific preventive, diagnostic or prognostic strategies. Thus, longitudinally designed research in this area will be critical to further elucidate the mechanisms by which it develops and to improve treatment. Novel technological advances may assist the growing sports cardiology community in improving counseling of endurance athletes at risk for AF. At present, in light of our current knowledge, the potential risk of AF should not be used to limit the amount of physical activity.

Conflict of Interest
The authors have no conflict of interest.

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