The role of exercise in atrial fibrillation prevention and promotion: Finding optimal ranges for health

Short Title: *Elliott AD et.al.* Exercise and AF

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ABSTRACT

The cardiovascular benefits of regular exercise have been well described, including a significant reduction in cardiovascular morbidity and mortality for those meeting recommended guidelines. Yet the impact of physical activity on the incidence of atrial fibrillation (AF) has been less clear. This review seeks to define the optimal dose and duration for the prevention and treatment of AF. In doing so, we review the evidence that supports a decline in AF risk for those who achieve a weekly physical activity dose slightly above the current recommended guidelines. Furthermore, we identify the reduced AF incidence in those individuals who attain a cardiorespiratory fitness of 8-METs or more during maximal exercise testing. Finally, we review the evidence that shows an excess of AF amongst regular participants of endurance exercise.

INTRODUCTION

The incidence of atrial fibrillation (AF), the most common clinical arrhythmia, continues to grow.(1) Moreover, AF morbidity remains on the rise, leading to significant healthcare demands and poorer patient outcomes.(2) Although multiple factors contribute to the rise in AF incidence, the growing prevalence of obesity and other cardiovascular risk factors plays a significant role. The population attributable risk of AF for lifestyle-based risk factors (obesity, hypertension, type II diabetes) is almost 50%.(3) Given that exercise exerts largely favorable effects for the reduction of cardiovascular risk, the potential benefits for the prevention or management of AF may be considerable.

The health benefits of exercise at the higher end of the dose-spectrum, such as that common to endurance sports, are less certain. Whilst a reduction in mortality is maintained, there is little to suggest any additional benefit.(4,5) Although exercise favors cardiovascular health, there is concern regarding the potential for competitive endurance sports and exercise to contribute to, or directly cause, cardiac arrhythmias. Although ventricular arrhythmias or sudden cardiac death can occur more frequently in athletes with underlying predominately genetic disorders, observational studies have revealed a predisposition towards atrial arrhythmias amongst those with otherwise normal hearts.(6,7)

This review will seek to provide evidence that: (i) low physical activity and poor cardiorespiratory fitness contributes to increased AF incidence; (ii) exercise may provide therapeutic benefit in patients with AF; and (iii) endurance exercise significantly increases the risk of developing AF.

Physical Activity to Reduce AF Incidence

Total Dose of Physical Activity

The global burden of AF is growing rapidly, requiring urgent public health interventions to stem this rise.(8) Coronary heart disease and heart failure incidence are inversely related to physical activity levels.(9,10) However, the protective benefits of physical activity for AF are less clear.

Several studies report a reduction in AF incidence with greater levels of physical activity. In the Cardiovascular Health Study,(11) lower AF incidence with higher doses of weekly physical activity (expressed as the combined distance and pace walked) was observed. For those with the highest self-reported physical activity, there was a 46% reduction in AF risk. In large cohorts of Swedish men and women, daily walking or cycling lowered the risk of AF by 12% and 19%, respectively.(12,13) However, in the Women's Health Study, physical activity did not reduce AF incidence in adjusted analyses.(14) In later studies, the largest benefit of physical activity appeared to be mediated principally through a dampening of the AF risk associated with other AF risk factors. In the Atherosclerosis Risk in Communities study(15) and the Women's Health Initiative Study,(16) physical activity partially offset the elevated risk of AF with obesity. Although its magnitude may be debated, there appears to be an overall benefit of greater physical activity for the reduction of incident AF.

Intensity of Physical Activity

Most studies reporting the association between physical activity and AF have focused on measures of total exercise, without identifying the contribution of

exercise intensity. However, a small number of studies have reported AF risk according to the intensity of exercise.

Mozaffarian et.al, reported the self-rated intensity of physical activity and its subsequent AF risk.(11) A significant reduction in AF risk could be observed with moderate, but not high-intensity exercise. However, this model did not adjust for the total activity. Furthermore, details on the self-rating of exercise intensity were not clear, making it difficult to ascertain the precise level of exertion.

More recent studies have explored the interaction between moderate and more vigorous forms of physical activity on AF risk. Bapat et.al,(17) concluded that more intensive physical activity alone did not reduce AF risk. However, greater volumes of intentional exercise (sum of walking for exercise, sports, conditioning and dance) reduced AF risk only in participants who included some vigorous physical activity, such as conditioning activities. In contrast, recent Scandinavian data suggests that moderate physical activity, defined as walking or cycling >4 hours/week, reduces incident AF risk but this benefit is diminished in those who participate in more vigorous activities, including recreational and competitive sports.(18) Future studies in which the exercise intensity is objectively defined will enable better guidance on the most effective intensity of activity for modifying AF risk.

Defining the Optimal Dose

Using available evidence, it is possible to construct an analysis of the dose-response between physical activity and incident AF (Figure-1). The visual inspection of this plot highlights a modest benefit of physical activity at a dose of approximately 1000-1500

Met-minutes/week. Given the current guidelines recommending 150-minutes of moderate intensity activity/week (450-900 Met-minutes),(19) this analysis suggests that a ~10% decline in the risk of incident AF can be achieved by participating in regular physical activity in excess of the recommended guidelines. As an example, ~220-minutes/week of moderate to brisk walking (4.5-Mets) would achieve a weekly dose of 1000-MET-minutes.

The existing data should be considered in the context of several important points. First, the majority of studies quantify physical activity by self-report on study entry, leaving the potential for reporting bias and time-varying changes. Developments in the field of wearable technologies may provide more objective reporting of physical activity. Second, the detection of AF by hospital admissions or medical records, lacks sensitivity for asymptomatic or subclinical AF, or cases requiring minimal management. For example, studies using annual ECGs and hospital records showed a cohort wide incidence of 23 events/1000-person-years.(11) In contrast, studies relying primarily on self-reported AF incidence,(14) demonstrated a cohort-wide incidence of <2 events/1000-person-years. This illustrates the pivotal role of study design and AF ascertainment method in observational studies relating to AF incidence.

Beyond Activity: Cardiorespiratory Fitness and AF Risk

Cardiorespiratory fitness (CRF) is a strong predictor of mortality in healthy participants and patients with existing cardiovascular disease.(20,21) Intriguingly, some studies propose that it is CRF, rather than physical activity *per se*, that reduces mortality.(22)

The first evaluation of the relationship between CRF and incident AF came from 1950 middle aged men in the Kuopio Ischemic Heart Disease Study who underwent exercise testing at baseline to determine peak oxygen consumption (VO_{2peak}).(23) Incident AF was assessed by hospital discharge diagnoses, study ECGs and inpatient claims data over a 19.5-year follow-up. After full adjustment for known risk factors, there was a significant reduction (30%) in AF risk for participants in the third quartile of CRF (Mean CRF: 9.3-METs) but not those in the upper quartile (Mean CRF: 11.6-METs).

In a larger sample from the Henry Ford Exercise Testing Project,(24) 64,561 adults (46% female) were followed for a mean of 5-years. In this sample of patients who underwent physician-referred exercise testing, incident AF was ascertained using medical claims. High CRF was associated with a 56% reduction in AF risk, after adjustment for multiple risk factors. For every 1-MET achieved during treadmill testing, the risk of AF was reduced by 7%.

The benefits of CRF on AF risk reduction were recently confirmed in an analysis of 5962 veterans followed for a median of 8 years,(25) in which AF incidence was determined by review of medical records. High CRF was associated with a 63% reduction in AF during follow-up. Furthermore, for each additional 1-MET achieved, the risk of AF declined by 21%.

Despite CRF showing a strong, inverse relationship with subsequent AF risk (Figure-2), interpretation of this data should consider the elevated cardiovascular risk in most of the cohorts studied as well as variation in the ascertainment of AF and absence of any time-varying measures in the prediction models.

Exercise-Based Rehabilitation for Patients with AF

Although exercise, physical activity and CRF provide benefit from the perspective of primary prevention, there has been an absence of studies assessing the benefit of exercise specifically for patients with AF. However, the favorable effects of lifestyle interventions including weight loss and risk factor management, including recommendations for exercise have shown significant clinical benefit.(26-29)

The earliest data regarding exercise training was derived from patients with permanent AF. In two separate randomized studies, exercise training improved quality of life and exercise capacity amongst patients with permanent AF. (30)Collectively, although these studies indicate that patients with permanent AF gain significant health and functional benefits from exercise training, they do not address the role of exercise in the management of patients with non-permanent AF.

In over 300 overweight or obese patients with paroxysmal or persistent AF, the CARDIOFIT study(31) assessed the role of CRF, measured at baseline, and its subsequent change over a 4-year follow-up. There were two notable findings from this study. First, those with the highest baseline CRF greater (>100% age and gender predicted values) were almost three times more likely to maintain arrhythmia freedom at final follow-up, without catheter ablation or anti-arrhythmic medication. Second, patients who gained CRF (>2-MET gain) throughout the follow-up were over two times more likely to maintain sinus rhythm. Importantly, the benefits of CRF in this study were achieved independently of weight change throughout follow-up, which has been demonstrated to promote arrhythmia freedom.(27, 28)

The role of exercise training in patients with non-permanent AF was recently confirmed in a single center, randomised controlled trial of 12-weeks aerobic

interval training versus usual medical care.(32) In this cohort, AF burden declined by approximately 50% in the exercise group, and increased in the control group. Furthermore, AF symptoms and quality of life improved significantly for the exercise group.

Alternative forms of activity such as yoga have been shown to reduce symptomatic and asymptomatic AF episodes when performed twice weekly for three months.(33) This finding warrants further investigation both as a stand-alone intervention and perhaps in a multidisciplinary approach including more traditional forms of exercise.

To date, only one study has attempted to compare two types of exercise intervention in patients with AF.(34) Amongst 76 patients with paroxysmal or persistent AF, randomization to either low or high-intensity, group-based exercise training over 12 weeks did not result in any between-group differences in peak oxygen uptake or AF burden, recorded by daily ECG. Although this study did not specifically report the change in AF burden from baseline to follow-up, it does suggest that exercising at higher intensities may not provide additional gain.

Although the evidence so far is limited, there appears to be a significant clinical benefit from the prescription of exercise to patients with AF.(35) Exercise lowers AF burden alongside and improves AF-specific symptoms and health-related quality of life. The key questions that remain unanswered are: (i) whether these findings can be translated into larger randomised studies with extended follow-up; and (ii) what are the mechanisms that promote the benefit of exercise in AF patients.

How Does Physical Activity Reduce the Incidence of AF?

Although few studies have explored the mechanisms underlying the favorable benefits of exercise on AF, the current data offers several insights (Figure-3). The CARDIO-FIT study(31) showed that patients with significant gains in CRF also demonstrated lower blood pressure, inflammation and improved glycemic control, suggestive of a global improvement in risk factors. Furthermore, there were notable improvements both in LV size and diastolic function, and a significant reduction in LA size. When achieved in tandem, the benefits for patients with AF were considerable. However, alongside increases in weekly exercise, patients in CARDIO-FIT were also encouraged to lose weight, which may accentuate this benefit. In the later randomised controlled trial by Malmo et.al,(32) there was modest weight loss (~1.6Kg), with a subtle reduction in blood lipids. Interestingly, blood pressure remained the same and there was no change in LA size, although improvements in LA and LV function were observed. This study therefore suggests that the benefit of exercise on AF burden is not mediated solely through large shifts in weight or modifiable risk factors.

The possibility that electrophysiological or autonomic changes promote the benefits of exercise in AF cannot be excluded. Exercise training improves autonomic tone principally by increasing vagal activity and reducing sympathetic activation.(36,37) Simultaneous sympathovagal discharges have been reported to precede the initiation of atrial arrhythmias.(38) Therefore, interventions that lower sympathetic activity may also reduce AF burden. Indeed, in heart failure patients, exercise training reduces sympathetic activation.(39)

In addition to these potential mechanisms, there is a positive benefit of exercise on other AF-specific risk factors, including pericardial fat,(40) and

obstructive sleep apnea.(41) It is likely that a reduction of AF risk factors and favorable changes in mechanistic promoters of AF converge to provide an anti-arrhythmic effect of regular exercise.

Too much of a good thing? Endurance exercise and AF

At the upper end of endurance training, there is a paradoxical increase in AF risk. Early case-control studies demonstrated an over-representation of athletes amongst patients with so-called 'lone' AF.(42,43) Similarly, studies of athletes versus non-athletes support an excess of AF amongst endurance athletes.(44-47) In an early meta-analysis of six studies, athletes had a five-fold increase in the risk of AF compared to age matched controls (OR 5.3, 95% CI: 3.6-7.9).(48) More recently, in a comparison of participants from an annual cross-country ski race (mean age 69-years) versus a cohort from a population-based health survey (mean age 72-years), the prevalence of AF was 13% amongst athletes versus 9.8% amongst non-athletes (OR 1.81, 95% CI: 1.04-3.14).(49) Some caution should be taken when interpreting many of these studies. First, AF is commonly ascertained by self-report, resulting in reporting bias. Second, recruitment bias may be evident in those studies where athletes and control participants were not recruited simultaneously.

More compellingly, cohort studies with extended follow-up lend weight to the hypothesis that endurance exercise promotes AF. In over 16,000 males followed for 12-years in the Physicians' Health Study, Aizer et.al, identified a 50% increase in the risk of AF for those who engaged in jogging 5-7 times/week.(50) Similarly, Andersen et.al,(51) reported arrhythmia incidence amongst over 52,000 former participants of a long-distance cross-country ski race. The authors reported the

arrhythmia incidence by: a) number of race completions, as a surrogate of training history; and b) proximity to the winners finishing time, as a surrogate of performance. AF occurred more frequently in participants with ≥5 race finishes, compared to those with only 1 race finish (OR 1.29, 95% CI: 1.04-1.61). However, there was no significant elevation of AF risk as a result of faster finishing time.

There are several important points to consider in the interpretation of this evidence. First, risk estimates vary widely between studies, impairing the precise estimation of risk associated with endurance exercise. There is also evidence that high-intensity exercise training may be protective in females, yet proarrhythmogenic in males.(52) Second, there is a lack of objectivity in the reporting of training history, leading to inconsistencies between studies. Third, the ascertainment of AF continues to be an ongoing weakness. Finally, there remains a possibility that the symptoms of AF episodes may be more noticeable to an athlete, either at rest or during exercise, thus creating the potential for reporting bias. Future studies that provide the longitudinal assessment of athletes, including their exercise exposure, coupled with objective identification of AF diagnoses, will be critical in understanding the risk of AF associated with exercise.

Mechanisms for AF promotion with endurance sports

Recently, Wilhelm et.al,(53) proposed three potential mediators of atrial arrhythmogenesis in athletes; ectopic triggers, modulators and an altered atrial substrate. Studies in both humans and animals have shed some light on these and other potential pathways (Figure-4).

Seminal work by Haissaguerre et.al,(54) revealed that ectopic beats originating from the pulmonary veins frequently leads to the initiation of AF. Amongst former professional cyclists, atrial ectopy was no different to that of age-matched golfers.(47) However, in runners, more extensive training history was associated with an increase in atrial ectopic burden,(46) albeit lower than that typically seen in AF patients.(55)

Shifts in autonomic balance as a result of training have been shown in humans and animal models.(56,57) Increased autonomic activation can initiate pulmonary vein activity as well as leading to macro-reentry pathways by shortening the atrial refractory period.(58) Furthermore, abrupt shifts between vagal dominance and sympathetic drive, may facilitate the onset of AF.(59) In a rat model, Guasch et.al,(57) demonstrated enhanced vagal activity following 16 weeks of training. This alteration was temporally associated with an increase in AF inducibility. Interestingly, the reversal of vagal enhancement and AF inducibility was evident following detraining, supporting a contribution of autonomic shifts in the promotion of atrial arrhythmogenesis. However, in a mouse model of endurance training, inhibition of vagal tone did not eliminate AF susceptibility following training,(60) therefore suggesting that additional factors may be critical in the development of AF in endurance athletes.

Atrial fibrillation occurs in the presence of an abnormal atrial substrate.(61) In athletes, the development of bi-atrial dilatation is well established and may contribute to the promotion of AF with exercise training.(62) Fibrosis is a common feature of the atrial substrate in both obesity(63) and hypertension.(64) In preclinical models, the development of fibrosis in the atria and ventricles of endurance-trained

rats is associated with an increase in the susceptibility to AF and ventricular arrhythmias.(57,65) Interestingly, atrial fibrosis did not fully resolved with detraining(57) despite a reversal of AF susceptibility.

The mechanisms leading to the abnormal atrial substrate in athletes are likely multifactorial, including repeated stretch and activation of pro-fibrotic pathways alongside inflammation in the atria. The latter was confirmed in a mouse model whereby pharmacological inhibition of the pro-inflammatory cytokine TNF-α prevented the induction of fibrosis in the atrial wall following training, subsequently lowering the inducibility of AF.(60)

Other potential mechanisms contributing to the excess of AF in athletes may be related to body stature. Recent evidence has highlighted the role of height and lean body mass(66) as a positive predictor of incident AF. In recent case-control data, both height and endurance exercise were significantly associated with AF in multivariate analyses.(62) Detailed anthropometric data from longitudinal studies in athletes will provide valuable insight into whether body stature and lean body mass contribute to AF risk amongst athletes.

Where to from here?

There is expanding evidence regarding physical activity, endurance exercise and their relationship with incident AF. The remaining knowledge gaps will need to be addressed with studies leveraging both scientific and technological advances. First, large epidemiological studies, in which physical activity may be quantified with the assistance of wearable devices, will be pivotal in eliminating the bias of self-reported exercise. In such studies, specific attention should be paid to the ascertainment of AF

beyond just medical records. Second, a longitudinal, prospective study of endurance athletes versus age-matched controls coupled with detailed phenotyping is required to advance our understanding of: (i) how endurance exercise modulates the risk of AF; and (ii) the mechanisms promoting AF in this cohort. Such studies should not only take advantage of new approaches to quantify exercise habits, but also advances in cardiac imaging to assess changes in the atrial substrate with training. Furthermore, assuming that endurance exercise does contribute to the promotion of AF, randomized studies comparing treatment strategies may be warranted.

Summary

From current evidence, moderate physical activity at the recommended guidelines may be insufficient to reduce incident AF. However, at a weekly physical activity dose >1000-MET-minutes, or approximately 3.5-hours of moderate walking/week, there appears to be a reduction in the risk of AF by approximately 10% (Figure-5).

In addition, greater CRF appears to reduce the risk of AF development to a greater degree than physical activity alone. A CRF of >8-METs (or a peak VO_2 >28 ml/kg/min) is associated with a lower incidence of AF. Routine exercise testing may therefore offer the opportunity to identify patients with higher AF risk.

The arrhythmogenic effects of endurance exercise are becoming well established, although the specific dose, above which AF risk is elevated, remains uncertain. Although some studies have advocated for a 2000-lifetime-hour threshold,(62) this likely lacks specificity in identifying at-risk individuals. Instead, cardiologists and sports physicians should choose to remain vigilant for arrhythmias in those individuals engaging in high volumes of endurance exercise. Strategies for

the management of AF in athletes is beyond the scope of this review but has been discussed elsewhere.(35)

Finally, for the patient with existing non-permanent AF, exercise training appears to confer an anti-arrhythmic benefit in both short and long-term follow-up. Although there is limited data to develop specific guidelines, an exercise volume of 210-minutes/week with the inclusion of vigorous exercise would be an effective guideline. However, further studies justifying the benefits of exercise for patients with AF are urgently needed.

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FIGURE LEGEND

Figure-1. Upper: Risk associated with levels of weekly physical activity for individual studies in which the exercise dose can be computed. Lower: Estimated best-fit model assessing the AF risk change (95% CI in shaded area) with increasing doses of physical activity (MET-mins), plotted using local polynomial regression.

Figure-2. Bubble plot depicting data from three studies assessing the relationship between CRF and AF incidence. Symbol colors indicate the study, whilst symbol size is proportional to group sample size. AF incidence rates were calculated from reported study data. A lower incidence of AF can be seen in study groups with a CRF >8-METs.

Figure-3. Potential mechanisms contributing to the beneficial effects of exercise in patients with non-permanent AF.

Figure-4. Summary of potential mechanisms promoting atrial arrhythmogenesis in endurance-trained athletes.

Figure-5. Recommendations for physical activity and exercise in the prevention and treatment of AF. Current evidence suggests a lower risk of AF in those who participate in >220-minutes of moderate activity, or who demonstrate a CRF >8-METs. For patients with existing non-permanent AF, exercise up to 210-minutes/week and aerobic interval training have been shown to lower the burden of AF, and reduce long-term recurrences of AF, alongside appropriate risk factor management. Adapted from Elliott et.al,(35) and Lau et.al.(29)