Mini Review

Title: The counterintuitive role of exercise in the prevention and cause of atrial fibrillation

Short title: Exercise and AF Pathophysiology

Benjamin JR Buckley[1], Gregory YH Lip[1,2], Dick HJ Thijssen[3,4]

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK

[2] Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[3] Liverpool Centre for Cardiovascular Science, Liverpool John Moores University, Liverpool, UK

[4]Research Institute for Health Science, Department of Physiology, Radboud university medical centerum, Nijmegen, The Netherlands

Corresponding author

Dr Benjamin JR Buckley

Benjamin.Buckley@liverpool.ac.uk

Author Contributions

BJRB conceived and drafted the manuscript; GYHP and DHJT edited and revised the manuscript. BJRB created the figure. BJRB, GYHL, and DHJT approved the final version of manuscript.

Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia characterised by irregular atrial activity. AF is related to increased risk of thromboembolic events, heart failure, and premature mortality. Recent advances in our understanding of its pathophysiology include a potentially central role for inflammation and presence of cardiovascular risk factors. The role of physical activity and exercise in the development and progression of AF, however, are not yet fully understood. Physical activity is protective for modifiable cardiovascular risk factors, including those associated with AF. Indeed, emerging research has demonstrated beneficial effects of exercise on AF-specific outcomes, including AF recurrence post-ablation. Counterintuitively, the prevalence of AF in veteran endurance athletes seems higher compared to the general population. In this review, we discuss the novel evidence and underlying mechanisms underpinning the role of exercise as medicine in the development and management of AF, but also the counterintuitive detrimental role of excessive endurance exercise. Finally, we advocate regular (but not long-term high-intensity endurance) exercise training as a safe and effective strategy to reduce the risk of incident AF, and to minimise the associated risk of secondary cardiovascular events.

Key words: Atrial Fibrillation, Exercise, Physical Activity, Pathophysiology

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting more than 33 million people worldwide and the prevalence is expected to rise exponentially with an ageing population (1, 2). AF is associated with an increased incidence of stroke, coronary events, and development of dementia (3, 4). The risk of incident AF is associated with various cardiovascular risk factors, which in turn contribute to the risk of AF-related complications (5). AF is characterised by irregular, usually fast, atrial activity with consequent deterioration of atrial function. AF can be paroxysmal, persistent, or permanent in nature, with the latter associated with worse prognosis (6). The pathophysiological processes involved in the development of AF include cardiac structural abnormalities such as left ventricular hypertrophy and left atrial enlargement, upregulated inflammatory pathways, exacerbated by cardiovascular disease and/or risk factors, and genetic predisposition (7-10). These mechanisms are discussed in detail, in relation to excessive exercise training and the development of AF in section 2.

The primary aims of treatment for AF are stroke prevention (i.e. oral anticoagulation), symptom management with heart rate or rhythm control, and management of cardiovascular and comorbidities (11). Whilst drug therapies aim to control arrhythmia, they are associated with adverse side effects and high healthcare costs (12, 13). Furthermore, ablation successfully reduces AF episodes and burden in some with paroxysmal AF, though ~40% demonstrate AF recurrence within 3 months post-procedure (14). This highlights the need for additional strategies to reduce risks for AF development and progression, lower the risk of AF-related cerebrovascular events (e.g. stroke), and improve quality of life (15, 16). Regular physical activity (PA) is a well-established, non-pharmacological therapy that enhances cardiometabolic health (17). Counterintuitively, excessive endurance training seems to increase the risk of incident AF. Key characteristics of this 'athletic AF' often include patients age $\leq$60 years, prolonged practice of endurance training, preserved ejection fraction, minor substrate criteria, and absence of common AF risk factors (18). Although our understanding of PA, exercise and AF has improved in recent years, many questions remain unanswered.

In this review, we first discuss novel evidence and potential underlying mechanisms supporting the role of regular exercise as medicine in the development and management of AF. Second, we review the literature regarding the potential detrimental role of excessive

endurance exercise on AF and its pathophysiological mechanisms. Finally, we summarise the evidence and provide future perspectives for the role of regular PA and exercise in the management of AF.

1. Physical activity and exercise in the prevention and management of AF

Primary prevention of AF

Regular PA reduces the risk of numerous chronic diseases, preserves physical and mental health as we age, and extends longevity (17). Indeed, regular aerobic exercise training is a well-known preventative tool for cardiovascular disease able to reduce common risk factors (hypertension, hypercholesterolaemia, hyperglycaemia), and alleviate (or even reverse) vascular dysfunction (19, 20). In line with these observations, there is now promising evidence for the prevention of AF via regular PA. Light-to-moderate-intensity PA has been associated with significantly lower AF incidence in older adults (21). Specifically, one fourth of new cases of AF in older adults may be attributable to absence of moderate leisure-time PA. In a database study of nearly 5,800 participants, although vigorous-intensity PA nor overall 'intentional exercise' load were independently associated with incident AF, modelling both together resulted in a significantly reduced incidence of AF in the top tertile of total exercise compared with those who reported no exercise (22).

In a recent UK Biobank cohort analysis (*n*=402,406), Elliott et al. (23) found that achieving >500 MET-mins/week (metabolic equivalents) was associated with reduced risk of incident AF. Given the PA guidelines (150 minutes moderate-intensity or 75 minutes vigorous-intensity PA) equate to $\geq$450 MET-mins/week, the findings from Elliott et al. provide evidence that these general PA guidelines not only promote cardiovascular risk factor control, but also independently reduce AF development. In fact, exceeding current PA guidelines, i.e. 500-1500 MET-mins/week, was associated with 5-10% and 6-20% reduced incidence of AF in males and females, respectively. This is supported by a large population-based cohort study (*n*=>500,000), which found a U-shaped dose-response relationship between PA level and AF risk (24). Achieving 500-1000 MET-mins/week was associated with a 12% reduction in incident AF. Those achieving <500 or >1000 MET-mins/week however, demonstrated an attenuated risk reduction. The attenuated risk reduction observed at higher levels of PA is not a consistent finding in the literature. The association of accelerometry-derived MVPA and

incident AF was explored in >5000 participants split into quartiles of ascending MVPA levels (25). At 3.5 years follow-up, the risk of AF reduced in a dose-response manner, with the biggest reduction in risk at the highest PA level (38% reduced risk of AF in quartile 4).

These recent studies support the notion that regular PA is protective from incident AF. The varying effects of PA intensity, however, are not yet fully understood. Morseth *et al*. (26) found a significantly reduced risk of incident AF when participants walked or cycled >4 hours/week. Yet, this positive effect was diminished when individuals participated in vigorous-intensity PA. Whether this effect is related to intensity, or to the interwoven relation between PA volume and intensity, remains unclear. Nonetheless, an attenuation of the effect size of larger volumes and/or intensity of PA is also supported by others, with some suggestion for the presence of strong between-individual differences. The potential negative effects of excessive endurance training and the impact of sex differences are discussed in section 2. Despite the complex nature of the dose-response relationship between PA, exercise and AF, the majority of studies suggest beneficial effects in the primary prevention of AF when adopting or modestly exceeding (2-3 times) current PA guideline levels.

Secondary prevention of AF

Pathak et al. (27, 28) found that greater cardiorespiratory fitness (CRF) was associated with increased freedom of AF and for every 1 MET increase in CRF (via exercise training) AF recurrence was reduced by 9%. Similarly, in >64,500 adults Qureshi et al. (29) observed that every 1 MET increase in CRF was associated with a 7% lower risk of incident AF. More recently, Garnvik et al. (30) collected self-reported PA and estimated CRF from 1,117 patients with prevalent AF over ~8 years. Primary findings showed that meeting the PA guidelines resulted in a 45% and 50% lower risk of all-cause and cardiovascular disease mortality, respectively, compared with inactive patients. In addition, each 1 MET increase in CRF was associated with 12% lower all-cause mortality and 15% lower cardiovascular disease mortality. Furthermore, achieving less than the recommended PA levels was associated with a reduced risk of mortality compared with inactive patients, advocating that, even below the recommended levels of PA, some PA is better than nothing for secondary prevention of AF. Whilst these observation studies provide promising evidence for the benefits of regular PA in the secondary prevention of AF, future study designs that can infer causation are needed.

One randomised controlled trial (RCT) demonstrated that weight reduction with intensive risk factor management (e.g. goals for regular exercise, lipid management, glycaemic control, and blood pressure reduction) resulted in beneficial cardiac remodelling and reduced AF burden and severity in overweight/obese patients (27, 31). The authors proposed that such beneficial effects may be attributable to a decrease in left atrial size and ventricular wall thickness (i.e. anti-AF cardiac remodelling). It is important to emphasize that the ARREST AF trial targeted multiple risk factors and it is therefore not possible to attribute these beneficial effects to PA alone.

Another RCT compared cardiac rehabilitation to usual care for patients treated with catheter ablation for 210 patients with AF (32). Findings revealed a significantly higher (~1 MET) CRF at 4-months in the cardiac rehabilitation group compared to usual care. In addition to physical symptoms, over one third of AF patients have elevated levels of depression and anxiety (12) and impaired quality of life (33) compared to the general population. Symptoms of depression have also been documented as the strongest independent predictor of future quality of life in AF patients and thus NHS burden (12). Osbak et al. (34) conducted a small-scale RCT reporting that 12-weeks of exercise training significantly increased exercise capacity and improved quality of life in patients with AF. Given exercise elicits an effect size over three times that of anti-depressant medication in reducing depression (35), it is an extremely promising addition to routine AF care. Whilst this work highlights the ability of AF patients to improve fitness, cardiac structure and their quality of life, further work is needed to investigate the impact of exercise-based rehabilitation in patients with AF on clinically relevant outcome measures such as mortality, morbidity, and adverse events.

A recent systematic review of four interventional studies (*n*=498 participants) found lifestyle and risk factor management significantly decreased AF episode severity, frequency, and duration (36). Supporting the notion of exercise as an AF-specific medical intervention, one previous study demonstrated improved sinus rhythm maintenance in patients with persistent AF, following external electrical cardioversion and rhythm control therapy (usual care) plus exercise, counselling, and dietary restriction compared to usual care alone (37). Exercise interventions may not only be beneficial for AF-specific outcomes but may also reduce the risk of AF associated secondary cardiovascular events. Indeed, Proietti *et al*. (38) observed that regular exercise in patients with AF was associated with lower risk of all-cause mortality

and thromboembolic events irrespective of sex, age, or risk of stroke. Finally, one RCT demonstrated that 12-weeks of aerobic interval training significantly reduced AF burden (measured via implantable loop recorders) from 8.1 to 4.8%, with no significant change in the no exercise control (39). Collectively, PA provides a promising first line treatment for individuals diagnosed with AF, associated with enhanced quality of life (34), AF-specific outcomes (37), and secondary cardiovascular events (30).

What potential mechanisms explain the benefits of regular physical activity in AF?

Several pathways have been suggested to contribute to the benefits of regular PA in the primary and secondary prevention of AF. The most important pathways have been discussed below and presented in Figure 1.

Traditional cardiovascular risk factors. Cardiovascular risk factors including hypertension (40), diabetes mellitus and metabolic syndrome (41), obesity (42, 43), and obstructive sleep apnoea (44) have been shown to independently increase incident AF. Indeed, hypertension and obesity are associated with structural (atrial hypertrophy, fibrosis, and dysfunction) and electrical (decreased conduction velocity) remodelling of the atria, in addition to the presence of enhanced inflammatory markers (45). The structural, conduction, and sinus node abnormalities leading to AF, also contribute to an abnormal atrial substrate (46). Correspondingly, aggressive cardiovascular risk factor management has been shown to markedly improve sinus rhythm and AF burden (likely via improvement in the AF substrate) (27). In addition, improved CRF is associated with improved AF-free survival, AF burden and symptom severity (28). Pathak et al. (28) proposed that long-term improvements in fitness resulted in significantly reduced blood pressure, inflammation, and left atrial size, and improved blood lipid status and glycaemic control, all of which contributed to a reduced AF burden. Although the benefits of regular PA partly relate to improvement in traditional cardiovascular risk factors, the overall effect of PA on risk factors is small to modest.

Cardiac remodelling. At a cardiac level, aerobic exercise training induces positive cardiac remodelling (enlargement in cardiac dimension, improved contractility, and increased blood volume) leading to an improvement in cardiac function and maximal cardiac output. Such adaptations are associated with signalling pathways underlying cellular, molecular and metabolic adaptations (47). Aerobic exercise training also promotes mitochondrial biogenesis

and oxidative capacity in cardiac myocytes, which contributes to a reduced risk of cardiovascular disease and enhanced cardiac function (48). Regular exercise (4-5 sessions/week) is associated with attenuation of age-related cardiac remodelling including decreased compliance and distensibility (i.e. cardiac stiffness) (49).

Impact on thrombogenesis. AF is associated with a prothrombotic or hypercoagulable state by fulfilment of Virchow's triad for thrombogenesis (50). In AF, there are data supporting the presence for 1. 'abnormal blood flow' (which we recognise as intra-atrial stasis, often within dilated cardiac chambers); 2. 'abnormal vessel wall' (seen as structural heart disease and intrinsic endocardial/endothelial damage/dysfunction), and 3. 'blood constituent abnormalities' (referring to coagulation, fibrolysis and platelet abnormalities, in association with inflammation and other growth factors that promote thrombogenesis). PA and exercise impact these components of Virchow's triad; for example, regular exercise suppresses pro-inflammatory cytokine production, enhances anti-inflammatory mediators and antioxidant development, and promotes fibrinolytic activity (51). Moreover, 12-weeks of high intensity interval training has been shown to improve platelet mitochondrial function in heart failure patients (52).

Endothelial function. Endothelial damage/dysfunction may provide the final common pathway of the combined effect of traditional cardiovascular risk factors (53). AF patients demonstrate an impaired endothelial function (as measured by flow-mediated dilation) (54) and some research suggests vascular dysfunction precedes incident AF (55). Exercise training has well known beneficial effects on vascular function and structure. A specific and potent impact of exercise training relates to improved artery endothelial function, primarily through increased production and bioavailability of endothelium-derived nitric oxide (19). Thus, exercise induced improvement in endothelial function may contribute to a lower risk for AF development, recurrence, and risk for secondary cardiovascular events.

2. Excessive endurance exercise and AF

Despite compelling evidence for exercise as medicine in AF, research has demonstrated that, counterintuitively, long-term endurance training increases the risk of incident AF (56, 57). The heightened prevalence of AF is not uniform across elite athletes but seems to favour a high-volume of endurance training such as cycling, running, and cross-country skiing (58). In a

Swedish cohort study (*n*= >52,000), repeated participation and faster finishing time in long-distance cross-country ski races (surrogate marker of exercise training history) were associated with increased risk for AF (59). In agreement, Myrstad et al. (60) found that in older Norwegian men, a history of endurance sport practice was a risk factor for AF, with an effect comparable to traditional risk factors for AF (e.g. coronary heart disease and hypertension). A later study by Myrstad et al. (61), combined two independent cohorts and demonstrated a graded-dose-response relationship with an adjusted odds ratio for lone AF 1.26 (95% CI 1.10 to 1.44) per 10 years of exercise training.

There seems to be sex-related differences in terms of high levels of PA and risk of AF. For example, Elliott et al. (23) found that vigorous-intensity PA was protective in females, whereas in males, increasing levels of vigorous-intensity PA was associated with progressive AF incidence, leading to a significant 12% increased AF risk at 5000 MET-min/week. Such sex-dependent responses to vigorous-intensity exercise in AF have been previously alluded to (62), yet the mechanisms underpinning these interactions are not yet fully understood. It is however thought that men may be at an elevated risk of AF due to larger atria and a more extensive remodelling compared with females (63). In summary, the relationship between PA and AF is complex, and sex seems an important, yet not yet fully understood factor. Future work is needed to tease out the mechanisms involved in the sex-related differences observed in the associations of PA and AF.

Collectively, studies pertaining to the most active (lifelong) athletes provide evidence that 'more is not always better'. Whilst lower doses of regular exercise are associated with lower incidence of AF, these benefits disappear when examining AF prevalence in cohorts who perform very high volumes of high-intensity endurance exercise. This supports the presence of a J-shaped curve between PA/exercise and incident AF (Figure 1) (26, 64). Defining the dose of exercise associated with potentially detrimental effects on the primary and secondary prevention of AF is challenging, and importantly limited by a lack of prospective studies that objectively report exercise volume and AF occurrence. At least, the potentially 'harmful' dose of exercise seems substantially higher than the recommended PA guidelines (with the latter being AF protective).

Indeed, we have incorporated a large area of potential variance within figure 1 (shaded area of interest) to denote uncertainty surrounding a number of important mediators regarding

excessive exercise levels and risk of AF. These include sex (whereby males seem to be at a higher risk as exercise levels increase), intensity/type of PA (it is believed vigorous-intensity endurance exercise may increase risk, though the impact of high-intensity interval training on AF risk is unknown), age (as age increases, so does the risk of AF), and genetic predisposition (there is a genetic risk of AF, independent of training response). It is also important to note research caveats relating to trial design and sample size, for example the relatively small participant numbers at the highest of activity levels (i.e. far right of the curve; Figure 1). Below, we discuss the potential mechanisms which may explain the counterintuitive higher risk for AF in those who engage in excessively high levels of vigorous-intensity PA and exercise.

What pathophysiological mechanisms may contribute to the higher AF burden in athletes?

The pathophysiology of exercise-induced AF is not yet fully understood, though atrial remodelling, inflammation, and autonomic imbalance may represent central underlying mechanisms (Figure 1). Counterintuitively, these factors seem involved in both the beneficial and deleterious mechanisms between PA, exercise, and incident AF. Whereby, with excessive exercise levels (well exceeding the recommended guidelines) physiological atrial remodelling becomes pathological remodelling (i.e. facilitates an AF substrate), inflammation is enhanced (compared to a reduction with guideline PA levels), and vagal tone increases beyond an upper (arrhythmia-specific) healthy threshold (Figure 1). Animal models have demonstrated that long-term, vigorous-intensity endurance exercise promotes adverse cardiac remodelling and an arrhythmia substrate (65). Following 16-weeks of endurance exercise (1h treadmill running/day) murine models demonstrated increased AF susceptibility via autonomic changes, atrial dilation, and fibrosis (66). Below, these potential pathways have been discussed in further detail.

Atrial remodelling. Increased left atrial size is an independent risk factor for lone AF in normal and clinical populations (9). In contrast, despite up to 20% of athletes presenting with enlarged left atrial cavities, evidence linking this adaptation to incident AF is unclear (67). Exercise-induced atrial enlargement may therefore be physiological rather than pathophysiological, at least in athletes. Thus, left atrial dilation may not be a central component of ‘athletic AF’.

Atrial fibrosis is another component of the atrial arrhythmogenic phenotype (68). One study reported 50% (6/12) male endurance athletes demonstrated evidence of myocardial fibrosis by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR). This was in contrast to no LGE demonstrated in 17 young athletes or 20 age-matched sedentary controls (69). The study found that years of training ($p<0.001$) and number of competitive marathons ($p<0.001$) predicted prevalence of LGE via CMR. Supported by mural models, 16-weeks of endurance training resulted in left and right atrial fibrosis (66). Specifically, Guasch et al. observed that fibrosis concomitant with vagal enhancement (see below) resulted in heightened AF susceptibility. Following a detraining period, AF susceptibility was fully reversed without a reversal in atrial fibrosis. Thus, although an important component, atrial fibrosis is not the sole mechanisms involved in exercise-induced AF susceptibility.

Angiotensin II and transforming growth factor beta 1 (TGFβ1) are major pro-fibrotic signalling molecules, both also involved in platelet-derived and connective tissue growth factors (70). Elevated angiotensin II has been shown to precede atrial fibrosis in clinical populations such as heart failure and angiotensin-converting enzyme inhibition (at least partly) reduces atrial fibrosis (71). This highlights the multifactorial nature and seemingly central role of atrial fibrosis in 'athletic AF'.

Inflammation. Inflammation is a well-established risk factor for incident AF and shares common pathways with fibrosis (10). Several proinflammatory markers have been linked with AF such as C-reactive protein (CRP), tumour necrosis factor (TNF-a), and interleukin (IL)-2, IL-6, IL-8 (72). In fact, a causal relationship between TNF-a and exercise-induced AF has been established in murine models (73). Acute exercise studies may shed light on the pathophysiological mechanisms of repeated endurance exercise over years of training and incident AF. In humans, Wilhelm et al. (74) demonstrated enhanced proinflammatory markers (TNF-a, IL-6, and CRP) and atrial remodelling following a single mountain marathon. Findings revealed a post-race (exercise-induced) atrial myocardial oedema and increased proinflammatory markers. Further, the increase in proinflammatory markers were higher than that previously reported in a flat marathon study (75), supporting the notion of an intensity-dependent inflammatory response. Although further research is required to investigate causation, recent work has implied cardiac dysfunction following intense endurance exercise was associated with increased expression of pro-inflammatory cytokines

(76). Such findings demonstrate how repeated episodes of high-intensity endurance exercise may contribute to an overall proinflammatory state, contributing to an AF substrate.

Autonomic imbalance. Bradycardia in athletes is likely explained through cardiac remodelling, but also upregulated vagal tone and HCN4-channels (77). Athletic bradycardia, although cardio-protective, has been implicated in the development of AF (78). For example, abrupt shifts in autonomic tone, as seen during the onset and recovery of exercise training has been shown to precede the onset of paroxysmal AF (79). There are also several characteristics that support the involvement of vagal tone in AF more generally.

Several studies have reported an increased onset of AF at night (when vagal tone is highest) and during eating (i.e. vagal stimulation) (80). Supported by animal models, bradycardic responses to blood pressure elevation with phenylephrine (reflecting vagal upregulation), was approximately doubled following 16-weeks of endurance exercise training compared to no change in sedentary controls (66).

In addition, early and delayed afterdepolarizations are thought to cause ectopic and re-entry arrhythmic activity, promoted by prolonged repolarization and Ca2+ handling abnormalities, respectively. Liu and Nattel (81) suggested that vagal stimulation promoted AF via prolongation of the atrial effective refractory period (ERP; during which a new action potential cannot be initiated, though individual cells/sites can depolarize), which was not seen during sympathetic stimulation. This effect occurs via activation of acetylcholine-dependent potassium currents. Increased vagal tone as a result of endurance exercise has been shown to elicit heterogeneous shortening of the action potential duration (APD) via increased sensitivity to acetylcholine, secondary to a reduction in regulators of G-protein signalling proteins (82). Thus, an increased ERP and a correspondingly reduced APD may be a key mechanism in the development of 'athletic AF'.

Despite some existing mechanistic insights highlighted above, further research is needed to elucidate the autonomic and associated molecular characteristics, which contribute to AF in humans (especially endurance athletes), particularly with regard to individual and subpopulation heterogeneity.

3. Summary and future perspectives

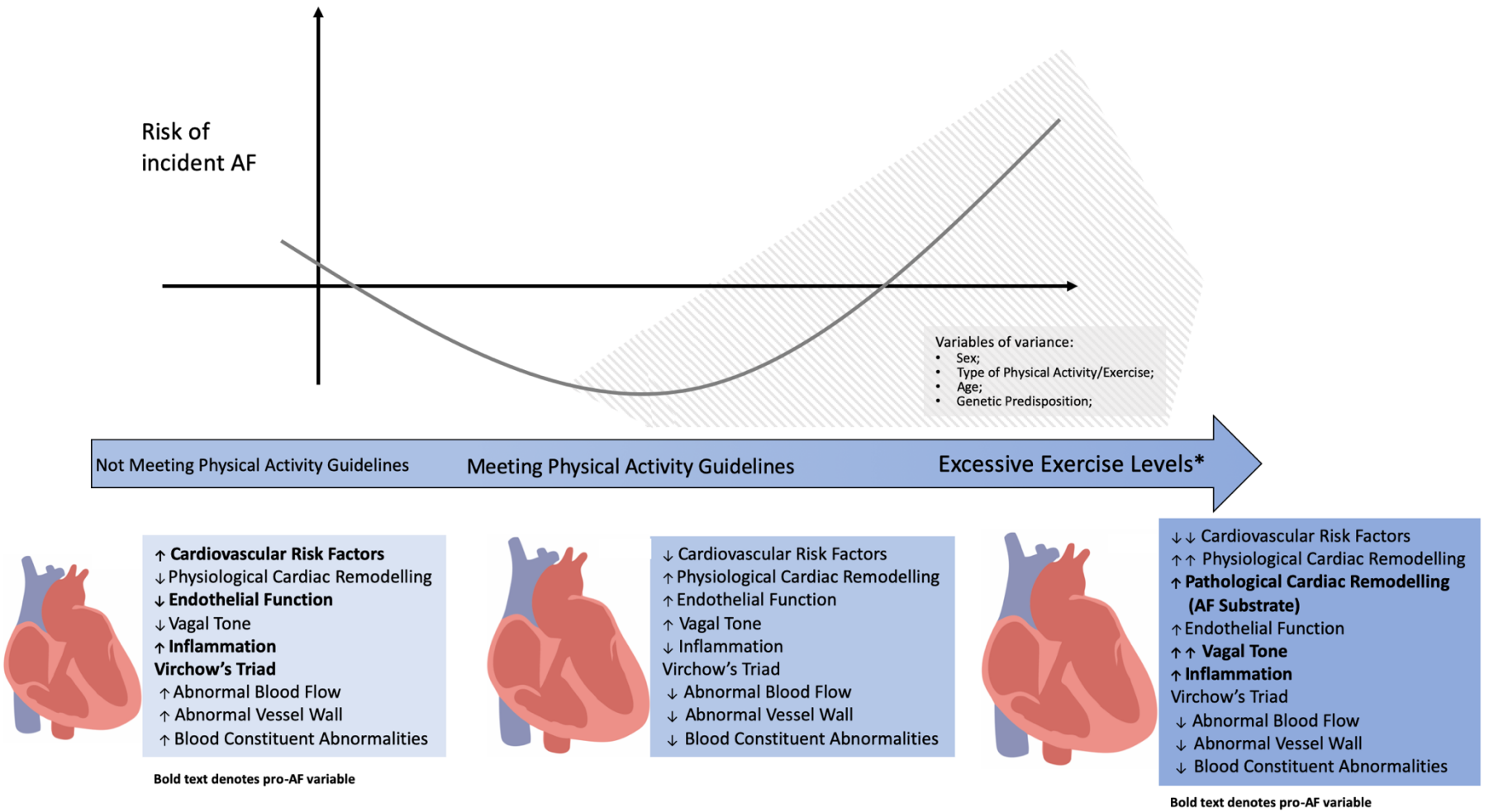
Regular PA and exercise training induce a dose-dependent decline in risk of incident AF and secondary cardiovascular events, which may be explained through its effect on traditional cardiovascular risk factors, inflammation, cardiac remodelling, endothelial function, and autonomic balance. As levels of PA and exercise increase beyond that recommended, the protective health impacts on AF development attenuate. In fact, as one moves further to the right of the dose-response curve, e.g. excessive endurance exercise, AF risk returns to normal or may even exceed the risk for incident AF found in inactive cohorts (Figure 1). Potential pathological mechanisms relating to this counterintuitive role of (too much) exercise on AF, include an AF substrate (atrial enlargement, atrial fibrosis, myocardial inflammation) and upregulated vagal tone.

Nevertheless, further work is needed to investigate the effects of PA on AF in humans, independent of other target risk factors such as body mass, blood pressure, and lipids, for example. In addition, given the relatively small sample size of the most active study participants, further research is needed to elucidate the seemingly enhanced risk of AF in these cohorts. It is possible components of 'athletic AF' are reversible with detraining, as shown in animal models, though research is needed in humans to confirm the reversibility of underlying mechanisms and indeed how such recommendations are received by athletes.

Although there remains uncertainty as to the upper 'safe' threshold of exercise and incident AF, there is no evidence to suggest that exercise training within current guidelines causes or exacerbates AF. Conversely, recent evidence suggests three times the recommended PA levels (and even beyond for females) is AF protective (23). It is only at exceptionally high levels of vigorous endurance training do we see an increased risk of AF (e.g. >5000 vigorous MET-mins/week). This increased risk of AF appears to be more pronounced in males than females and research is therefore needed to confirm sex-specific, safe upper levels of PA for AF protection. In addition, further work is needed to determine the effect of different PA modes (e.g. continuous endurance training, high-intensity interval training, and habitual PA) on AF risk.

Better understanding of the mechanisms underpinning PA, exercise and AF will contribute to optimal prescription of exercise for AF patients and improve understanding of AF in athletes. Such insight may relate to optimisation (e.g. type, dose, mode of exercise) and wider prescription of regular PA in the primary and secondary prevention of AF. Moreover, research should also consider the wider benefits of regular PA in these populations, especially since AF

388 patients are of increased risk for cerebrovascular complications and cognitive decline. Finally,
389 better insight is required to guide and treat the most active AF patients where excessive
390 amounts of PA have contributed to the development of AF. Nonetheless, the key message
391 remains that exercise should be regarded as medicine for patients with AF, demonstrating a
392 dose-dependent relationship, with excessive amounts corresponding to an “overdose” in the
393 treatment of AF.



*Excessive exercise levels refers to that of a training load that far surpasses the recommended guidelines of 150-minutes of moderate-intensity or 75-minutes of vigorous-intensity physical activity per week. Further research is however required to determine an upper 'safe' level, though up to three-fold the recommended physical activity levels (and even beyond for females) seems to confer AF-specific cardio-protection.

Figure 1. Central illustration presenting a J-shaped dose-response curve with reduced incident AF as physical activity levels increase from inactive (below guideline amounts) up to guideline levels of physical activity. Beyond guideline amounts, excessive exercise levels (e.g. long-term high-intensity endurance training) may result in an increased risk of incident AF. The proposed physiological mechanisms of beneficial effects of guideline levels of physical activity on AF and pathological mechanisms of inactivity (left) and excessive levels of exercise (right) are also presented. The shaded area of interest, which increases in size towards the right of the x-axis, denotes the proposed variance in high levels of endurance training and risk of AF. These variables of variance include sex (whereby males seem to be at a higher risk as exercise levels increase), type of physical activity (it is believed vigorous-intensity endurance exercise may increase risk, though the impact of high-intensity interval training on AF risk is unknown), age (as age increases, so does the risk of AF), genetic predisposition (there is a genetic risk of AF, independent of training response). It is also important to note research caveats relating to a variety of trial designs, sample size, and small participant numbers at the highest of activity levels (far right of the curve).

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.
2. Lip GYH, Fauchier L, Freedman SB, Gelder I, Natale A, Gianni C, et al. Atrial fibrillation. Nature Reviews Disease Primers. 2016;2(1):nrdp201616.
3. Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, et al. Oral Anticoagulation and the Risk of Stroke or Death in Patients With Atrial Fibrillation and One Additional Stroke Risk Factor: The Loire Valley Atrial Fibrillation Project. Chest. 2016;149(4):960-8.
4. Kim D, Yang PS, Yu HT, Kim TH, Jang E, Sung JH, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. Eur Heart J. 2019;40(28):2313-23.
5. Aronson D, Shalev V, Katz R, Chodick G, Mutlak D. Risk Score for Prediction of 10-Year Atrial Fibrillation: A Community-Based Study. Thromb Haemostasis. 2018;118(9):1556-63.
6. Force ESCT, Gorenek B, Pelliccia A, Benjamin EJ, Boriani G, Crijns HJ, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). Europace. 2016;19(2):euw242.
7. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123(14):1501-8.
8. Li YG, Pastori D, Farcomeni A, Yang PS, Jang E, Joung B, et al. A Simple Clinical Risk Score (C2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects: Derivation in 471,446 Chinese Subjects, With Internal Validation and External Application in 451,199 Korean Subjects. Chest. 2019;155(3):510-8.
9. Fatema K, Barnes ME, Bailey KR, Abhayaratna WP, Cha S, Seward JB, et al. Minimum vs. maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. European J Echocardiogr J Work Group Echocardiogr European Soc Cardiol. 2009;10(2):282-6.
10. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol. 2012;60(22):2263-70.
11. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017;14(11):627-8.
12. Schnabel RB, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, et al. Depression in atrial fibrillation in the general population. Plos One. 2013;8(12):e79109.
13. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373(9665):739-45.
14. Wood KA, Barnes AH, Paul S, Hines KA, Jackson KP. Symptom challenges after atrial fibrillation ablation. Hear Lung J Acute Critical Care. 2017;46(6):425-31.
15. Dagres N, Chao T-F, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? Europace European Pacing Arrhythm Cardiac. 2018;20(9):1399-421.

16. Hachinski V, Einhäupl K, Ganten D, Alladi S, Brayne C, Stephan B, et al. Preventing dementia by preventing stroke: The Berlin Manifesto. Alzheimer's & Dementia. 2019;15(7):961-84.
17. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary Behavior, Exercise, and Cardiovascular Health. Circ Res. 2019;124(5):799-815.
18. Sanchis-Gomar F, Perez-Quilis C, Lippi G, Cervellin G, Leischik R, Löllgen H, et al. Atrial fibrillation in highly trained endurance athletes - Description of a syndrome. Int J Cardiol. 2017;226:11-20.
19. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. Physiol Rev. 2017;97(2):495-528.
20. Buckley BJR, Watson PM, Murphy RC, Graves LEF, Whyte G, Thijssen DHJ. Carotid Artery Function Is Restored in Subjects With Elevated Cardiovascular Disease Risk After a 12-Week Physical Activity Intervention. The Canadian journal of cardiology. 2019;35(1):23-6.
21. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2008;118(8):800-7.
22. Bapat A, Zhang Y, Post WS, Guallar E, Soliman EZ, Heckbert SR, et al. Relation of Physical Activity and Incident Atrial Fibrillation (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2015;116(6):883-8.
23. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, et al. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. European Heart Journal. 2020;41(15):1479-86.
24. Jin MN, Yang PS, Song C, Yu HT, Kim TH, Uhm JS, et al. Physical Activity and Risk of Atrial Fibrillation: A Nationwide Cohort Study in General Population. Sci Rep. 2019;9(1):13270.
25. O'Neal WT, Bennett A, Singleton MJ, Judd SE, Howard G, Howard VJ, et al. Objectively Measured Physical Activity and the Risk of Atrial Fibrillation (from the REGARDS Study). Am J Cardiol. 2020;128:107-12.
26. Morseth B, Graff-Iversen S, Jacobsen BK, Jorgensen L, Nyrnes A, Thelle DS, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromso Study. Eur Heart J. 2016;37(29):2307-13.
27. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64(21):2222-31.
28. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol. 2015;66(9):985-96.
29. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA, et al. Cardiorespiratory Fitness and Risk of Incident Atrial Fibrillation: Results From the Henry Ford Exercise Testing (FIT) Project. Circulation. 2015;131(21):1827-34.
30. Garnvik LE, Malmo V, Janszky I, Ellekjaer H, Wisloff U, Loennechen JP, et al. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: the HUNT study. Eur Heart J. 2020;41(15):1467-75.
31. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310(19):2050-60.

32. Risom SS, Zwisler AD, Rasmussen TB, Sibilitz KL, Madsen TL, Svendsen JH, et al. Cardiac rehabilitation versus usual care for patients treated with catheter ablation for atrial fibrillation: Results of the randomized CopenHeartRFA trial. Am Heart J. 2016;181:120-9.
33. Aliot E, Botto GL, Crijns HJ, Kirchhof P. Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. EP Europace. 2014;16(6):787-96.
34. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. Am Heart J. 2011;162(6):1080-7.
35. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. Journal of Psychiatric Research. 2016;77:42-51.
36. Larsen RT, Gottliebsen CR, Wood KA, Risom SS. Lifestyle interventions after ablation for atrial fibrillation: a systematic review. Eur J Cardiovasc Nur. 2020;0(0):1474515120919388.
37. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. Eur Heart J. 2018;39(32):2987-96.
38. Proietti M, Boriani G, Laroche C, Diemberger I, Popescu MI, Rasmussen LH, et al. Self-reported physical activity and major adverse events in patients with atrial fibrillation: a report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry. Europace. 2017;19(4):535-43.
39. Malmo V, Nes BM, Amundsen BH, Tjonna AE, Stoylen A, Rossvoll O, et al. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. Circulation. 2016;133(5):466-73.
40. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. Circulation. 2009;119(16):2146-52.
41. Mohanty S, Mohanty P, Di Biase L, Bai R, Pump A, Santangeli P, et al. Impact of metabolic syndrome on procedural outcomes in patients with atrial fibrillation undergoing catheter ablation. J Am Coll Cardiol. 2012;59(14):1295-301.
42. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. Journal of the American College of Cardiology. 2011;57(17):1745-51.
43. Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm. 2013;10(1):90-100.
44. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013;62(4):300-5.
45. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. Heart Rhythm. 2010;7(9):1282-90.
46. Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, et al. Paroxysmal Lone Atrial Fibrillation Is Associated With an Abnormal Atrial Substrate. Journal of the American College of Cardiology. 2009;53(14):1182-91.

47. Seo DY, Kwak HB, Kim AH, Park SH, Heo JW, Kim HK, et al. Cardiac adaptation to exercise training in health and disease. Pflugers Archiv European J Physiology. 2020;472(2):155-68.
48. Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Frontiers Cardiovasc Medicine. 2019;6:69.
49. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, et al. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. J Am Coll Cardiol. 2014;64(12):1257-66.
50. Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications. Cardiovasc Res. 2018;115(1):31-45.
51. Chen YW, Apostolakis S, Lip GY. Exercise-induced changes in inflammatory processes: Implications for thrombogenesis in cardiovascular disease. Ann Med. 2014;46(7):439-55.
52. Chou CH, Fu TC, Tsai HH, Hsu CC, Wang CH, Wang JS. High-intensity interval training enhances mitochondrial bioenergetics of platelets in patients with heart failure. Int J Cardiol. 2019;274:214-20.
53. Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G. Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? Hypertens Dallas Tex 1979. 2011;57(3):363-9.
54. Komatsu T, Kunugita F, Ozawa M, Satoh Y, Yoshizawa R, Owada S, et al. Relationship between Impairment of the Vascular Endothelial Function and the CHA2DS2-VASc Score in Patients with Sinus Rhythm and Non-valvular Atrial Fibrillation. Intern Medicine Tokyo Jpn. 2018;57(15):2131-9.
55. Shaikh AY, Wang N, Yin X, Larson MG, Vasan RS, Hamburg NM, et al. Relations of Arterial Stiffness and Brachial Flow-Mediated Dilation With New-Onset Atrial Fibrillation: The Framingham Heart Study. Hypertension. 2016;68(3):590-6.
56. Mont L, Elosua R, Brugada J. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter. Europace European Pacing Arrhythm Cardiac. 2008;11(1):11-7.
57. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace. 2008;10(5):618-23.
58. Eijsvogels TMH, Fernandez AB, Thompson PD. Are There Deleterious Cardiac Effects of Acute and Chronic Endurance Exercise? Physiol Rev. 2016;96(1):99-125.
59. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. Eur Heart J. 2013;34(47):3624-31.
60. Myrstad M, Løchen ML, Graff-Iversen S, Gulsvik AK, Thelle DS, Stigum H, et al. Increased risk of atrial fibrillation among elderly Norwegian men with a history of long-term endurance sport practice. Scand J Med Sci Spor. 2014;24(4):e238-44.
61. Myrstad M, Nystad W, Graff-Iversen S, Thelle DS, Stigum H, Aaronaes M, et al. Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter. Am J Cardiol. 2014;114(8):1229-33.
62. Andrade JG, Deyell MW, Lee AYK, Macle L. Sex Differences in Atrial Fibrillation. Can J Cardiol. 2018;34(4):429-36.
63. Sanchis L, Sanz-de La Garza M, Bijnens B, Giraldeau G, Grazioli G, Marin J, et al. Gender influence on the adaptation of atrial performance to training. European Journal of Sport Science. 2017;17(6):720-6.

64. Morseth B, Lochen ML, Ariansen I, Myrstad M, Thelle DS. The ambiguity of physical activity, exercise and atrial fibrillation. Eur J Prev Cardiol. 2018;25(6):624-36.
65. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation. 2011;123(1):13-22.
66. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. J Am Coll Cardiol. 2013;62(1):68-77.
67. Pelliccia A, Maron BJ, Di Paolo FM, Biffi A, Quattrini FM, Pisicchio C, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol. 2005;46(4):690-6.
68. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac Fibrosis in Patients With Atrial Fibrillation: Mechanisms and Clinical Implications. J Am Coll Cardiol. 2015;66(8):943-59.
69. Wilson M, O'Hanlon R, Prasad S, Deighan A, Macmillan P, Oxborough D, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. J Appl Physiol (1985). 2011;110(6):1622-6.
70. Leask A. Getting to the heart of the matter: new insights into cardiac fibrosis. Circ Res. 2015;116(7):1269-76.
71. Nattel S, Burstein B, Dobrev D. Atrial Remodeling and Atrial Fibrillation. Circulation: Arrhythmia and Electrophysiology. 2008;1(1):62-73.
72. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21(9):1064-70.
73. Aschar-Sobbi R, Izaddoustdar F, Korogyi AS, Wang Q, Farman GP, Yang F, et al. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFalpha. Nat Commun. 2015;6(1):6018.
74. Wilhelm M, Zueger T, De Marchi S, Rimoldi SF, Brugger N, Steiner R, et al. Inflammation and atrial remodeling after a mountain marathon. Scand J Med Sci Sports. 2014;24(3):519-25.
75. Scherr J, Braun S, Schuster T, Hartmann C, Moehlenkamp S, Wolfarth B, et al. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. Med Sci Sports Exerc. 2011;43(10):1819-27.
76. Gerche AL, Inder WJ, Roberts TJ, Brosnan MJ, Heidbuchel H, Prior DL. Relationship between Inflammatory Cytokines and Indices of Cardiac Dysfunction following Intense Endurance Exercise. Plos One. 2015;10(6):e0130031.
77. D'Souza A, Bucchi A, Johnsen AB, Logantha SJ, Monfredi O, Yanni J, et al. Exercise training reduces resting heart rate via downregulation of the funny channel HCN4. Nat Commun. 2014;5(1):3775.
78. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. Am J Cardiol. 2011;108(4):580-5.
79. Tan AY, Zhou S, Ogawa M, Song J, Chu M, Li H, et al. Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines. Circulation. 2008;118(9):916.
80. Carpenter A, Frontera A, Bond R, Duncan E, Thomas G. Vagal atrial fibrillation: What is it and should we treat it? Int J Cardiol. 2015;201:415-21.
81. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol-endoc M. 1997;273(2 Pt 2):H805-16.

82. Chen P-S, Chen LS, Fishbein MC, Lin S-F, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res. 2014;114(9):1500-15.