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EDITORIAL

Atrial fibrillation in athletes and the interplay between exercise and health

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This editorial refers to 'Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study'†, by K. Andersen *et al.*, on page 3624

Exercise is one of the most powerful lifestyle intervention strategies for the primary and secondary prevention of cardiovascular disease. There is a wealth of evidence regarding the lower ranges of the exercise dose–response relationship providing concrete evidence for the current recommendations of at least 30 min of moderate intensity exercise on most days as a means of reducing cardiovascular events.[1] However, there is an increasing proportion of today's society engaging in sports practices which vastly exceed these guidelines, and there has been very limited study of the upper ranges of the exercise dose–response relationship.[2] On the one hand are studies suggesting that long-term health and life expectancy of well-trained athletes is superior to that of the general population,[3–5] while, on the other, there is evidence suggesting an increased prevalence of arrhythmias and chronic structural remodelling of the athletic heart.[6–9]

Atrial fibrillation (AF) may therefore represent the most intriguing and best evidenced example of the interplay between exercise and cardiac health. AF can be diagnosed in ~1% of the population by age 60 and in > 10% when older than 80 years,[10] making it the most prevalent sustained arrhythmia in adults. In cohorts of young or middle-aged subjects, AF is relatively uncommon, thus implying that large cohorts would be required to provide sufficient power to identify any excess in prevalence due to sports practice. In this context, it is not surprising that Pelliccia *et al.* found only very few cases of AF despite significant left atrial enlargement in a fairly large ($n = 1777$) athletic cohort aged 24 ± 6 years.[11] In contrast, Baldesberger *et al.* were able to identify an excess of AF when comparing a small cohort of 62 former professional cyclists with 62 ex-golfers aged 66 ± 7 years.[6] Although one must always consider type 1 errors (false discoveries) in studies of small sample size, it may also be that a true exercise-induced excess in AF prevalence becomes appreciable when the cohort reaches an age in which AF is more common and when the amount of exercise practised is relatively extreme. In this context, the recent study of Andersen *et al.* is remarkable.[12] The group of participants in the popular Vasaloppet 90 km cross-country ski race was young and healthy when one considers the likelihood of identifying incident AF. Less than 10% of the cohort was aged >60 years and those with significant co-morbidities were few, as evidenced by the exclusion of participants with known cardiovascular disease and by the fact that the cohort had better health behaviour and overall longevity than the average Swedish population.[13] Many of the established risk factors for AF, such as hypertension, heart failure, diabetes, and obesity,[14] are likely to be under-represented within this group of cross-country ski enthusiasts and, thus, we might expect such a low prevalence of AF that detecting any residual risk attributable to exercise dose would be difficult. However, the very large cohort size of 52 755 athletes and the creative measures of exercise enabled the authors to define a 'dose–response' curve that provides further circumstantial evidence for the premise that AF risk is increased in the very fittest athletes and in those who perform exercise over many years. Andersen *et al.* investigated the primary endpoint of any arrhythmia, which was a composite of brady- and tachyarrhythmias, and determined that those completing the race within 60% of the winner's time were 1.3 times more likely to be diagnosed with an arrhythmia than those who took more than twice the time to complete the race. Similarly, those who had completed the race ≥5 times had a 1.3-fold increase in arrhythmic risk as compared with those who completed the race only once. The primary endpoint was predominantly driven by AF, with a similar trend seen in bradyarrhythmias (though fewer events, making definitive conclusions difficult). There was no apparent association between exercise measures and supraventricular arrhythmias other than AF/atrial flutter, and there were too few ventricular arrhythmic events to draw conclusions.

One of the biggest limitations when trying to interpret the data of Andersen *et al.* is trying to work out a reference point against which to interpret the described prevalence of arrhythmias. The lowest prevalence of arrhythmias was observed in the slowest athletes who had raced least; but what is the critical 'cut-off' concerning the amount of exercise that leads to an elevated risk for developing AF? We are frequently asked: 'How many hours of exercise and at what

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intensity before I am at risk of AF?', but there are numerous complexities which make it difficult to give prescriptive guidelines. First, as summarized in *Figure 1*, arrhythmias such as AF are the clinical expression of an interplay between host, environmental, and disease-specific factors. Host factors include age, gender, other genetic factors (from single-gene mutations to multiple nucleotide polymorphisms), obesity, alcohol consumption, sleep apnoea, and others.[15] Disease-related factors include atrial stretch, autonomic balance, and systemic and local inflammation, while environmental factors include dietary factors, concurrent illnesses, and exercise.[15] It is extremely difficult to define the magnitude of the risk attributable to exercise in isolation. In particular, the influence of gender is an important case in point. A massive limitation of all exercise studies, including that of Andersen *et al.*, is the lack of data pertaining to females. There is currently no evidence that sports' training constitutes a risk for AF in females, but this is largely due to the gross underrepresentation of females in sports cardiology research.

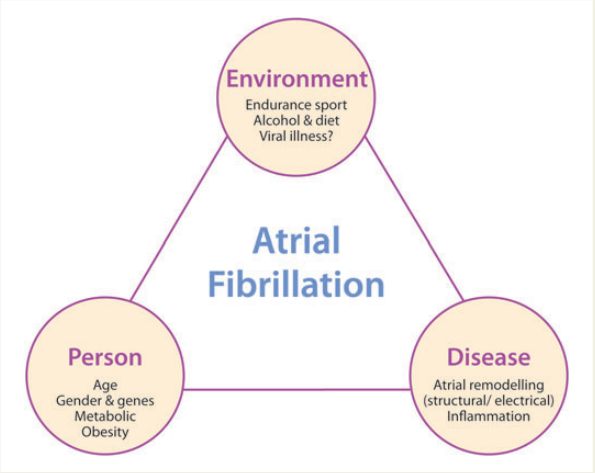

Figure 1 Interplay between environment, person, and disease in the clinical expression of atrial fibrillation.

The second issue in trying to define clinical recommendations on the perfect amount of exercise to minimize the risk of arrhythmias relates to the difficulties in comparing measures of exercise dose across studies. Various questionnaires have been developed to assess the duration, frequency, and intensity of physical activity, but they remain fairly coarse estimates for defining exercise exposure subject to considerable bias.[16] For example, the subjective assessment of exercise intensity is inversely associated with a person's fitness, such that jogging, for example, will be rated as 3/10 intensity by someone of excellent fitness, but as 7/10 by someone with poor fitness.[17] A similar effect can be seen when comparing literature across various disciplines; what is seen as vigorous exertion in cardiovascular epidemiology studies would not

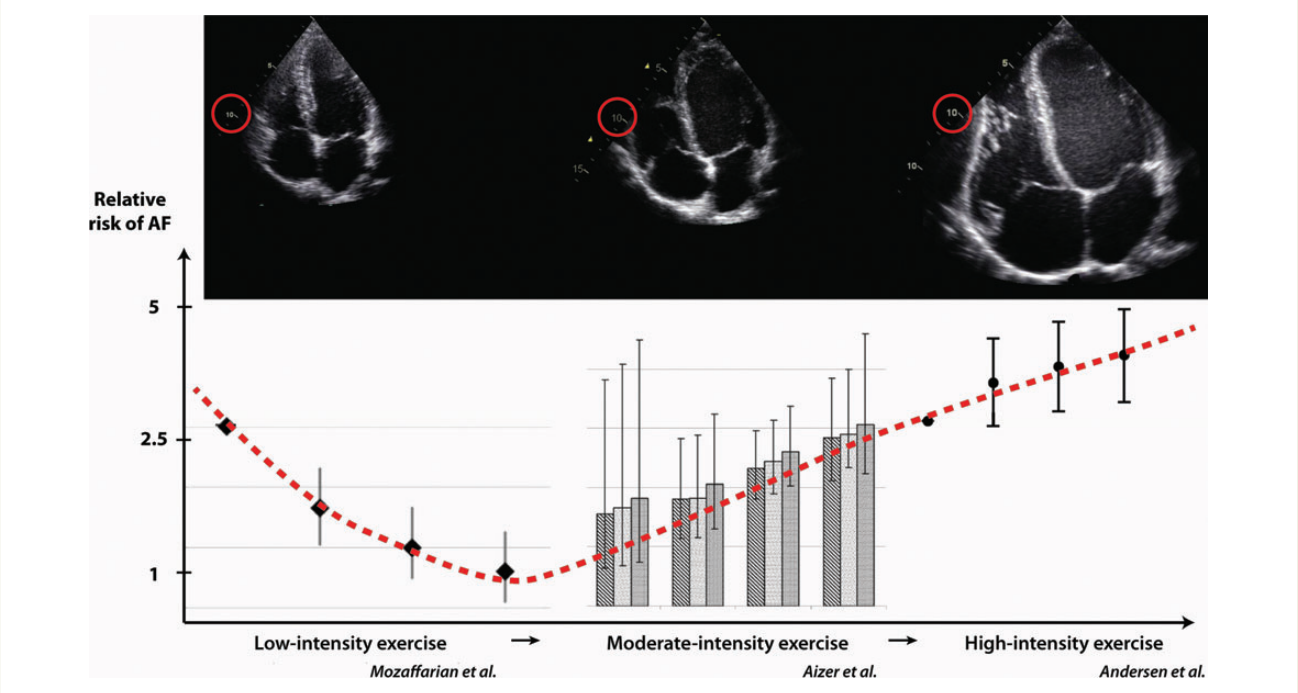

Figure 2 U-shaped relationship between the exercise dose and the relative risk of developing atrial fibrillation (AF). Composite data from three separate trials along the *x*-axis demonstrating an association between reducing prevalence of AF with increasing exercise of low intensity but then an increasing risk of AF with moderate and intense exercise. The echocardiogram examples above demonstrate the progressive cardiac remodelling from a typical sedentary subject (left), a leasure-time athlete (middle), and a professional cyclist (right). The 10 cm marker on the echocardiogram is highlighted with a red circle and the images have been scaled relative to this. The inference is that as exercise dose increases, the heart gets bigger and the risk of AF increases. Whether or not there is a causal relationship between cardiac enlargement and arrhythmias is still to be determined.

even be considered warm up tempo in sports science parlance.[18] The term 'high intensity exercise' can be used to describe walking up a flight of stairs in some studies of AF[18] or, in the case of the study of Andersen *et al*.,[12] can be applied to 90 km of cross-country ski racing. With this in mind, we have tried to construct a 'guestimate' of relative exercise doses in three landmark studies investigating the interaction between exercise and AF incidence. Our best attempt at trying to integrate data across very disparate studies is presented in *Figure 2*. The risk of AF decreases as one engages in regular physical activity of mild to moderate exertion, as evidenced by the study of elderly subjects by Mozaffarian *et al*.[19] However, as reported by Aizer *et al*., when the level of exertion is equivalent to jogging, then a greater prevalence of AF is appreciable in those jogging daily as compared with those jogging 1–2 times/week.[20] A reasonable 'guestimate' when considering the level of physical conditioning required to compete in the Vasaloppet ski race would suggest that Andersen *et al*. complete the sporting spectrum by describing people mostly of moderate to extremely high physical conditioning. Thus, some picture of the exercise dose–response curve emerges, with a U-shaped pattern suggesting that regular mild to moderate exercise may provide a degree of protection from AF while more sustained vigorous exertion represents a risk factor. This is supported by a number of case–control studies which have demonstrated a consistent association between endurance exercise and AF/atrial flutter.[6,21–27] With considerable caveats noted, these studies provide us with some idea to guide our answer regarding the dose of exercise required to promote AF. Perhaps they also provide a clinical clue that we should be advising our athletes with AF to reduce their training intensity and volumes, but certainly not to cease exercise practice all together. The wisdom of such advice will really only be known after well-designed studies specifically address the efficacy of such interventions.

Whilst the study of Andersen *et al*. helps to expand our understanding of the epidemiology of exercise-induced arrhythmias, it does not provide any insights into underlying mechanisms. However, recent studies in animals and humans support the premise that exercise may serve as a trigger, a modulator, and contribute to the underlying substrate for the promotion of arrhythmias. A collaboration between the Barcelona group of Lluis Mont and the Montreal group of Stanley Nattel has demonstrated that a model of endurance training in rats (the 'marathon rat') can be used to demonstrate increased inflammation and fibrosis, and enhanced vagal responsiveness affecting the atria and right ventricle (curiously sparing the left ventricle) which predisposes the animals to both AF and right ventricular arrhythmias.[28,29] This resembles some of the observations in human athletes. Heidbuchel and La Gerche observed that endurance exercise can promote remodelling and arrhythmias which seems to favour the right ventricle disproportionately,[8,9] whereas Luthi *et al*.,[30] amongst others, have demonstrated biatrial remodelling. The other intrigue to which these studies are drawn is whether the remodelling associated with exercise training (the so-called 'athlete's heart') is an entirely physiological process. As detailed in *Figure 2*, increasing exercise training is associated with cardiac remodelling which can be profound. It remains to be determined whether those athletes with the biggest hearts are at greatest risk of arrhythmias.

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