Exercise and Atrial Fibrillation: The Dose Makes the Poison? 
A Narrative Review

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ABSTRACT
“All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison” (Paracelsus, ~ 1538 AD). This well-known quote seems to aptly summarize the current understanding of the interaction between exercise and atrial fibrillation (AF). A host of data strongly suggests that regular exercise has a protective effect against developing AF. A small but well-conducted group of trials also demonstrates beneficial effects of exercise in the treatment of AF. Recently, however, potentially detrimental effects of large volumes of high-intensity exercise on the probability of developing AF have moved into the sports-cardiological focus. This effect is well documented for elite athletes; data regarding the general population is less clear. This review presents the current data regarding the protective, therapeutic and potentially risk-enhancing effects of exercise regarding AF. The authors demonstrate that the benefits are clear and strongly outweigh the potential disadvantages.

Key Points
- A sedentary life-style increases the life-time risk of atrial fibrillation (AF).
- Exercise is a beneficial tool in preventing atrial fibrillation. Men seem to maximize their benefit by exercising between 1.5 and 4 hours/week, while up to 6 hours/week seem safe regarding any potential risk-elevation. In men who perform very high volumes of high intensity exercise (i.e. > 8 hours/week) the AF-risk may be increased. No such risk-elevation has been observed in women (see Fig. 1 (central illustration)).
- Patients already diagnosed with atrial fibrillation seem to benefit from therapeutic physical activity. Based on current data, moderate-intensity exercise for 2 to 3 hours/week seems to be a sensible recommendation. High-intensity interval training may be a safe and beneficial alternative or supplement.
- Exercise is beneficial as a preventive and therapeutic tool. Increasing one’s risk of atrial fibrillation through recreational exercise is extremely unlikely, while the general health benefits are well documented.
Introduction

Atrial fibrillation (AF) is the most common lasting arrhythmia worldwide. It is characterized as “a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction” [1]. While the current prevalence lies at around 3%, demographic change and a strong age-association of AF lead to rising numbers of patients. Thus, the prevalence is 10% in people >65 years old and >15% among the >80-year-olds [1]. In the coming decades, the prevalence of AF in Europe is calculated to reach ~25 million patients [2, 3], likely further elevated by inactivity and different levels of activity and atrial fibrillation.

In the coming decades, the prevalence of AF in Europe is calculated to reach ~25 million patients [2, 3], likely further elevated by inactivity and different levels of activity and atrial fibrillation.

The development of AF does not seem to be monocausal but rather the result of multifactorial processes and risk factors such as older age, arterial hypertension or inflammatory processes [1]. These coincide with the general risk factors of cardiovascular disease, but a strong elevation of the body mass index could be especially relevant [10]. Exercise may have to be listed among these risk factors, albeit only in men and only above a (very high) threshold of training volume [11].

Atrial fibrillation can appear paroxysmally for only short durations, may terminate spontaneously or may persist for longer periods. Some patients have accepted to live with atrial fibrillation permanently [1]. Symptoms can vary greatly intra- and interindividually between α-, oligo- and highly symptomatic episodes. Symptoms can include one or more of the following: Palpitations, dyspnea, fatigue or angina pectoris. Patients in AF may be able to perform physical work or physical exercise without relevant impairment or suffer large reductions in cardiorespiratory performance [1].

Treatment strategy depends on symptoms, age, co-morbidities and patient preference. A key element is oral anticoagulation due to the elevated risk of ischemic stroke among patients with AF [1]. The arrhythmia itself can be treated by rate control (slowing down a tachycardic arrhythmic heart beat) or rhythm control (re-establishing and maintaining sinus rhythm). The latter includes medication, cardioversion and ablation therapy (i.e. pulmonary vein isolation, etc.) [1]. More recently life-style interventions including physical activity have broadened the therapeutic strategy (see chapter Exercise in the treatment of AF).

Exercise and Atrial fibrillation

Physiological and anatomical mechanisms of the interaction between exercise and AF

Regarding the effects of physical activity in preventing AF the modulation of classic cardiovascular risk factors is likely to play a key role. A vast host of evidence demonstrates beneficial effects of regular physical activity on many key risk factors for AF: Hypertension, obesity, diabetes mellitus, coronary artery disease, hyperlipoproteinemia [1]. Several factors are likely associated on a (patho)physiological, anatomical and structural level with the effects of exercise (or its absence) on AF. Exercise modulates inflammatory and antioxidative processes, blood-flow associated transmitter emissions (i.e. vasodilation via nitric oxide) and several metabolic processes [12, 13]. These may influence the development of atrial enlargement and fibrosis and the whole complex process called atrial remodeling; likely associated with changes in electrical conduction, generating a substrate for the occurrence and perpetuation of AF [14]. These mechanisms likely affect the preventive and therapeutic benefits of exercise. Moderate physical activity has been demonstrated to oppose and reverse atrial fibrotic changes in what has been called “reverse remodeling” [15]. While exercise acutely elevates atrial pressure and inflammatory processes during the activity, in the long-run blood-pressure and inflammation are reduced in active compared to inactive subjects. The association between

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<th>Risk factor</th>
<th>Preventive and therapeutic range</th>
<th>Potential risk factor if ≥8h of high-intensity training per week for many years</th>
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<tr>
<td>Sedentary</td>
<td>−1 h of light training to −6 h of intense training per week</td>
<td>Endurance athletes</td>
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An inactive lifestyle increases the risk of atrial fibrillation (AF). Regular physical activity (as little as 1 h/week) of light and/or higher intensities helps to prevent the development of AF. It also reduces the AF-burden and increases the quality of life in patients with AF. Men training at high intensities and high volumes (i.e. ≥8 h of fast jogging/week) for many years may increase their risk of getting AF; however, the health-benefits of this training greatly outweigh the risk-increase.
professional athletic careers and an increased risk of AF may be due to the high frequency and duration of the phases of cardiac volume overload and upregulation of inflammatory processes. This may lead to atrial enlargement and fibrotic restructuring [16, 17]. Also, the increased vagal activity leading to reduced resting heart rates in professional (endurance) athletes may increase the risk of ectopic beats and electric re-entry-processes [13, 18].

Exercise as prevention- and risk-factor?
While some therapeutic effects of exercise for AF have been demonstrated in prospective randomized controlled trials [19–21], insights regarding its preventive effect are based on observational data [3, 22, 23]. This is to be expected, as randomizing large numbers of participants to “active” vs. “inactive” for many years of prospective analysis is unethical and unfeasible. However, as has been the case for classic cardiovascular risk-factors like smoking and low-density-lipoprotein(LDL)-cholesterol, large prospective observational studies allow an assessment of inactivity as a risk-factor for AF while statistically minimizing confounding. A challenge for these studies is the heterogeneous definition of “exercise,” “activity & inactivity” and “training”. Initial trials and meta-analysis only assessed the volume of physical activity without considering levels of intensity. Newer trials try to specify, but self-reported activity data remains at risk for inaccuracies. Thus, for example the often applied and repeatedly validated international physical activity questionnaire – short form (IPAQ-SF) – has been deemed “rather inaccurate” in a meta-analyses of validation studies [24]. The metabolic equivalent (MET) has been a helpful tool in more recent studies to classify activities by intensities. It also allows for easier inclusion of different exercise forms into assessments of cumulative activity by grouping activities into MET-minutes or MET-hours [23].

By now many observational reports demonstrate that exercise has a protective effect against AF, but may also function as a risk factor. The key variables seem to be volume, intensity and sex [13].

Moderate physical activity
In a large meta-analysis in 2016 Mohanty et al. assessed 22 cohort-, case-control- and observational studies with a total of > 650,000 participants, deducing that an inactive life-style increases the lifetime risk of AF 2.5-fold independent of the participants’ sex. Moderate physical activity, albeit defined very differently in this heterogeneous study-collective, reduced the risk of AF ~ 9 % in women and ~ 18 % in men when compared to the inactive group [3]. These results are plausible considering the well documented inverse association between cardio-respiratory fitness and the incidence of atrial fibrillation [25–27]. In military veterans elevated fitness – often a result of regular moderate intensity training – was significantly associated with a reduced likelihood of developing AF [28].

In 2020 Elliott et al. [23] published a large prospective observational analysis including > 500,000 participants who were observed since 2007. Data was collected using the IPAQ-SF questionnaire, and in contrast to the heterogenous data of the meta-analysis by Mohanty et al. from 2016 [3] this study could work with homogenous definitions of physical activity in a similarly large total cohort. The total amount of physical activity was documented as well as the time spent in vigorous physical activity (defined as ≥ 8 MET). The following activity-groups were assessed regarding their association with the risk of AF and compared to the inactive participants: 500, 1,000, 1,500, 2,000, 2,500, and 5,000 MET-min/week. A similar stratified analysis was conducted only for vigorous activities [23].

The results of this study underscore the protective effect of exercise against developing AF, starting at an activity level of 500 MET-min per week (i.e. biking leisurely at 100 W for 30 minutes 3x/week). This benefit increased among men up to 1500 MET-min/week (i.e. moderate bike riding for 4 hours/week) and was without upper limit for women. Absolute risk reduction in this zone was between 5 and 10 % for both sexes [23]. These findings underscore the prior documentation of the benefits of moderate activity [22, 29, 30]. In conclusion, moderate levels of physical activity and elevated cardio-respiratory fitness showed a protective effect in men and women.

Vigorous physical activity
Varying definitions of “vigorous” exercise reduce the comparability of different publications as well as their pooled assessment in meta-analyses. More recent studies aimed to clearly define assessed volumes and intensities of exercise. In their 2016 meta-analysis including data of 100,000 women Mishima et al. [3] found a reduced risk of AF by 28 % in women who regularly exercised vigorously, without any reduction of this benefit even with very high volumes of vigorous exercise. The data sets of the approx. 80,000 men included were highly heterogenous, but suggested a 2.5- to 3.5-fold AF-risk increase for those engaging in high volumes of vigorous physical activity [3]. The positive association between all volumes of vigorous physical activity and an AF-risk-reduction was underlined in the large study based on the UK Biobank data with the largest risk-reduction of 16 % documented at 2,500 MET-min/week [23]. The isolated analysis of vigorous exercise in men showed no significant risk reduction, but at a volume of 5,000 MET-min/week (i.e. 8 hours of fast jogging/week) an observed risk-increase of 12 % [23].

Mishima et al. [29] published a large meta-analysis with the most recent evaluation of the association between exercise and incidence AF. Prospective cohort studies with a minimum follow-up of 4 years were included. However, exercise levels pooled moderate and intensive activities by translating all data into MET-min/week, thus disenabling any differentiation of effects between moderate and intense forms of exercise regarding AF-risk. The authors found that meeting the World Health Organization (WHO)-recommendations [31] of exercise resulted in a 6 % risk-reduction of incident AF. An analysis of the most active sub-group resulted in a risk reduction of 8 %. No increase of AF-risk was documented for any assessed exercise volume, but the beneficial association between exercise and freedom from AF became less clear for training volumes above 2,000 MET-min/week.

A sub-group analysis by gender found persistent beneficial effects among women meeting the WHO-recommendations (9 % risk reduction) and women exceeding them (12 % risk reduction). In men, meeting WHO-recommendations reduced AF-risk by 4 %, while the most active male subgroup showed no effect for AF-risk.
**Atrial Fibrillation in Athletes**

An elevated life-time risk of atrial fibrillation among athletes is a well-established phenomenon [11, 32–35]. Data ranges from small retrospective case-control studies to larger prospective cohort studies. Reviews and meta-analyses define between a 2.5- and 5-fold increase in AF-risk for athletes compared to the general population [32]. Most studies conclude that sports disciplines with high volumes and intensities of endurance training (i.e. marathon running, cycling, cross-country skiing, etc.) convey the highest risk-increase [34]. Importantly, > 90 % of data regarding AF-risk in athletes has been collected in men [33]. Athletes combine many of the well documented and suspected AF-risk factors (see Fig. 2). Based on the current understanding of the mechanistic link between exercise and AF (i.e. less atrial enlargement in female than male athletes; see section above titled Physiological and anatomical mechanisms of the interaction between exercise and AF) a reduced risk among female athletes compared to male athletes seems plausible. Generally, the endurance athlete well exemplifies the tendency deduced in the large observational studies that high levels of endurance exercise may increase AF-risk in men.

**Exercise as therapeutic agent**

While a lot of observational data has been accumulated regarding the association of inactivity and different activity modalities with the risk of AF, data regarding the therapeutic effect of exercise for patients with AF is scarce. In 2014 and 2015 initial non-randomized interventions demonstrated that life-style-adaptations including exercise regimens reduced the incidence, duration and subjective burden of AF-episodes [36]. The few prospective randomized controlled trials are small but promising: In 2016 Risom et al. [20] demonstrated in 200 AF-patients that moderate physical activity improved cardiorespiratory fitness and quality of life without producing relevant adverse events. In the same year Malmo et al. [21] showed a reduction of paroxysmal AF-load between 4 and 8 % in patients undergoing high-intensity interval training twice a week compared to standard care. Most recently a trial by Elliot et al. [37] found that a six months vigorous exercise regimen among patients with paroxysmal AF halved the risk of AF-recurrence; a benefit that was sustained for another six months follow-up even after the exercise-intervention period had ended. Several reviews summarizing the available data draw the conclusion that exercise seems to be a beneficial therapy modality in the treatment of AF, but further study is needed [38–40]. Trials assessing safety, feasibility and exercise modalities are ongoing [12]. Current guidelines by the European Society of Cardiology (ESC) include recommendations for the practical approach to exercise in AF-patients [41]. Thus, exercise receives a IA-recommendation as a preventive measure of AF. Athletes engaging in high volumes of vigorous exercise experiencing AF should be counselled regarding the effects of the different exercise forms regarding development and recurrence of AF (IB).

Patients currently in AF may participate in exercise (IIaC), ideally with heart-rate monitoring via ECG or subjective symptoms. If AF is well tolerated, exercise may be considered without any antiarrhythmic therapy in patients without structural heart disease (IIaC) [41]. Generally, a cardiological work-up is recommended, including a screening for atherosclerotic disease and for further potential causes of AF. Contact sports or those with elevated trauma risk should be avoided in anticoagulated patients. Beta-blockers as the most common form of rate control may negatively impact physical performance and are on the doping list in case of specific sports. An interventional approach using ablation is recommended (IB) for physically active AF-patients, if symptomatic and/or unwilling to undergo medical therapy due to its potentially performance limiting effects. The rate and rhythm control strategy must be tailored to the individual, but the risk of 1:1-conducted atrial flutter must be considered in patients taking class I anti-arrhythmic drugs without a beta-blocker. In these patients, a restraint from intense physical exercise is recommended for at least two days after the use of Flecainide or Propafenone; alternatively a prophylactic ablation of the cavo-tricuspid-isthmus should be considered (IIaC) [41].

**Summary and Conclusion**

Atrial fibrillation is the most common lasting arrhythmia and is strongly age associated. Due to demographic changes and the high prevalence of risk factors, the number of AF-patients is rising. While medical (rhythm and rate-control) and interventional therapies are improving continually, the focus is starting to include the potential of life style interventions, including exercise as a key component: Exercise seems to benefit in the prevention and therapy of AF, but may also play a role as a risk factor. Key factors regarding the latter are volume and intensity of training, as well as sex.
Fig. 1 summarizes the association between exercise and atrial fibrillation: While women seem to reduce their risk of AF with exercise regardless of volume and intensity, current data suggest that an optimal preventive range for men lies within 1.5 to 4 hours of moderate exercise per week. High intensity exercise for >8 hours per week may increase the life-time risk of AF in men, but this remains to be elucidated. Athletes, as a select group with very high life-time training volumes and intensities, seem to have an increased AF-risk of up to five times.

Data assessing the effects of exercise training in AF-therapy are scarce. The little available evidence is promising and strongly suggests that exercise increases cardiorespiratory fitness and reduces the burden of AF in affected patients. Further research is needed.

The mechanisms of the effects of exercise on AF-risk and therapy include direct effects on cardiac structure such as atrial size and fibrosis, as well as the influence of exercise on AF-risk factors such as arterial hypertension or diabetes. While certain volumes and intensities of exercise may slightly increase the risk of AF (in men), based on vast amounts of data underlining its cardiovascular benefits, exercise should be recommended and implemented in prevention and therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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