Diagnosis, pathophysiology, and management of exercise-induced arrhythmias

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Abstract

The cardiovascular benefits of physical activity are undisputable. Nevertheless, growing evidence suggests that both atrial fibrillation and right ventricular arrhythmias could be a side effect of exercise in some individuals. Exercise-induced atrial fibrillation is most commonly diagnosed in middle-aged, otherwise healthy men who have been engaged in endurance training for >10 years, and is likely mediated by atrial dilatation, parasympathetic enhancement and, possibly, atrial fibrosis. The relationship between physical activity and right ventricular arrhythmia is complex and involves genetic and exercise factors that in few athletes eventually lead to right ventricular dilatation, followed by subsequent myocardial fibrosis and lethal ventricular arrhythmias. Sinus bradycardia and atrioventricular conduction blocks are common in athletes, most of whom remain asymptomatic, although incomplete reversibility has been shown after exercise cessation. Cardiac ablation is evolving as a first-line tool for athletes with exercise-induced arrhythmia who are eager to remain active.

Regular physical activity of moderate-to-vigorous intensity should be encouraged in all healthy individuals and most patients with cardiovascular conditions on the basis of its effects on lowering risk factor burden, improving wellness, and potentially reducing overall mortality.[1] Although the benefits of exercise have been scientifically proven and are well-established, early reports that observed an increase in sudden cardiac death during, or shortly after, intense physical activity led researchers to question whether intense exercise was harmful.[2] Further research in this area demonstrated that underlying cardiac abnormalities, either congenital or acquired, were present in most of these athletes.[3–5] Therefore, exercise was considered a mere trigger for ventricular arrhythmias and sudden death, paving the way for preparticipation screening programmes aimed at identifying underlying cardiac conditions.[6,7]

However, in the past two decades, a growing core of evidence supports the premise that strenuous physical activity is not only able to trigger cardiac events, but can promote the development of cardiovascular disease in individuals with no previous cardiovascular abnormalities.[8–11] Most of this research has focused on the identification of arrhythmias originating in both the atrium and the right ventricle. Specifically, the role of exercise in the development of atrial fibrillation (AF) has been acknowledged.[12] Conversely, the evidence supporting an involvement of the right ventricle in the genesis of potentially lethal ventricular arrhythmias is less established. Furthermore, the left ventricle remains relatively preserved in most studies. Some reports have suggested that extreme forms of exercise might paradoxically increase atherosclerotic complications.[11]

Two consequences of exercise-induced arrhythmias underscore their importance as public health concerns. First, the lifestyles of young athletes are generally seen as a hallmark of a healthy way of life and, for some individuals, an example to be followed. Public confusion and uncertainty surrounding the diagnosis of a cardiac arrhythmia, or

live broadcasting athletes dying suddenly in sports events has a negative effect on the media and society. If not properly addressed, this issue might result in reduced physical activity among individuals and a subsequent rise in the burden of cardiovascular disease. Second, most exercise-induced cardiac conditions are diagnosed in individuals engaged in vigorous physical activities. Considering that the number of individuals undertaking extreme forms of exercise has been readily increasing for the past 20 years,[13] it is conceivable that the number of individuals affected with exercise-induced arrhythmias could also progressively increase over the next decade.

Therefore, why and how these apparently paradoxical effects of exercise fit into actual knowledge, and how they should be approached are crucial for all health-care personnel and policy makers to understand. In this Review, we will present the evidence supporting the existence of exercise-induced arrhythmias, its mechanism of action and discuss the specific considerations for the clinical approach of these patients.

[H1] Atrial arrhythmias

AF is the most common sustained arrhythmia in clinical practice. AF is characterized by a loss of synchronous atrial electrical activity and contraction, and results in increased thromboembolic and heart failure risk, impaired quality of life, and a two-fold higher risk of adjusted mortality.[14] Hypertension and structural heart disease are two of the most frequent causes of AF in the general population. Cardiovascular abnormalities are absent in up to 10% of patients with AF; risk factors for the development of AF in these patients include obstructive sleep apnoea, obesity, and intense exercise.[15]

The first evidence linking exercise and AF was first published in the late 1990s,[8,9] prompting much debate amongst researchers, with one side drawing attention

to the growing core of evidence, and the other highlighting the potential biases and inconsistences in the data[13,16]. The rationale behind these debates are the seemingly conflicting results derived from a multitude of different methods and analyses used, an intrinsic limitation of the retrospective nature of most studies. Central to this limitation is the considerable variability in ways in which physical activity has been quantified. Physical activity is intuitive, but difficult-to-quantify; several approaches have been taken to assess physical activity,[17] including the evaluation of cohorts of well-trained athletes, performing questionnaires, or objectively assessing cardiovascular fitness (Box 1). Remarkably, as the core of published studies grows, the association between physical activity and AF becomes consistent all across these methods (Figure 1).

1.1. [H2] Exercise-induced AF

The first association observed between exercise and AF came from studies that found an unexpected over-representation of endurance athletes in a lone AF cohort[9] and an increased risk of AF in veteran orienteer runners.[8] Subsequent studies were performed in elite athletes who had been engaged in marathon running,[18] cycling[19], or cross-country skiing[20,21], which showed that elite athletes were at a 4 to 15-fold increased risk of AF than the general, sedentary population. Aizer and colleagues provided the first evidence that this association was not limited only to elite athletes, but also affects the most active individuals in the general population.[22] In their work, jogging for 5-7 days per week increased the risk of AF by 1.7 fold in individuals aged <50 years. Subsequent larger studies provided further confirmatory data of this association among the general population. In a study including >300,000 Norwegian men and women, men engaged in regular intensive physical activity (defined as participation in hard training or sports competitions, regularly and several times per

week) were at a three-fold increased risk of being prescribed flecainide (a surrogate for AF diagnosis).[23] Drca and colleagues found that Swedish men who vigorously exercised >5 hours per week at the age of 30 years had a 1.2-fold increased risk of being diagnosed with AF in later life.[24] To date, the largest of such studies was conducted in >1.1 million men undergoing mandatory conscription in Sweden during a 23-year period; these men were followed-up for an average of 26 years. Better cardiovascular fitness, objectively assessed through a bicycle ergometer test, correlated with a progressive increase in the incidence of AF. For example, the quintile with the highest fitness had 1.31-fold higher risk of AF than the quintile who were least fit.[25] In general, a low comorbidity burden is common in these abovementioned cohorts.

Conversely, several studies have failed to show this association, or have even found that physical activity protects from the development of AF. Moderate doses of exercise in individuals with specific cardiovascular conditions are thought to decrease arrhythmic risk. At the epidemiological level, objectively assessed physical fitness was negatively correlated with the incidence of AF in a middle-to-advanced-aged cohort of >64,000 individuals with a high burden of cardiovascular risk factors and cardiomyopathies.[26] Estimated physical activity in older individuals has been found to reduce[27] or have no effect[28] on the incidence of AF.

Clinical trials have consistently reported that moderate doses of physical activity might be of therapeutic value in patients who have already been diagnosed with AF. Physical activity is an important component in the multidimensional secondary prevention approach aimed at controlling risk factors for AF, particularly in obese patients presenting with one or more risk factors,[29] where the magnitude of AF recurrence prevention seems similar to that of some antiarrhythmic drugs. These benefits might be, at least in part, attributable to better control of classical risk factors

for AF, including hypertension or diabetes mellitus.[29] Remarkably, weight loss after regular training might contribute to AF burden reduction.[30] Nevertheless, the effects of exercise on improving physical fitness are additive to those of weight loss, and among obese patients with AF, those who are less fit at baseline or present with lower fitness improvement after the completion of a training programme are at a highest risk of AF recurrence.[31] An improvement in AF control can be detected early after beginning a training programme. In the short term, AF burden was almost halved in a secondary prevention trial in patients averaging 60 years old who were randomized to aerobic interval training three times per week for 12 weeks compared with those receiving usual care.[32] Furthermore, in patients with diastolic heart failure, physical training improved diastolic function and reversed atrial remodelling.[33]

Remarkably, most of the aforementioned studies have evaluated leisure-based physical activity. Occupational physical activity has been repeatedly shown not to be associated with an increased risk of AF.[34,35] A low occupational physical intensity in most individuals, and a predominantly strength work load in those workers with the heaviest physical activity (in contrast to endurance training in athletes) likely account for the lack of an association between occupational physical activity and AF.

[H2] Exercise-induced atrial flutter

AF and atrial flutter share some basic pathophysiological and clinical features. While most research work has linked physical activity with increased risk of AF, data on atrial flutter are much less abundant. Long-term endurance sportsmen were over-represented in a cohort of patients with lone atrial flutter,[36] yielding an odds ratio of 5.33 (95% CI 2.1 - 13.53). The arrhythmic risk conferred by exercise evolves earlier and more intensely for atrial flutter than for AF.[37] Some analyses in large cohorts [21,24,25,27,28,38] and a study in veteran elite cyclists[19] indistinctly defined AF and atrial

flutter as outcomes, but did not provide separate results for both arrhythmias.[24,38] Overall, the risk of atrial flutter is also considered to be increased as a consequence of physical activity; nevertheless, the impact of AF is higher owing to its remarkably larger relative contribution to overall atrial arrhythmia burden.

[H2] Identifying the risk of AF

Current evidence from global studies suggests that the relationship between exercise and AF is complex and likely relies on the balance between baseline cardiovascular risk factors, the type, intensity, and duration of physical activity, and individual susceptibility. Published studies have largely failed to isolate each of these factors, thereby accounting, at least in part, for the conflicting conclusions (Box 2).

An association has been reported between AF and physical activity in men[18,22,24,25,39], but the effects of exercise in women remain controversial (Figure 2A). In a retrospective study, Drca and colleagues found that self-reported sporting activity in 30-year old individuals did not predict AF incidence in women,[38] in contrast to their findings in men.[24] Two large studies that confirmed an association between exercise and AF also provided sex-based subanalyses.[21,23] The results were similar for men and women in the study by Andersen and colleagues, although the lower sample size of females likely explains the lack of statistically significance[21]. In a larger Norwegian cohort involving >140,000 men and >160,000 women, physical activity was associated with a three-fold increase in the incidence of AF in men, but not women.[23] In a cohort including >1,400 women, >40 years of intense endurance training associated with a nonsignificant (p=0.07) two-fold increased risk of AF.[40] Although a similar a U-shaped relationship between physical activity levels and AF risk in both males and females was identified in a study published in 2016, formal statistical analyses were not reported.[35] Conversely, in agreement with findings in men, physical activity was protective against

AF in two cohorts of postmenopausal women[41] and women in their 6th decade of life[42] who had a high burden of cardiovascular risk factors. Studies specifically focusing in women are insufficient and heterogeneous. Overall, there is inadequate evidence to reliably affirm a proarrhythmogenic effect for exercise in women.[43] It is likely that sex physiological differences, attenuated exercise-induced cardiac remodelling, or a lower exercise intensity in women than in men could also contribute to the lack of an evident exercise-induced increased risk of AF.[44]

The risk of AF conferred by exercise progressively increases with the intensity of exercise (Figure 2B). AF risk in athletes (relative risk of 4 - 15) is higher than in studies conducted in the general population (relative risk in the most active individuals of 1.2 – 2). The risk conferred by exercise progressively increased over jogging intensity and duration in a cohort of healthy middle-aged male physicians.[22] A gradient of risk exists even within highly trained individuals. In a cohort of >50,000 individuals participating in a 90 km ski cross-country race, those who performed better (with a finish time of <2.4 times the winning time) were at a 1.2-fold higher risk of AF over a 9-year follow-up than those who took longer to finish the race.[21]

The type of exercise that yields the most remarkable proarrhythmogenic effect has not been systematically studied, but a detailed analysis of published studies yields rather robust conclusions. To date, most small studies confirming an association between physical activity and AF have been conducted in endurance sports practitioners (for example, marathon runners, cyclists, and cross-country skiers)[18–21,45] or mixed sports (for example, handball players).[46] Jogging, but not other sporting activities, increased risk of AF in a large study.[22] A subanalysis of the FUTURE study[47] in patients with lone AF yielded an odds ratio of 9 for AF in endurance sports practitioners in comparison to team sports. To date, there has not been any studies showing an

increased incidence AF in strength sport practitioners. Remarkably, in the large population-based Swedish study, cardiovascular fitness assessed in a bicycle ergometer test, but not muscular strength tested using a hand dynamometer, was associated with incidence of AF during follow-up.[25]

The incidence of AF progressively increases over the number of years of active exercise participation. Most studies show that athletes diagnosed with AF have been engaged in regular training for at least ten years (Figure 2C). A study published in 2014 found that the risk of AF increases after 20 years of active sport participation, and progressively increases with a longer duration of exercise.[37] In patients with lone AF in the FUTURE study,[15] lifetime accumulated physical activity was the strongest predictor of AF prevalence, above ongoing exercise and physical activity density (hours of physical activity per year). In this study, >2,000 hours of lifetime vigorous exercise was associated with an odds ratio of ≈4 for AF.

Exercise-induced AF commonly affects middle-aged individuals. Total accumulated lifetime physical activity is a critical factor in the development of AF,[15,37] thus justifying that young athletes are infrequently diagnosed with AF.[48] A link between physical activity and AF has been consistently confirmed when physical activity was assessed in middle-aged individuals, but nonexistent when assessed in later stages of life (Figure 2D). A substudy of the Physicians Health Study found that physical activity before, but not after, the age of 50 years predicted incidence of AF.[22] The 50-year threshold was recently reinforced in a subanalysis of the study by Morseth and colleagues.[35] Further supporting his notion, Drca and colleagues found that participation in sporting activity at age 30 years, but not at 60, predicted a higher incidence of AF in the elderly.[24] Two factors likely explain the lack of a proarrhythmogenic effect of exercise in the elderly. First, physical activity in aged individuals is likely of a lower

intensity than in young or middle-aged individuals and, therefore, is associated with lower haemodynamic overload.[49] Second, the accumulation of risk factors in the elderly might override the potential deleterious effects of intense physical activity.[24,27,50]

Nevertheless, variability still remains within the high-risk population, that is apparently healthy middle-aged individuals who have participated in intense, endurance physical activity for long periods of time. AF only affects a limited number of athletes, in whom genetic background likely fosters a deleterious response to similar amounts of physical activity. A small subset of highly trained athletes present with atrial dilatation and dysfunction, leading to increased atrial wall stretch during physical activity that might increase the risk of maladaptive remodelling in the atrium.[51] However, no individual susceptibility factors have been found for exercise-induced AF.

Overall, an increasing body of evidence supports a U-shaped relationship between total amount of physical activity and incidence of AF,[15,35,52] largely shaped by the presence of risk factors, exercise intensity, and genetic background and variability (Figure 3A). According to this hypothesis, both exercise duration (Figure 3B) and intensity (Figure 3C) result in a U-shaped dose-response curve in terms of risk of AF. Low-to-moderate doses of physical activity reduces the risk of AF, particularly in those individuals with other risk factors (for example, heart failure, hypertension, and aging), whereas increasing doses might prompt an increased risk.

[H2] Pathophysiology of exercise-induced AF

The mechanisms by which a previously healthy atrium develops an arrhythmogenic substrate after several years of physical activity are likely multifactorial and involve physiological (athlete's heart), but also pathological components of

exercise-induced cardiac remodelling (Figure 4). Notably, while some data has been obtained in athletes, most pathology insights have been acquired from animal models and, until they have been confirmed in human, caution is warranted when translating these conclusions.

Sinus bradycardia and delayed atrioventricular conduction are well-known features of the athlete's heart. Nevertheless, their underlying mechanisms are still controversial; although some studies claim a critical role of primary electrical remodelling, classic theories have relied on parasympathetic tone enhancement as a central mechanism in athlete's bradycardia.[53,54] Notably, parasympathetic tone also shortens the atrial refractory period, facilitating re-entry formation and AF establishment.[55] Therefore, parasympathetic tone enhancement is a likely candidate that contributes to exercise-induced pathology. Indeed, AF events in parasympathetic-predominant circumstances (for example, sleeping or after meals) are common in trained individuals.[9,56] In nonprofessional athletes participating in a 10-mile race, those with the heaviest lifetime accumulated workload presented with a higher prevalence of AF and a deeper parasympathetic enhancement than less-trained athletes.[57] Furthermore, autonomic tone imbalance was a critical contributor to exercise-induced AF substrate in a heavy endurance, treadmill-trained animal model.[58]

Atrial structural remodelling, namely atrial dilatation and fibrosis, is progressively being recognized as a contributor to exercise-induced proarrhythmogenic arrhythmia. Atrial dilatation has been considered a physiological component of the cardiac remodelling to exercise, but at the same time it increases the critical myocardial mass needed to establish the basic mechanisms of AF.[59] Indeed, atrial dilatation frequently contributes to AF establishment in hypertension or heart failure, and to AF

self-perpetuation mechanisms.[60] To date, there is no robust evidence proving that atrial dilatation in athletes is structurally different from that of pathological settings.

Collagen fibres interspersed between cardiomyocytes impede normal electrical conduction in the atrium and promote heterogeneous electrical conduction and re-entry formation. Fibrosis has became a structural hallmark of AF pathology.[61] Atrial fibrosis was first described in an animal model of exercise-induced AF. A group of rats were trained on a treadmill at a high intensity for 16 weeks and tested for AF inducibility at the end of the experimental protocol.[58,62] Trained rats were more readily inducible than their sedentary littermates, and AF inducibility was associated with a ~60% increase in atrial fibrosis.[58,62] Similar results were later shown in a swim-trained mice model.[63] Evidence for atrial fibrosis has not yet been found in athletes, but is supported by some indirect data. Veteran athletes present with higher levels of profibrotic markers such as plasmatic fibrosis turnover markers carboxyterminal propeptide of collagen type I (PICP), carboxyterminal telopeptide of collagen type I (CITP), and tissue inhibitor of matrix metalloproteinase type I (TIMP-1),[64] galectin-3,[65] and certain circulating pro-fibrotic microRNAs such as mir-21.[66] Endurance athletes show an accumulated physical activity-dependent P-wave prolongation;[67] notably, P-wave duration does not correlate to atrial size in athletes.[68] Surgical atrial samples have shown that P-wave duration associates with atrial fibrosis and flags those individuals at an increased risk of AF.[69]

The mechanisms leading to collagen deposition in the atrium of athletes remain largely unknown. Repetitive exercise training have been suggested to promote structural damage[70], which eventually leads to the formation of fibrosis. A study using an animal model demonstrated that the renin-angiotensin-aldosterone system participates in exercise-induced fibrosis.[71] Other studies have proposed that exercise-induced

hypertension could underlie the instauration of maladaptive atrial processes in some athletes,[18,72] but current evidence does not support this notion.[73]

Haemodynamic overload during strenuous exercise training might trigger mechanisms involved in myocardial fibrosis formation. Intense exercise increases atrial wall stretch.[74] Tumour necrosis factor-α mediates stretch-promoted local myocardial inflammation, and has a central role in exercise-induced fibrosis in a preclinical model.[63] Intense bouts of physical activity yield transient, duration-dependent, and intensity-dependent systemic inflammation that might also contribute to exercise-induced cardiac maladaptation. Interestingly, cardiac dysfunction following strenuous bouts of exercise correlates with systemic inflammation.[75] Overall, either systemic or local, acute bouts of exercise has been shown to cause myocardial inflammation and apoptosis in an animal model.[76] In athletes, the P-wave is transiently prolonged after completing a marathon, however, this effect cannot be explained by atrial dilatation; atrial inflammation and oedema are more likely explanations.[77]

Environmental factors might also contribute to exercise-induced AF, though most of them remain speculative. Strenuous exercise sessions prompt acute, transient abnormalities in immune response, including variable degrees of immunosuppression.[78] Although conflicting data have been published and limitations been claimed, several studies have found a higher incidence of upper respiratory tract infections in athletes.[79,80] Infections with cardiac tropism have been hypothesized to develop variable degrees of myocardial inflammation. Ventricular mid-myocardial or subepicardial fibrotic patches are a characteristic sequela of myocarditis;[81] atrial myocarditis often co-exists with ventricular myocarditis[82] and likely causes atrial fibrosis. Interestingly, data from animal models suggest that exercise exacerbates deleterious consequences of infectious myocarditis.[83] Therefore, it might be plausible that infections by cardiotropic

viruses during post-exercise immunosuppression can induce subclinical myocarditis that, either exacerbated or not by subsequent exercise, could contribute to atrial fibrosis formation.

Performance-enhancing drugs are used by some professional and amateur athletes, but their contribution to exercise-induced AF pathology remain speculative owing to the obscure nature of drug doping. Remarkably, almost 70% of veteran cyclists included in the study by Baldesberger and colleagues admitted to using performance-enhancing drugs, mainly amphetamines or anabolic steroids.[19] Case-reports have provided the basis for a role of anabolic steroid use in the development of AF.[84] Chronic anabolic steroid administration has been associated with prolonged atrial electromechanical delay among professional bodybuilders.[85] However, contrary to this hypothesis, there are no reports showing an increased incidence of AF in disciplines associated with high prevalence performance-enhancing drug use, such as bodybuilding and wrestling.[86]

In addition to promoting a proarrhythmogenic substrate, repetitive exercise training might also trigger AF events. Whereas chronically elevated parasympathetic tone might have a role in AF promotion at rest,[58] increased sympathetic tone during physical exertion might also trigger AF events.[56] Haemodynamic overload during physical activity increases atrial wall stretch, which increases arrhythmogenicity through connexin inactivation and atrial conduction slowing[87,88]. Atrial premature beats might act as AF triggers in the presence of a suitable substrate. The burden of premature atrial complexes is mildly increased in veteran athletes in some,[57,69] but not all studies[19]. The clinical relevance of exercise-induced atrial ectopic beats still remains to be elucidated.

[H2] Clinical management of AF in the athlete

The contribution of vigorous physical activity to the global incidence and prevalence of AF is unknown. Some studies suggest that exercise contributes to AF pathology in ~40% of patients with AF in the absence of other cardiovascular conditions (that is, lone AF).[9,15] Unfortunately, there are currently no effective tools to flag those athletes at a high risk of exercise-induced AF who would be candidates for primary prevention strategies. An early diagnosis upon clinical suspicion seems to be the only feasible approach to prevent AF progression.[60] A prolonged PQ interval has been associated with the development of exercise-induced AF,[20,46] but the clinical use of this measure as a marker of AF risk is hampered by its low predictive value.

Among athletes, AF is one of the most common causes of palpitations,[89] and is associated with an extensive symptomatology[56] and poor subjective health status.[90] AF events can present at rest or during exercise.[9,56] Physical performance commonly decreases during AF episodes owing to the loss of the atrial contribution to cardiac output. Of note, an unexplained decrease in physical performance might be the only clinical symptom of exercise-induced AF and should raise awareness of AF as a potential diagnosis. On the other hand, few of the affected athletes will remain almost asymptomatic or present with minor symptoms that will not prevent them from competing at a high level.[56]

Upon clinical suspicion of AF, efforts should be directed towards obtaining an electrocardiogram (ECG) during symptoms, including a rest 12-lead ECG, Holter ambulatory recordings, or implantable devices, if needed. Smartphone applications are an effective tool to quickly and easily obtain an ECG during short-term symptoms[91]; nevertheless, expensive add-on hardware are required to obtain reliable single-lead ECG recordings. Treadmill stress tests might serve to uncover AF in athletes complaining of

palpitations during physical activity. Athletes diagnosed with AF should be managed using contemporary standards and in a manner similar to other patients with AF.[12] Even in the presence of an evident endurance training history, secondary causes of AF should always be ruled out, including (but not limited to) thyrotoxicosis, cardiomyopathies, or masked hypertension (Figure 5).

Although AF undeniably impairs quality of life and physical performance in affected athletes, whether they have adverse survival prognosis and complication rates are unknown. Notably, the rate of stroke is higher in veteran athletes with AF than in athletes without AF, and similar to the stroke rate in the comparable (nonathletic) AF population.[90] The stroke risk attributable to AF is higher in athletes than in nonathletes,[92] although the well-known decrease in atherosclerotic risk factors in active individuals likely justifies the higher relative contribution of AF.

AF confers a 1.5-1.9-fold increased mortality risk in the general population.[93] Data on mortality for athletes with AF are not yet available. Given that exercise-induced AF mostly affects middle-aged individuals with a low comorbidity burden (lone AF), mortality should remain largely unaffected. In the absence of cardiovascular comorbidities such as hypertension or heart failure, the risk of cardiovascular complications is low.[94,95] These data suggests that AF might not have a negative survival effect at diagnosis in the largely middle-aged cohort of athletes, but might have deleterious effects in later stages of life.

[H3] Therapeutic approach

The most appropriate approach for treating exercise-induced AF remains unknown, including whether specific considerations should be taken into account (Figure 5). In this regard, the anticoagulation strategy is critical and should follow the

same recommendations as for the general population[12] (that is, in patients with nonvalvular AF with a CHA_2DS_2VASc score ≥1 or for short-term peri-cardioversion or peri-ablation periods).

Avoiding the aetiologic factor (in this case, exercise) seems to be the common sense approach, but robust and consistent evidence of benefit for this recommendation is lacking. A small subgroup of 4 athletes with AF showed significant improvement in symptoms after deconditioning, to the point when they were able to reinitiate training.[89] Furthermore, Heidbuchel and colleagues found that athletes who abandoned training after an atrial flutter ablation developed less AF than those who continued exercising.[96] Results from a study using an animal model suggest that the atrial arrhythmogenic substrate might regress shortly after abandoning physical activity.[58]

In clinical practice, deconditioning is further jeopardized by individual, nonmedical factors. First, in our own experience, a substantial proportion of athletes with AF suffer from addiction to physical activity, which affects up to 25% of young university students living in the USA.[97] In a subgroup of these patients, addiction might lead to negative symptoms and even social isolation. Second, professional athletes might not be willing to retire owing to economic losses. On the other hand, regular, moderate physical activity should be encouraged for its effects in improving quality of life in patients with AF.[98]

Medical therapy should follow the general guidelines for patients with AF,[12] with particular attention to doping issues and their effect on cardiac performance. In general, an athlete will be willing to follow a rhythm-control strategy if they decide to remain in competitive sports. If class Ic antiarrhythmic drugs (for example, flecainide) are used, β-blockers are also required to avoid rapid ventricular rate in the case of type Ic flutter. An exercise test is advisable before returning to regular training in those

athletes employing a rate-control strategy or those who develop symptoms during exercise.

AF ablation has a central role in the treatment of young and middle-aged symptomatic patients. In this regard, ablation might be considered as first-line therapy in athletes with AF.[12] Treatment outcomes are similar in athletes undergoing AF ablation and other patients with AF but no concomitant cardiovascular conditions,[99] particularly for endurance trained athletes.[100] Symptomatic athletes who undergo AF ablation might be able to return to high-level sporting competition.[101]

[H1] Ventricular arrhythmias in athletes

Ventricular arrhythmias - mostly isolated ventricular premature beats - are common in athletes, but it remains unclear whether ventricular arrhythmia burden is higher in athletes than in sedentary individuals.[102,103] A common concern is whether athletes with ventricular arrhythmias are at an increased risk of sudden death. Any excess of sudden cardiac death among athletes is considered to be attributable to underlying structural heart disease (such as hypertrophic cardiomyopathy, arrythmogenic right ventricular cardiomyopathy [ARVC], and channelopathies). In this regard, the more frequent and complex the identified ventricular arrhythmia (from frequent isolated ventricular premature beats to sustained ventricular arrhythmias), the higher the prevalence of an underlying cardiomyopathy.[104]

ARVC is a hereditary cardiac condition predominantly affecting the right ventricle, and is most commonly due to mutations in proteins involved in desmosome assembly. The pathophysiology of ARVC involves fibro-fatty replacement of the myocardium, along with right ventricular (RV) dilatation and dysfunction. These factors

are associated with an increased risk of ventricular tachycardia and fibrillation and, in some patients, symptoms of heart failure. Over the past few years, a link between ARVC and physical activity has been proposed. Strenuous physical activity has been suggested to contribute, either as a central aetiologic factor or as a promoter of disease progression, to the pathology of ARVC. However, the evidence for this association is limited and, in some cases, controversial.

[H2] Describing the ARVC-continuum.

In 2003, Heidbuchel and colleagues first reported on a group of well-trained endurance athletes who presented with complex symptomatic ventricular arrhythmias[10] or aborted sudden cardiac death likely originating from a mildly dysfunctional right ventricle.[10,105] A subset, but not all, of these athletes fulfilled criteria of a diagnosis of ARVC, but contrary to expectations, there was a distinct lack of evidence of inheritance. The authors speculated that endurance training had central role as an aetiologic factor in these patients, a fact that was also supported by a lower-than-expected prevalence of ARVC-causing mutations.[106] Similarly, patients with ARVC in the North American Multidisciplinary Study[107] without a desmosome mutation were more often competitive athletes. These findings have resulted in the conception of the term 'gene-elusive ARVC'. In a single-centre cohort study, patients with gene-elusive ARVC were more likely to be endurance athletes, and had a more intense history of physical activity than patients with desmosome mutations.[108]

Whereas Heidbuchel and colleagues focused their analysis in a highly selected group of diseased individuals,[10,105] studies that have assessed alternative methodological approaches using unselected cohorts of athletes have failed to identify a deleterious effect of exercise in the right ventricle. Andersen and colleagues did not find an increased diagnoses of ventricular tachycardia, ventricular fibrillation, or cardiac

arrest in cross-country skiers participating in the Vasaloppet race[21] or in the male Swedish population undergoing conscription in 23-year period.[25] However, these complex data need to be carefully interpreted. Patients with an underlying cardiomyopathy (that is, definite or probable ARVC) are usually excluded from competitive sport participation and, therefore, selection bias is a possibility in small sample studies. Moreover, actual evidence suggests that the prevalence of exercise-induced ARVC-like cardiomyopathy, if eventually confirmed, would be low and largely influenced by individual susceptibility. We speculate that such a low prevalence would hamper its assessment in unselected or large cohorts with a limited statistical power to identify these small subpopulations.[13]

Although the evidence for a pure exercise-induced ARVC-like cardiomyopathy is limited, there is a growing proof supporting that regular exercise is an important factor that promotes ARVC progression. Desmosome mutation carriers engaged in regular vigorous physical activity present with an earlier clinical ARVC diagnosis,[107] increased ventricular arrhythmia incidence[107,109] and greater RV structural and functional remodelling[107,110] than their sedentary counterparts. Furthermore, strenuous bouts of exercise is a common trigger for sudden cardiac death in affected patients.[4]

Overall, these findings suggest, with different degrees of evidence, that exercise might cause and aggravate similar forms of ARVC. Whether these represent two extremes of a pathological and clinical continuum (Figure 6) still remains to be established.

[H2] Pathophysiology of gene-elusive ARVC

The identification of the mechanisms underlying maladaptive RV remodelling as a substrate for arrhythmias in athletes is complicated by the complex interaction of genetics and the effect of exercise. Data specifically focusing on exercise-induced, gene-elusive ARVC are scarce. Ventricular arrhythmias were more readily inducible in an electrophysiological study in intensively trained rats than in their sedentary littermates.[62] Selective RV dilatation and increase in myocardial fibrosis (while absent in the left ventricle) was proposed to have a central role in exercise-induced ventricular arrhythmogenesis.[62] Notably, no fatty replacement of the RV myocardium was observed.

Robust evidence for RV fibrosis in highly trained athletes are lacking. As previously mentioned, veteran athletes show an increase in markers of plasma fibrosis.[64,111] Endomyocardial biopsies in athletes with ventricular arrhythmias have provided some insight into the arrhythmogenic substrate in humans. Dello Russo and colleagues observed fibro-fatty replacement in 5 of 13 athletes and active myocarditis foci in 7 of 13 athletes with symptomatic ventricular arrhythmias but no apparent structural heart disease.[112] Furthermore, fibrosis was found in 3 of 8 patients with ventricular arrhythmias in the series by Heidbuchel and colleagues.[10] Late-gadolinium enhancement is a promising technique to noninvasively measure myocardial fibrosis; however, the sensitivity of conventional magnetic resonance techniques to detect diffuse fibrosis is low.[113] Several small cohort studies including unselected athletes have failed to identify RV fibrosis by mean of late-gadolinium enhanced magnetic resonance.[114–116]

Interestingly, although ischaemic and myocarditis fibrotic patches were found in group of highly trained athletes,[117,118] left ventricular (LV) ultrastructure remained preserved in most athletes.[62,114,119] Therefore, a central issue in these athletes with ventricular arrhythmias is the rather selective and specific effect on the right ventricle,

with mild or no LV involvement.[120] Cardiac magnetic resonance (CMR) is the gold standard technique for morphological and functional assessment of the right ventricle. Current evidence obtained through CMR imaging points to imbalanced remodelling of the right and left ventricle in highly trained individuals, with disproportionate RV enlargement.[114,119] Strenuous bouts of exercise can induce transient intensity-dependent and duration-dependent RV dilatation and dysfunction, whereas the left ventricle remains relatively preserved.[119,121] La Gerche and colleagues provided remarkable insights into the mechanism of this selective RV effect by showing that right-left haemodynamic and morphological differences provoke a small (~14%) increase in LV wall stress during exercise, but a notable (~125%) increase in the right ventricle, leading to a higher workload.[115] Notably, there are large inter-individual differences in RV adaptation, which are not solely related to previous training[116], but also to individual susceptibility.[121] As for exercise-induced AF, performance-enhancing substances have been postulated as aetiologic factors of exercise-induced ventricular arrhythmias in some case reports,[122] and their use should be inquired in all affected athletes. Nevertheless, the contribution of these performance-enhancing substances on ventricular arrhythmias remains speculative.

[H2] Athletes with RV arrhythmias

The presence of ventricular arrhythmias in athletes is a complex situation that needs to be approached by an experienced cardiologist or sport physician (Figure 7). The first step in diagnosis involves ruling out an underlying cardiomyopathy. In the absence of a cardiomyopathy, idiopathic ventricular arrhythmias (that is, outflow tract and fascicular ventricular tachycardia) might benefit from ablation procedures.

Particular attention should be directed to those athletes with RV dysfunction, as they might occasionally fulfil criteria for ARVC diagnosis. Nevertheless, some athletes could develop incomplete forms of exercise-induced ARVC-like cardiomyopathy, particularly in the presence of complex ventricular arrhythmias and accompanying symptoms. Risk stratification in these cases is not well established. Athletes with potentially deleterious ventricular arrhythmias that originated in the right ventricle might present with a normal RV function at baseline, but show abnormalities in systolic function during a moderate-intensity exercise test.[123] An exercise test can also serve to unmask Epsilon-waves in individuals with underlying, clinically unapparent desmosome mutations.[124]

The prevalence of gene-elusive (or exercise-induced) ARVC is unknown, but it is likely very low, as previously discussed. Patients are commonly diagnosed in the third or fourth decade of life,[10,105,106,108] and are likely to have experienced high intensity endurance training (such as marathon running and cycling) that has been sustained for years.[10] Furthermore, although there is no evidence sustaining this hypothesis, genetic predisposition is likely to have an important role in these patients.

[H3] Therapeutic approach

The therapeutic approach for patients with RV arrhythmias are largely unknown. For those fulfilling ARVC criteria, well-established guidelines published by major scientific societies prohibit competitive sports (class I evidence) and encourage avoiding high intensity dynamic sports in general (class IIa evidence). [125,126] Deconditioning after an ARVC diagnosis has been suggested to delay the initiation of symptoms and reduce the cardiovascular complication rate.[107]

The therapeutic approach for those athletes presenting with symptomatic ventricular arrhythmias and mild RV dilatation that are not diagnostic of ARVC is uncertain. Radiofrequency ablation should be performed if uncertainty with right ventricular outflow idiopathic tachycardia are clinically reasonable. In any case, a close follow-up and a clinical approach similar to that for patients with ARVC seems prudent.

[H1] Bradyarrhythmias and conduction blocks

In contrast to exercise-induced tachyarrhythmias, the occurrence of bradyarrhythmias and conduction blocks in athletes has been recognized for decades, particularly sinus bradycardia and different degrees of atrioventricular block. Sinus bradycardia occurs frequently in athletes and, in conjunction with eccentric LV hypertrophy, provides some cardiac output reserve that helps supply the high metabolic demands during exercise. Overall, sinus bradycardia at rest (with heart rate between 30-60 bpm) is found in 50-80% of athletes[127,128] and might occasionally be associated with long (>3 s) sinus pauses.[129]

Although sinus bradycardia is an indisputable consequence of exercise, its causes still remain unresolved. A reduction in heart rate could potentially result from changes in the autonomic tone (that is, an increase in the parasympathetic tone or a decreased sympathetic tone) or a reduction in the intrinsic heart rate. Classic theories consider parasympathetic tone enhancement a critical driver of reduced heart rate, a process mediated by an increase in vagal nerve activity[130] and/or enhanced sensitivity of the heart to acetylcholine owing to the downregulation of regulatory G-protein signalling.[58] Nevertheless, this long accepted notion has been challenged in in the past few years by studies showing that the intrinsic heart rate (that is, heart rate in the

absence of autonomic tone drivers) is lower in athletes than in sedentary individuals.[131,132] Studies using animal models support this hypothesis and suggest that potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4) downregulation in the sinus node and a decrease in the resulting I_f current could be on the basis of these changes.[133] As of now, whether both mechanisms simultaneously coexist or drive heart rate in different settings or sporting activities remain unknown.

A delayed conduction in the atrioventricular node characteristically manifests in athletes as a first (that is, PR interval >200 ms) or a type I second degree atrioventricular block (Wenckebach block). Case reports on high-grade atrioventricular blocks potentially related to endurance training are infrequent and controversial, and should not be considered as a normal feature of the athlete's heart.[134] As for sinus bradycardia, recent insights challenge the classical view that parasympathetic enhancement controls the delayed atrioventricular node conduction.[132] However, there is no consistent evidence that structural (that is, fibrosis or connexin redistribution) or primarily electric disturbances underlie PR prolongation in athletes.

Sinus bradycardia and atrioventricular block have been considered as physiological changes secondary to long-term physical activity on the basis of generally good outcomes, a very low association with structural heart disease, and a low incidence of symptoms. Physiological exercise-induced bradyarrhythmias and blocks will become more evident in settings with parasympathetic predominance (such as during sleep) and disappear during exercise. However, even if bradycardia is reversible after deconditioning,[104,135] former athletes will still present with a lower heart rate than sedentary age-matched individuals,[19] owing to persistent exercise-induced changes. Certain degrees of irreversible sinus node dysfunction and atrioventircular block likely

explain the (still controversial) high rate of pacemaker implantation in veteran athletes.[19]

[H2] Clinical manifestations

Most sport-associated bradycardias in athletes remain asymptomatic. Only a minority of patients, particularly those with exaggerated sinus bradycardia or long pauses, will present with symptoms, generally in the form of fatigue, dizziness, or even syncope.[129,136]

[H2] Therapeutic approach

Most asymptomatic patients with exercise-induced bradyarrhythmias do not require any specific therapy; only those with extreme forms (for example, bradycardia <30 bpm or PR intervals >300 ms) will require additional assessment.[137] Abandoning or reducing the intensity or duration of physical activity might improve symptoms in those athletes with exercise-induced symptomatic bradycardia or atrioventricualr blocks.

Pacemaker implantation should be indicated following common use guidelines.[137,138] If a pacemaker is implanted, contact sports should be avoided in pacemaker-dependent patients, but could be allowed in certain nondependent patients.[137]

[H1] Conclusions

The causal role of strenuous exercise in AF epidemiology is now well-accepted, particularly for certain populations of well-trained individuals. The role of exercise as a central aetiologic factor in ARVC is much more controversial, and largely dependent on combination of exercise and the genetic background. Nevertheless, both atrial and

ventricular arrhythmias promoted by intense exercise are relatively new concepts, which still require substantial research and investigation. First, a confirmation of a central role of physical activity in patients with ARVC-like cardiomyopathies is warranted in large studies. However, there are other questions that still need to be answered. For example, what is the real prevalence and effect of ARVC-like cardiomyopathies on the population? To date, we only have estimations of the true effect of these arrhythmias with considerably variability between studies. A vigorous training history is evident in a veteran, long-term endurance athletes, but is uncertain in some physically active nonathletes. Diagnostic criteria should be established to provide reliable estimates in epidemiological studies and to focus on the target population.

Furthermore, can we provide a personalized approach for the treatment of these arrhythmias? Actual knowledge on the mechanisms of these arrhythmias is scarce and partial, and are largely derived from animal models. This lack of understanding is further complicated in the case of RV arrhythmias, in which the genetic susceptibility of the individual seems to be critical and overlaps with relatively well-known hereditary conditions such as ARVC. The aim to undertake a personalized approach[139] should foster research into the mechanisms of these arrhythmias occurring in young, otherwise healthy individuals to allow the establishment of primary prevention or effective early diagnosis strategies based on the underlying substrate. Finally, do exercise-induced AF and ARVC have anything in common? To date, we do not have any clinical evidence linking an exercise-induced atrial to RV arrhythmogenic substrate from an epidemiological point of view. Although some of the mechanisms involving haemodynamic overload, increased wall stress, and genetic susceptibility are likely coincident, further work is needed to understand these differences.

Acknowledgements

This work has received funding from from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633196 (CATCH ME project) and from Instituto de Salud Carlos III—Fondo de Investigaciones Sanitarias (PI13/01580 and PI16/00703).

Competing interests statement

No conflicts of interest to be disclosed.

Box 1 | Methods to estimate exercise

Use of physical activity questionnaires[22–24,38]

- Enables an estimate of current, past, and lifetime physical activity
- Subject to recall bias (self-reported)
- Validated questionnaires preferred

Cohorts of athletes[8,18–21]

- Assumes very hard training for long periods of time (lifetime accumulated)
- Subject to selection bias

Objective assessment of physical activity[25,26,52]

- Treadmill test commonly used
- Moderate correlation to amount of exercise practised
- Estimates current fitness only (not lifetime)

Box 2 | Factors involved in exercise-induced AF promotion

Exercise-related factors

- Intensity
- Duration
- Type of sport

Individual susceptibility

- Age
- Sex
- Comorbidities
- Genetic background?

Individuals at highest risk of exercise-induced AF.

- Male sex
- Middle aged at the time of diagnosis
- Involved in high intensity training
- Participate in endurance sports
- Training for >10 years

Figure 1 | Schematic summary of current evidence assessing the association between physical activity and atrial fibrillation (AF) risk. Positive studies (those with a finding that physical activity significantly increases AF/atrial flutter risk) are represented with a green circle; negative studies (those that rule out a significant proarrhythmic effect of exercise) with a red circle. Each circle contains the reference number. Studies exclusively analyzing women are not shown (see test and figure 2).

Figure 2 | Identification of individuals at risk of exercise-induced atrial fibrillation (AF). a | Representative large studies assessing the risk of exercise-induced AF according to the sex composition of the population. b | Relationship between exercise intensity and AF risk in those studies in which enough data was provided to estimate exercise intensity. Horizontal error bars represent the range of physical activity estimates, vertical bars the AF risk confidence interval. c | Vigorous training duration (in years) in athletes at increased risk of AF. d | Age at which physical activity was assessed in the most representative studies. Positive studies (those with a finding that physical activity significantly increases AF risk) are represented inside a green square; negative studies (those that ruled out a significant proarrhythmic effect of exercise) are shown in a red square.

Figure 3 | U-shape relationship between exercise dose and atrial fibrillation (AF) risk. a | Proposed overall curve. b | Clinical evidence for a U-shape relationship between exercise duration of vigorous physical activity (in years) and AF risk.[15] c | Clinical evidence for a U-shape relationship between exercise intensity of physical activity (in years) and AF risk. Data from Mozafarian *et al.*[27] (top right panel), Khan *et al*.[52] (top left panel), Morseth *et al.*[35] (lower right panel) and Myrstad *et al*[45] (lower left panel).

Figure 4 | Summary of some mechanisms potentially involved in exercise-induced atrial fibrillation (AF). Potential mechanisms are represented in the classic Coumel's triangle of arrhythmogenesis. A substrate for AF, including atrial dilation and, potentially atrial fibrosis is created over repetitive bouts of strenuous exercise. Parasympathetic enhancement, a characteristic of the athlete's heart, modulates the arrhythmic risk. AF events may be triggered by an increased atrial stretch during exercise or by a high burden of atrial premature beats

Figure 5 | Proposed clinical approach in athletes at suspicion of atrial fibrillation (AF) and with diagnosed AF. Upon clinical suspicion (palpitations, decreased performance, dizziness, arrhythmic beats on pulse palpation), a diagnostic ECG should be obtained before any therapeutic tools are used If AF is eventually, diagnosed, other secondary causes of AF should be ruled out. In the case of athletes with AF, shared decision making is of particular importance.

Figure 6 | Proposal for a schematic representation of the arrhythmogenic right ventricular cardiomyopathy (ARVC)-continuum in relation to the exercise dose. Patients with classic, non-exercise related ARVC and patients with a gene-elusive ARVC (or ARVC-like) cardiomyopathy in which exercise plays a central aetiologic role represent the two extremes of this continuum. Variable degrees of exercise and genetic susceptibility would contribute to intermediate forms of the disease. An overview of the most representative studies supporting the role of exercise in the development of ARVC are shown. Negative studies are not shown because they would largely vary depending on the outcome considered (clinical, morphological, and electrophysiological).

Figure 7 | Proposed clinical approach to athletes with RV arrhythmias. The presence of an underlying cardiomyopathy critically determines subsequent actions. The most challenging decisions are probably in those athletes with ventricular arrhythmias

and a dysfunctional RV but no definite ARVC criteria. Some factors such as the response to exercise or detraining, or a close follow-up after an ablation (in those with suspected idiopathic VT) may be of diagnostic value.

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Biographies

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