Accepted: 5 December 2016

DOI: 10.1111/sms.12830

CASE SERIES AND REVIEW ARTICLE

WILEY

Excess of exercise increases the risk of atrial fibrillation

A. Müssigbrodt[1,†] | A. Weber[1,†] | J. Mandrola[2] | Y. van Belle[3] | S. Richter[1] | M. Döring[1] | A. Arya[1] | P. Sommer[1] | A. Bollmann[1] | G. Hindricks[1]

[1]Department of Electrophysiology, University of Leipzig, Heart Centre, Leipzig, Germany

[2]Baptist Health Louisville, Louisville, KY, USA

[3]Centre Hospitalier Universitaire, Liège, Belgium

Correspondence
Andreas Müssigbrodt, Department of Electrophysiology, University of Leipzig, Heart Center, Leipzig, Germany.
Email: andreas.muessigbrodt@gmail.com

An interesting and still not well-understood example for old medical wisdom "Sola dosis facit venenum" is the increased prevalence of atrial fibrillation (AF) in athletes. Numerous studies have shown a fourfold to eightfold increased risk of AF in athletes compared to the normal population. Analysis of the existing data suggests a dose-dependent effect of exercise. Moderate exercise seems to have a protective effect and decreases the risk of AF, whereas excessive exercise seems to increase the risk of AF. The described cases illustrate clinical manifestations within the spectrum of AF in elderly athletes, that is, exercise-induced AF, vagal AF, chronic AF, and atrial flutter. As the arrhythmia worsened quality of life and exercise capacity in all patients, recovery of sinus rhythm was desired in all described cases. As the atrial disease was advanced on different levels, different treatment regimes were applied. Lifestyle modification and temporary anti-arrhythmic drug therapy could stabilize sinus rhythm in one patient, whereas others needed radiofrequency ablation to achieve a stable sinus rhythm. The patient with the most advanced atrial disease necessitated anti-arrhythmic drug therapy and another left atrial ablation. All described patients remained in sinus rhythm during the long-term follow-up.

KEYWORDS
athlete, atrial fibrillation, excess, exercise, inflammation, sports

1 | INTRODUCTION

Regular physical activity is beneficial for health in human beings. It reduces both morbidity and mortality and can contribute to physical and mental well-being. A lack of physical activity associates with an increased risk of health problems.[1,2]

However, physical activity and the benefits for health seem not to be linearly correlated. In contrast, there is a growing body of epidemiological and experimental evidence that not only a lack of activity might be harmful, but also excessive exercise might lead to sequelae with negative impact on health and well-being.

An interesting and still not well-understood example for old medical wisdom "Sola dosis facit venenum" is the increased prevalence of atrial fibrillation (AF) in athletes.

Provocatively spoken, what if the common theme in AF pathogenesis is excess? In obese patients, the excess is too many calories; in patients with sleep apnea, the excess is atrial stretch; and in athletes, the excess component is too much exercise.

2 | MATERIAL AND METHODS

We present four selected cases of AF in athletes and discuss potential pathophysiological mechanisms and options for treatment and prevention. All patients gave their consent for the publication of the clinical information. The chosen

[†]These authors contributed equally and share first authorship.

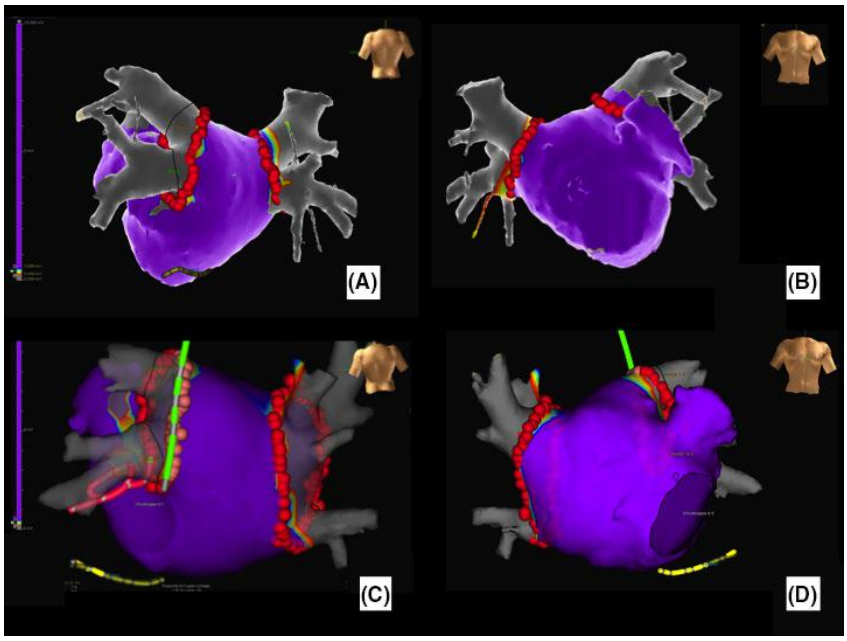

FIGURE 1 Electro-anatomic maps of the left atria (LA) of patients 2 and 3. Purple color signifies voltage above 0.5 mV, which is presumed as normal. Red dots around the pulmonary veins symbolize radiofrequency ablation lesions. The yellow catheter is a decapolar catheter within the coronary sinus. The green catheter is a temperature probe in the esophagus. (A) Posterior view of the electro-anatomic map of the LA of patient 2. (B) Anterior view of the electro-anatomic map of the LA of patient 2. (C) Posterior view of the LA of patient 3. (D) Anterior view of the LA of patient 3

references have been selected upon relevance from medical database research.

3 | RESULTS

3.1 | Case presentation

3.1.1 | Case 1

A 48-year-old male cyclist developed an erratic tachycardiac heart rhythm while on a training ride. An ECG confirmed AF with a well-controlled rate. Examination, thyroid testing, and echocardiography showed a structurally normal heart. His left atrial diameter was 39 mm. He had no other medical problems and no risks for ischemic heart disease.

His training history included more than 20 years of high-level competitive running, triathlon, and cycling. At the time of the AF diagnosis, he was training for the national championship competition in cycling. He estimated his lifetime training volume as 15 000 hours.

Initial treatment with flecainide was started and resulted in cardioversion within 24 hours. The drug was continued for a month. He also stopped training for that month. After discontinuing the drug and resuming training, frequent atrial ectopy ensued, with up to 5000 premature atrial complexes per day. Two other transient self-terminating episodes of AF occurred later in that year.

This amateur athlete, who was also a healthcare professional, was able to reduce training volume, improve his sleep, and dietary patterns, and the AF and ectopy resolved without ablation. A year later, he resumed training, albeit at lower levels, without any symptoms of arrhythmia.

3.1.2 | Case 2

A 62-year-old man complained of irregular palpitations that occurred 2-3 hours after cycling training sessions. A monitor confirmed AF. He had no other medical history and did not smoke. His examination revealed normal findings, including a height 175 cm and weight of 60 kg.

He had a 17-year history of regular endurance exercise. He reported a lifetime training volume of 200 000 km and 8000 hours; he completed 60 long-distance races of up to 250 km.

Coronary arteriography was normal. Echocardiography revealed a left ventricular ejection fraction (LVEF) of 55%; left atrial (LA) diameter measured in the parasternal long axis was 28 mm. Initial treatment with flecainide caused fatigue and vertigo, and the drug did not reduce AF burden. He requested interventional treatment.

We performed pulmonary vein isolation with RF energy. During the intervention, we could observe a fast tachycardia from the right superior pulmonary vein. After pulmonary vein isolation, we could not induce any arrhythmia. A left atrial voltage map showed normal voltage, so no further lesions were performed (Figure 1A and B). He remained free of any arrhythmia at 6-month follow-up and has returned to endurance sport activity.

3.1.3 | Case 3

A 54-year-old man complained of progressive dyspnea and palpitations of 14-month duration. These symptoms correlated with the onset of AF, which, initially, was paroxysmal, but turned persistent after 2 months. Examination revealed an irregular rhythm but was otherwise normal (height 176 cm, weight 76 kg).

He had participated in endurance sport for the previous 32 years. He estimated his training volume in various sports (mostly running and cycling) to be 20 000 hours. He ran 17 marathons.

Initially, he had cardioversion, AF but recurred 1 week later. Amiodarone was started, and soon thereafter, he developed sustained left atrial flutter. A second cardioversion was performed; again, the arrhythmia recurred. Echocardiography done after this recurrence revealed a severely reduced LVEF of 25% with normal left ventricular end-diastolic diameter (48 mm) and dilated LA (46 mm). Coronary angiography was normal. After an ICD was recommended, he presented to our institution for a second opinion.

We felt rhythm control was indicated due to the likelihood of tachycardia-mediated cardiomyopathy. He underwent PV isolation with RF energy. LA voltage mapping showed normal voltage (Figure 1C and D).

At follow-up 2 years after ablation, he remained in sinus rhythm. His symptoms resolved, and a repeat echocardiogram showed complete recovery of LV function. He has now reduced his sports activities but still participates in running events, eg, half-marathons.

3.1.4 | Case 4

A 70-year-old woman reported reduced exercise capacity and palpitations for 5 years. She noted little difficulty with activities of daily living but had significant dyspnea during sports activities, such as running, cycling, and cross-country skiing.

She was first diagnosed with persistent AF 2 years ago, but, given the abrupt onset of symptoms, she likely had it for the entire 5 years. Her only other medical problem was degenerative arthritis, which led to a total hip replacement.

She reported a 50-year history of endurance sports activities. In her twenties, she participated in national and international cross-country racing, including the 1968 Winter Olympic games in Grenoble. After retirement from Olympic competition, she continued to train and race in running, cycling, triathlon, and skiing events. She completed more than 100 triathlons, even after hip replacement. A conservative estimate of her lifetime training volume was 30 000 hours.

Echocardiography revealed severe LA dilation (52 mm) and a normal LVEF (60%). She had had multiple failed cardioversions, with and without flecainide. After the shock, sinus rhythm would last only days, but during those days, she felt better.

We discussed all treatment options with the patient, including medical treatment for rate control and AF ablation to achieve sinus rhythm. Together with the patient, we decided for AF ablation because she had symptomatic drug refractory AF. We first performed PV isolation with RF energy, and then proceeded to LA voltage mapping. This map revealed widespread low-voltage areas in the septal and posterior segments of the LA (Figure 2A and B). Pulmonary veins were

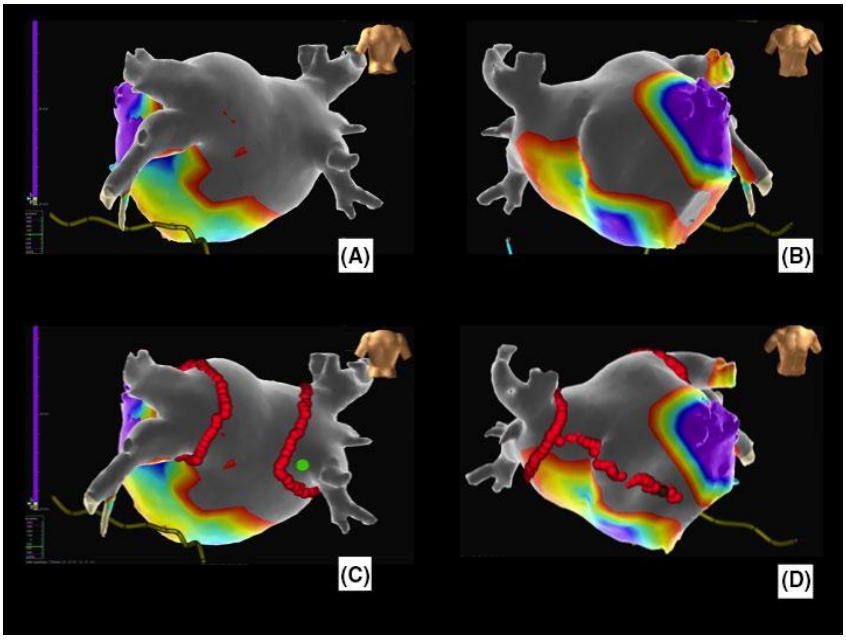

FIGURE 2 Electro-anatomic maps of the left atria (LA) of patient 4 at the first intervention. Purple color signifies normal voltage above 0.5 mV, whereas gray color symbolizes scar. Red, green, and blue colors symbolize reduced voltage as a sign of diseased myocardium. Red dots around the pulmonary veins symbolize ablation lesions. The yellow catheter is a decapolar catheter within the coronary sinus. (A) Posterior view of the electro-anatomic map of the LA of patient 4 before the intervention shows extensive posterior scar. (B) Anterior view of the electro-anatomic map of the LA of patient 4 shows septal scar. (C) Posterior view of the LA of patient 4 with circular ablation lesions around the pulmonary veins. (D) Anterior view of the LA of patient 4 with septal ablation line from the tricuspid annulus to the right superior pulmonary vein

isolated by antral radiofrequency ablation. After pulmonary vein isolation, we could observe sporadic isolated electrical activity within the left superior and right superior pulmonary veins. Atrial burst stimulation induced left atrial flutter, which was terminated with linear septal ablation from the right superior pulmonary vein to the anterior mitral annulus (Figure 2C and D). We then induced cavo-tricuspid isthmus-dependent (typical) flutter, which was also ablated. No further ablation was performed because of non-inducibility of any atrial tachycardia.

The patient had early recurrence of AF, which was successfully treated with a 3-month course of flecainide. At 6-month follow-up, left atrial flutter recurred and was cardioverted. We then changed drug therapy to amiodarone, but, again, left atrial flutter recurred. At the second left atrial procedure, we re-isolated the pulmonary veins, and performed a posterior box lesion and septal ablation with complete encircling of all scar areas.

She has remained in sinus rhythm at 2-year follow-up and pursues regular sports activities.

4 | DISCUSSION

4.1 | Case presentation

The above-described cases illustrate clinical manifestations within the spectrum of AF in elderly athletes. Case 1 describes an amateur endurance athlete with exercise-induced AF that responded well to lifestyle modification, case 2 shows an amateur endurance athlete with vagally induced paroxysmal AF, case 3 gives an example of an amateur endurance athlete with chronic AF and—as a rare presentation—tachycardia-associated cardiomyopathy, and finally, case 4 gives an example of a former professional athlete with long-standing chronic AF and manifest scar in a severely affected left atrium. Case 4 also shows that AF may also affect female athletes. All patients have a long-time history of intensive endurance sports as the only known modifiable risk factor for AF. Other typical risk factors such as obesity or arterial hypertension were not found. A possible dose-effect ratio is suggested by the fact that athlete 4 as the most severely affected athlete has the longest history of intensive endurance sports. Rhythm control was successfully achieved with lifestyle modifications in one patient. As conservative treatment was not successful, interventional treatment was performed in the other patients.

4.2 | Epidemiology

Numerous studies have shown a fourfold to eightfold increased risk of AF in athletes compared to the normal population. AF was found in up to 12% of athletes.[3-6] The dilemma is that some publications suggest that exercise is associated with an INCREASED risk of AF,[3-5] whereas others describe the exact contrary: Exercise is associated with a DECREASED risk of AF.[7,8] NO IMPACT of regular physical activity on the risk of AF was observed in a meta-analysis with more than 95 000 subjects.[9]

So what's true? As many of the observational studies examined, a limited number of mostly male athletes with retrospective analysis, selection bias, and other statistical pitfalls are possible. Taken together, however, thorough analysis of the existing data suggests a dose-dependent effect of exercise. Moderate exercise seems to have a protective effect and decreases the risk of AF, whereas excessive exercise seems to increase the risk of AF. Therefore, a U-shaped relation between the dose of exercise and the risk of AF has been proposed.[10] The left side of the curve, no exercise, and the right side of the curve, high levels of exercise, increase the risk of AF, whereas moderate doses of exercise are protective.[10]

The above-described cases are consistent with this dose-dependent relationship: Decades of intensive endurance sports seem to increase the risk for AF.

But where are the lower and upper thresholds where sedentary lifestyle and intensive sports begin to detract from the benefits for health and longevity associated with moderate exercise? Calvo et al.[10] found an increased risk of AF with an accumulated lifetime endurance sport activity ≥2000 hours compared with sedentary controls (OR 3.88 [1.55-9.73]). In contrast, a history of ≤2000 hours of high-intensity training protected against AF when compared with sedentary controls (OR 0.38 [0.12-0.98]).

4.3 | Pathophysiology of arrhythmogenesis

In non-athletic patients, AF develops by a complex interplay between focal triggers, arrhythmogenic substrate created by anisotropy and fibrosis, autonomic imbalance, and genetics.[11] If these factors create a fibrillatory milieu in non-athletic patients, we propose similar mechanisms could induce AF in athletes.

4.4 | Triggers

Patterson et al.[12] studied the interplay between autonomic nerve activity and PV myocardium in a canine model. Using subthreshold high-frequency stimulation of autonomic ganglia, they demonstrated rapid firing within PV sleeves but not in left or right atrial myocardium. Vagal-mediated PV firing required parasympathetic and sympathetic neurotransmissions, intact Ca-signaling, and Na-Ca exchange. They proposed a unifying cause of triggering that applies well to the alternating high-vagal/high-sympathetic milieu of an endurance athlete: PV cells have inherently short action potential (AP) duration. Vagal stimulation further shortens AP

duration; then, sympathetic stimulation enhances Ca-current, which has a net depolarizing effect and may be enough to cause rapid repetitive firing.[12]

Support for this model of arrhythmogenesis comes from Sharifov et al.[13] who induced AF in an animal model with injection of acetylcholine into the sinus node artery and Aschar-Sobbi et al.[14] who noted atropine reduced the duration of AF in exercised animals. In healthy middle-aged men, a low exercise heart rate during a moderate workload, indicative of high-vagal tone, predicted future incident AF.[15]

4.5 | Substrate

Animal models that mimic human disease might help to improve our limited understanding of AF pathogenesis. In a goat model, Wijffels et al.[16] found that increasing periods of pacing-induced AF in a goat led to longer episodes of AF. Although atrial refractory period shortening (electrical remodeling) occurred almost immediately, persistent AF took 2 weeks to occur. This time gap led the authors to speculate that persistent AF required a "second factor," perhaps structural changes in the atria.

Nine years later, findings from Todd et al.[17] bolstered the concept that slower developing second factors promoted stability of AF. In a model of repetitive 4-week periods of maintained AF, they noted AF vulnerability—as measured by duration of AF per duration of burst pacing—increased after 3 months. Crucially, this progression occurred independent of atrial refractoriness.

In an effort to explore factors connecting AF and endurance exercise, Guasch et al.[18] compared rats that underwent an intensive endurance exercise program with sedentary control rats. Rats were trained to run 1 hour per day 5 days per week for 16 weeks, which the authors estimated would simulate a typical human endurance athlete.

Compared with controls, the exercised rats exhibited increased AF vulnerability, enhanced fibrosis, increased vagal outflow, enhanced end-organ sensitivity to vagal stimulation, and down-regulation of inhibitory g-proteins. Detraining over 4 weeks reversed parasympathetic tone and AF vulnerability, but atrial fibrosis and dilation did not completely resolve. Together with the suppressive effect of atropine on AF in exercise-trained rats, these results emphasized increased vagal tone as an important component of AF promotion with exercise. The authors proposed that AF occurs in endurance athletes because of atrial dilation, fibrosis, and autonomic imbalance.[18]

Support for the Guasch model of AF in athletes comes from a human study of 60 non-elite runners during and after a 10-mile running race in Bern, Switzerland. Wilhelm et al. found that p-wave duration, LA volume, vagal activity, and frequency of premature atrial beats correlated with lifetime training hours.[19,20]

Atrial tissue fibrosis identified by delayed enhancement magnetic resonance imaging is considered as an important factor in the arrhythmogenic substrate in AF.[21] Systematic research is needed to confirm this finding in athletic patients.

4.6 | Inflammation

An extensive evidence base suggests a relationship between inflammation and AF.[22] The challenge is knowing whether AF is a consequence of or cause of inflammation. Using a novel computer algorithm, Swanson hypothesized in 2006 that excessive endurance exercise or overtraining could lead to chronic systemic inflammation that—in turn—might increase the risk of AF.[23]

While regular exercise reduces inflammatory markers, long-term intense exercise may lead to chronic inflammatory states, perhaps via an over-training syndrome mediated by excess cytokines.[24] Vigorous exercise increases inflammatory factors such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha).[25-27] These factors are released by atrial stretch caused by elevated atrial pressure as occurs during vigorous exercise.[28]

In an animal model, Aschar-Sobbi et al. exposed mice to intense endurance exercise and compared them with sedentary controls. Vigorous exercise increased the susceptibility to induction of AF in mice and was associated with atrial macrophage infiltration and fibrosis. Exercise-induced atrial remodeling was prevented by treatment with the TNF-alpha inhibitor (etanercept) and was not seen in mice lacking TNF-alpha gene. Elevated cardiac TNF-alpha therefore seems to induce atrial fibrosis, myocardial hypertrophy, and susceptibility to AF.[14,29]

Similarly, Ozcan et al. documented spontaneous AF in mice with deletion of liver kinase B1. Liver kinase B1 (LKB1) is an important enzyme in cellular metabolism. Depletion of LKB1 leads to energetically unfavorable conditions and thereby facilitates inflammatory and neoplastic processes. Cardiac-specific LKB1 knockout (KO) mice show spontaneous development of AF and may therefore provide insight into electro-anatomical changes which might take place in human atria. In this animal model of inflammatory myocarditis, bi-atrial dilation was associated with apoptosis, necrosis, fibrosis, and loss of muscle mass with deformation of the intracellular myofibrillar structure, disorganization of extracellular space, and disruption of gap junctions. These processes began in SR and gradually worsened throughout paroxysmal AF and then chronic AF. By heterogeneous dispersion of atrial effective refractory period and conduction velocity, the atrial substrate became vulnerable to triggers and thereby prone to AF. Thus, inflammatory processes in the atrial myocardium may likely play an important role in the pathogenesis of atrial fibrillation.[30]

4.7 | Arterial hypertension

Arterial hypertension is a well-established risk factor for AF in non-athletes.[31] Acute arterial hypertension causes myocardial stretch with decreased action potential duration and heterogeneously decreased effective refractory period.[32] Chronic arterial hypertension leads to cardiac remodeling with impaired diastolic function and increased risk of AF.[31] Therefore, exercise-induced arterial hypertension can play a role in the pathogenesis of AF in athletes. Exercise-induced arterial hypertension was associated with greater myocardial mass, which consequently could lead to impaired diastolic function and increased risk for AF.[33,34]

Angiotensin II is a profibrotic hormone that could be involved in the cardiac remodeling as a result of endurance exercise and arterial hypertension. The inhibition of the renin-angiotensin system by Losartan was able to prevent exercise-associated myocardial fibrosis in rats [35] and to reduce the AF burden in non-athletic patients.[36]

4.8 | Genetic risk factors

As only a minority of athletes with a history of vigorous endurance sports develops AF, the question remains open, which factors finally determine the arrhythmogenic risk of the athletes' atria. Genomewide association studies have identified common variants in nine genomic regions associated with AF.[37] Even though genetic predisposition is one probable risk-modifying factor, to our knowledge, no typical genetic mutation has been identified in athletes with AF so far.

4.9 | Psychological stress

Another factor that may contribute to the pathogenesis of AF in endurance athletes includes psychological stress.[38]

There is a lack of systematic science regarding stress and AF in athletes although patients regularly report increased perception of palpitations in stressful situations. Researchers from the University of Kansas studied whether stress reduction by regular yoga practice would affect the AF burden. During the follow-up, patients in the yoga group compared with standard care group reported fewer symptomatic and non-symptomatic AF episodes, lower scores on anxiety measures, and higher scores on vitality and general health. Blood pressure decreased in the yoga group too.[39] Wahlstrom and colleagues from Stockholm analyzed the effect of yoga in patients with symptomatic AF. They found a decreased heart rate and blood pressure, and improvements in quality of life. These findings suggest that stress and anxiety may have a significant role in AF.[40] It still needs to be elucidated whether psychological stress plays a role in the pathogenesis of AF in athletes.

4.10 | Other factors

Tall stature has been identified as risk factors for AF in athletes. Tall stature is associated with increased LA size, which on its own also is a risk factor for AF.[41,42]

Male gender has also been identified as a risk factor for AF in athletes.[19,20] At a comparable amount of exercise training and performance, male athletes showed a more pronounced atrial remodeling and an altered diastolic function. An increased sympathetic tone and a higher blood pressure at rest and during exercise in males compared to females might cause an arrhythmia-susceptible left atrial substrate.[19,20] However, recent analysis suggests that vigorous endurance exercise might cause AF also among athletic women.[43]

4.11 | Treatment options

Studies that compare different treatment options of AF in athletes, that is, exercise abstinence vs anti-arrhythmic drug therapy vs catheter ablation, are lacking. Therefore, treatment recommendations are mainly based on pathophysiological considerations, small observational studies in athletes, and individual experience. Studies comparing different treatment options in non-athletes can also be taken into consideration.[44]

Assuming that the hypothesis—excessive exercise leads to inflammation and eventually fibrosis and changes in the autonomous nervous system—is true, sports-associated changes should be reversible, at least at an early stage of the disease process. Atrial fibrosis at a later stage of the sports-associated AF might not be reversed by abstinence from intensive exercise.

Clinical evaluation should include routine examination (inclusive ECG, echocardiography, laboratory testing) to diagnose or exclude treatable risk factors for AF, for example, arterial hypertension, valvular dysfunction, or hyperthyreosis.

Anticoagulation should correspond to current guideline recommendations. We suggest a gradual treatment approach. In order to facilitate this approach, we arbitrarily divided athletes with sports-associated AF into three groups that might represent a gradual increase in severity of atrial disease.

1. Athletes with evidence of increased number of symptomatic or asymptomatic atrial (and ventricular) premature contractions and athletes with recent-onset PAF or CAF (<12 months)
2. Athletes with evidence of long-standing PAF or CAF (>12 months)
3. Athletes with atypical, left atrial flutter

For athletes from group 1, we would recommend abstinence from intensive exercise for 3-6 months, similarly to the recommendations for the treatment of acute myocarditis.[45] To date, no systematic research on detraining as potential treatment for

AF in athletes has been published yet. Adjuvant anti-arrhythmic drug therapy, as flecainide, can be considered. Additional risk factors as arterial hypertension, overweight, and alcohol consumption should be treated if applicable.

For athletic patients at a later stage of the disease, groups 2 and 3—additional to the above-mentioned recommendations for athletes from group 1—ablation of AF can be considered.[46] From our point of view, pulmonary vein isolation (PVI) should be done in all AF ablation procedures; however, additional ablation beyond PVI may sometimes be necessary. PVI leads to freedom from AF in more than 80% of athletes during a follow-up of 3 years,[47] but may be less effective with closer and longer follow-up. It was as effective in AF associated with endurance sport practice as in other etiologies of AF.[48] Nevertheless, multiple procedures might be necessary to achieve long-term freedom from AF, that is, 46 procedures in 20 athletes with symptomatic AF (2.3±0.4 per patient) in one Italian study.[49] In older athletes with asymptomatic, long-standing AF frequency rate control might be a reasonable option.[46,50] Both patient and physician should decide together on the ultimate treatment strategy after discussion of all treatment options.[50]

5 | PERSPECTIVE

In years past, most experts considered atrial fibrillation that occurred outside specific circumstances, such as thyroid storm or post-cardiac surgery, to be a separate heart rhythm disease.

We now have come again to realize that AF occurs because of many "second factors." It seems to occur rather as a symptom of other disorders than as a stand-alone disease.[51]

In patients with AF and valvular heart disease, we understand the valve disease to be the underlying cause; in patients with obesity, we now see the excess adiposity as the primary problem, and in long-term endurance athletes with AF, it is increasingly clear that excess exercise over decades contributes to AF. In each of these cases, prevention and treatment of AF may have to include the removal of what causes the triggers and substrate changes.

For athletes with AF, a temporary break from intensive exercise followed by subsequent exercise reduction seems to be advisable.

CONFLICT OF INTEREST

None.

REFERENCES

1. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet*. 1953;265:1111–1120; concl.
2. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25(Suppl 3):1–72.
3. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis *Europace*. 2009;11:1156–1159.
4. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ*. 1998;316:1784–1785.
5. Müssigbrodt A, Hindricks G, Bollmann A. Atrial fibrillation in endurance athletes. *Ger J Sports Med*. 2010;61:190–200.
6. Myrstad M, Lochen ML, Graff-Iversen S, et al. Increased risk of atrial fibrillation among elderly Norwegian men with a history of long-term endurance sport practice. *Scand J Med Sci Sports*. 2014;24:e238–e244.
7. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation*. 2008;118:800–807.
8. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol*. 2015;66:985–996.
9. Ofman P, Khawaja O, Rahilly-Tierney CR, et al. Regular physical activity and risk of atrial fibrillation: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol*. 2013;6:252–256.
10. Calvo N, Ramos P, Montserrat S, et al. Emerging risk factors and the dose-response relationship between physical activity and lone atrial fibrillation: a prospective case-control study. *Europace*. 2016;18:57–63.
11. Bollmann A, Husser D. About arrhythmogenic triggers and substrates in aging atria: partners in crime for atrial fibrillation development? *J Cardiovasc Electrophysiol*. 2007;18:532–533.
12. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. *Heart Rhythm*. 2005;2:624–631.
13. Sharifov OF, Fedorov VV, Beloshapko GG, Glukhov AV, Yushmanova AV, Rosenshtraukh LV. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. *J Am Coll Cardiol*. 2004;43:483–490.
14. Aschar-Sobbi R, Izaddoustdar F, Korogyi AS, et al. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFalpha. *Nat Commun*. 2015;6:6018.
15. Grundvold I, Skretteberg PT, Liestol K, et al. Low heart rates predict incident atrial fibrillation in healthy middle-aged men. *Circ Arrhythm Electrophysiol*. 2013;6:726–731.
16. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.
17. Todd DM, Fynn SP, Walden AP, Hobbs WJ, Arya S, Garratt CJ. Repetitive 4-week periods of atrial electrical remodeling promote stability of atrial fibrillation: time course of a second factor involved in the self-perpetuation of atrial fibrillation. *Circulation*. 2004;109:1434–1439.
18. Guasch E, Benito B, Qi X, et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol*. 2013;62:68–77.
19. 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*. 2011a;108:580–585.
20. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. *Am J Cardiol*. 2011b;108:1489–1495.
21. Gal P, Marrouche NF. Magnetic resonance imaging of atrial fibrosis: redefining atrial fibrillation to a syndrome. *Eur Heart J*. 2015; doi: 10.1093/eurheartj/ehv514. [Epub ahead of print].
22. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J*. 2015;79:495–502.
23. Swanson DR. Atrial fibrillation in athletes: implicit literature-based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism. *Med Hypotheses*. 2006;66:1085–1092.

24. Smith LL. Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress? *Med Sci Sports Exerc*. 2000;32:317–331.
25. Bernecker C, Scherr J, Schinner S, Braun S, Scherbaum WA, Halle M. Evidence for an exercise induced increase of TNF-alpha and IL-6 in marathon runners. *Scand J Med Sci Sports*. 2013;23:207–214.
26. Stumpf C, Simon M, Wilhelm M, et al. Left atrial remodeling, early repolarization pattern, and inflammatory cytokines in professional soccer players. *J Cardiol*. 2016;68:64–70.
27. Weight LM, Alexander D, Jacobs P. Strenuous exercise: analogous to the acute-phase response? *Clin Sci (Lond)*. 1991;81:677–683.
28. Sun M, Chen M, Dawood F, et al. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. *Circulation*. 2007;115:1398–1407.
29. Saba S, Janczewski AM, Baker LC, et al. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-{alpha}. *Am J Physiol Heart Circ Physiol*. 2005;289:H1456–H1467.
30. Ozcan C, Battaglia E, Young R, Suzuki G. LKB1 knockout mouse develops spontaneous atrial fibrillation and provides mechanistic insights into human disease process. *J Am Heart Assoc*. 2015;4:e001733.
31. Seccia TM, Caroccia B, Muiesan ML, Rossi GP. Atrial fibrillation and arterial hypertension: a common duet with dangerous consequences where the renin angiotensin-aldosterone system plays an important role. *Int J Cardiol*. 2016;206:71–76.
32. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation*. 1997;96:1686–1695.
33. Leischik R, Spelsberg N, Niggemann H, Dworrak B, Tiroch K. Exercise-induced arterial hypertension - an independent factor for hypertrophy and a ticking clock for cardiac fatigue or atrial fibrillation in athletes? *F1000Res*. 2014;3:105.
34. Trachsel LD, Carlen F, Brugger N, Seiler C, Wilhelm M. Masked hypertension and cardiac remodeling in middle-aged endurance athletes. *J Hypertens*. 2015;33:1276–1283.
35. Gay-Jordi G, Guash E, Benito B, et al. Losartan prevents heart fibrosis induced by long-term intensive exercise in an animal model. *PLoS One*. 2013;8:e55427.
36. Takii E, Inage T, Yoshida T, et al. Beneficial effects of losartan for prevention of paroxysmal atrial fibrillation in patients with sick sinus syndrome: analysis with memory function of pacemaker. *Heart Vessels*. 2016;31:402–407.
37. Tsai CT, Hsieh CS, Chang SN, et al. Next-generation sequencing of nine atrial fibrillation candidate genes identified novel de novo mutations in patients with extreme trait of atrial fibrillation. *J Med Genet*. 2015;52:28–36.
38. O'Donnell K, Brydon L, Wright CE, Steptoe A. Self-esteem levels and cardiovascular and inflammatory responses to acute stress. *Brain Behav Immun*. 2008;22:1241–1247.
39. Lakkireddy D, Atkins D, Pillarisetti J, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: the YOGA My Heart Study. *J Am Coll Cardiol*. 2013;61:1177–1182.
40. Wahlstrom M, Rydell-Karlsson M, Medin J, Frykman V. Effects of yoga in patients with paroxysmal atrial fibrillation - a randomized controlled study. *Eur J Cardiovasc Nurs*. 2016; doi:10.1177/1474515116637734.
41. Grimsmo J, Grundvold I, Maehlum S, Arnesen H. High prevalence of atrial fibrillation in long-term endurance cross-country skiers: echocardiographic findings and possible predictors - a 28-30 years follow-up study. *Eur J Cardiovasc Prev Rehabil*. 2010;17:100–105.
42. Van Buuren F, Mellwig KP, Faber L, et al. The occurrence of atrial fibrillation in former top-level handball players above the age of 50. *Acta Cardiol*. 2012;67:213–220.
43. Myrstad M, Aaronaes M, Graff-Iversen S, Nystad W, Ranhoff AH. Does endurance exercise cause atrial fibrillation in women? *Int J Cardiol*. 2015;184:431–432.
44. Nielsen JC, Johannessen A, Raatikainen P, et al. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart*. 2016; doi: 10.1136/heartjnl-2016-309781.
45. Cooper LT. Myocarditis. *N Engl J Med*. 2009;360:1526–1538.
46. Kirchhof P, Benussi S, Kotecha D, et al. Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
47. Koopman P, Nuyens D, Garweg C, et al. Efficacy of radiofrequency catheter ablation in athletes with atrial fibrillation. *Europace*. 2011;13:1386–1393.
48. Calvo N, Mont L, Tamborero D, et al. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. *Europace*. 2010;12:30–36.
49. Furlanello F, Lupo P, Pittalis M, et al. Radiofrequency catheter ablation of atrial fibrillation in athletes referred for disabling symptoms preventing usual training schedule and sport competition. *J Cardiovasc Electrophysiol*. 2008;19:457–462.
50. Lane DA, Aguinaga L, Blomstrom-Lundqvist C, et al. Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace*. 2015;17:1747–1769.
51. Allessie M. The, "second factor": a first step toward diagnosing the substrate of atrial fibrillation? *J Am Coll Cardiol*. 2009;53:1192–1193.

How to cite this article: Müssigbrodt A, Weber A, Mandrola J, et al. Excess of exercise increases the risk of atrial fibrillation. *Scand J Med Sci Sports*. 2017;00:1–8. doi:10.1111/sms.12830.