Title:

Cardiac remodeling in veteran recreational endurance athletes with and without atrial fibrillation

The Birkebeiner II study

"Der große Sport fängt da an, wo er längst aufgehort hat, gesund zu sein"

-Berthold Brecht-

Acknowledgments

First and foremost, I would like to thank all the participants in the Birkebeiner II study for making this study possible. It was an honor to meet you all in person and to hear your unique stories. Thank you for your time and dedication.

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Abbreviations

AF: atrial fibrillation

EICR: exercise-induced cardiac remodeling

LA: left atrium/left atrial

RA: right atrium

LV: left ventricle

RV: right ventricle

$LAVI_{max}$: maximum left atrial volume indexed

$LAVI_{min}$: minimum left atrial volume indexed

LASr: left atrial reservoir strain

LAScd: left atrial conduit strain

LASct: left atrial contractile strain

SD-TPS: standard deviation of time to peak strain

LA MD: left atrial mechanical dispersion

LA/LV: maximum left atrial volume to left ventricular end-diastolic volume

RVFWSL: right ventricular free wall longitudinal strain

RV/LV ratio: right ventricular basal end-diastolic diameter/left ventricular end-diastolic dimension

RV inflow/outflow ratio: right ventricular basal end-diastolic diameter/right ventricular outflow tract diameter

RASr: right atrial reservoir strain

RAScd: right atrial conduit strain

RASct: right atrial contractile strain

ECG: electrocardiogram

AUC: area under the curve

Summary

Background: Data describing structural and functional exercise-induced cardiac remodeling in older veteran endurance athletes are scarce, and there is a need to increase the understanding regarding cardiac remodeling related to prolonged and vigorous endurance exercise. Atrial fibrillation (AF) is the most common cardiac arrhythmia in endurance athletes. Light and moderate exercise decrease the risk of AF, probably mainly by modifying risk factors like hypertension, diabetes mellitus, and obesity. Extensive endurance exercise, however, increases the risk of AF in men, possibly because of exercise-induced structural and functional remodeling of the heart.

Aims: We aimed to describe the cardiac traits of older subjects with and without AF exposed to prolonged endurance exercise with a special focus on atrial remodeling.

In particular, we aimed to investigate:

I. Left atrial structure and function in veteran athletes with AF and assess if left atrial strain by speckle tracking echocardiography is better than volumetric measurements to identify the athletes diagnosed with paroxysmal AF.
II. Structural and functional characteristics of the right heart in relation to prolonged endurance exercise and AF.
III. Left atrial electromechanical remodeling in male veteran athletes with and without AF and investigate the ability of left atrial mechanical dispersion to identify veteran athletes with paroxysmal AF.

Methods: To investigate cardiac structure and function affiliated with exercise-related AF, we invited veteran athletes with and without AF and controls from the general population with and without AF to attend a cross-sectional clinical study with a thorough cardiac evaluation. All invitees had formerly participated in The Birkebeiner Atrial Fibrillation study (2012). To comprise the entire range of activity levels in the population, The Birkebeiner Atrial Fibrillation study (2012) included earlier participants of the annual 54 km Birkebeiner cross-country ski race and earlier participants of a population-based health study. All veteran skiers with a history of AF living within a 2-hour perimeter from the study site (n=134), along

with skiers without AF (n=123) and control groups from the population-based health study in the same area with (n=81) and without AF (n=147) were invited. To increase the size of the non-athletic control group with AF, every male patient of the proper age visiting the AF outpatient clinic at Diakonhjemmet Hospital between May and September 2020 was consecutively invited to participate until reaching the same number of participants as in the athletic AF group. All participants answered a questionnaire and underwent a thorough echocardiographic exam, a resting electrocardiogram (ECG), a 24-hour Holter examination, and blood sampling. The AF diagnosis was verified according to guidelines. In Articles I and II, participants with heart failure (ejection fraction <35%), clinically significant heart valve disease, previous open-heart surgery, supraventricular tachycardia other than AF or AF during the examination were excluded. In Article III, an additional nine participants with paced rhythm or left bundle branch block were excluded from the analysis.

Results: Three hundred and ninety-four out of the 520 invited individuals (76%) participated. Article I and II included 302 participants: 62 recreational skiers with paroxysmal AF, 89 skiers without AF, 89 non-skiers without AF, and 62 non-skiers with paroxysmal AF. All study participants were men, with a mean age of 70.8 ± 6.7 years. The skiers had completed an average of 16 annual Birkebeiner ski races and performed endurance exercise for an average of 40-50 years. Article III included 293 participants: 57 skiers with AF, 87 skiers without AF, 88 non-skiers without AF, and 61 non-skiers with paroxysmal AF. Individuals with paroxysmal AF had significantly reduced reservoir and contractile atrial strain parameters and increased left atrial mechanical dispersion (assessed by the standard deviation of time to peak strain (SD-TPS)) compared with subjects without AF, regardless of athletic status. Left atrial reservoir strain (33.6% ± 4.8% vs. 28.3% ± 6.7% p<0.001), Left atrial contractile strain (18.3% ± 4.0% vs. 15.0% ± 5.2% p<0.001), right atrial reservoir strain (43.0% ± 7.9 vs. 39.9 ± 7.7% p<0.001), right atrial contractile strain (21.5% ± 4.7% vs. 20.0% ± 5.9% p = 0.02) and SD-TPS (28.7±15.4 ms vs. 36.9±18.1ms p<0.001). Left atrial reservoir strain demonstrated the best ability to identify athletes with paroxysmal AF in sinus rhythm (area under curve: 0.740 ±0.041). Excluding participants with AF, cardiac size was positively associated with cumulative years of reported regular endurance exercise in all four cardiac chambers (p for trend <0.001), with a disproportionate increase in right ventricular relative to left ventricular size (p for trend <0.001), but with proportionate remodeling within the right ventricle itself

(p for trend = 0.08). Despite athletic remodeling with larger cardiac chambers, functional parameters assessed by 2D speckle tracking echocardiography were similar in all four chambers in the group reporting > 40 years of regular endurance exercise and in those who reported never having performed regular endurance exercise.

Conclusions: Cardiac functional parameters assessed by speckle tracking echocardiography seem to remain normal in all four cardiac chambers in healthy male veteran endurance athletes, despite significant exercise-induced cardiac remodeling with increased chamber sizes. Our findings suggest atrial functional parameters are more closely linked to AF than volumetric atrial parameters in older veteran endurance athletes. That left atrial reservoir strain is the echocardiographic parameter with the best ability to identify veteran athletes with paroxysmal AF when in sinus rhythm and that right ventricular remodeling appears to be more pronounced than left ventricular remodeling in male recreational athletes exposed to prolonged endurance exercise.

Summary in Norwegian

Bakgrunn: Det foreligger sparsomt med data som beskriver strukturelle og funksjonelle hjerteforandringer hos eldre utholdenhetsutøvere. Denne kunnskapen er nødvendig for å kunne øke forståelsen av fysiologisk så vel som patologisk kardial remodellering hos de som eksponerer seg for langvarig utholdenhetstrening. Atrieflimmer (AF) er den vanligste hjerterytmeforstyrrelsen hos utholdenhetsutøvere. Utholdenhetstrening med lav til moderat intensitet og mengde senker risikoen for AF, trolig ved å modifisere kjente risikofaktorer som hypertensjon, overvekt og diabetes. Mye utholdenhetstrening over lang tid ser derimot ut til å øke risikoen for AF blant menn. Data som beskriver hjertets struktur og funksjon hos eldre atleter med og uten AF vil kunne gi oss bedre forståelse av treningsindusert remodellering, hjelpe oss å gjenkjenne patologisk kardial remodellering samt utvikle bedre hypoteser vedrørende hvorfor enkelte utøvere utvikler AF.

Formål: Formålet med denne studien var å beskrive hjertets struktur og funksjon hos eldre individer eksponert for langvarig utholdenhetstrening, med og uten AF, med spesielt fokus på atrial remodellering.

Vi ønsket spesielt å:

I. Beskrive funksjonen og strukturen til venstre atrium hos eldre mannlige atleter med AF og evaluere om venstre atriefunksjon vurdert ved hjelp av *strain* er bedre enn volumetriske mål til å identifisere atleter med paroksysmal AF.

II. Undersøke høyre hjertehalvdels strukturelle og funksjonelle karakteristika i relasjon til langvarig utholdenhetstrening, samt vurdere høyre atriefunksjon hos eldre mannlige atleter med og uten AF.

III. Beskrive elektromekanisk remodellering av venstre atrium hos eldre atleter med og uten AF ved hjelp av mekanisk dispersjon målt med *speckle tracking* ekkokardiografi, samt undersøke mekanisk dispersjons evne til å identifisere eldre atleter med paroksysmal AF.

Metode: For å beskrive hjertets struktur og funksjon i relasjon til langvarig utholdenhetstrening og AF inviterte vi veteranatleter med og uten AF samt kontroller fra bakgrunnsbefolkningen med og uten AF til en tverrsnittsstudie med en grundig hjerteundersøkelse. Alle inviterte hadde tidligere deltatt i Birkebeiner atrieflimmerstudien. For å favne hele spekteret av fysisk aktivitet i befolkningen, inkluderte Birkebeiner atrieflimmerstudien (2012) tidligere deltagere i det årlige 54 km lange Birkebeinerrennet på ski (Birkebeinere) og individer som hadde deltatt i en helserelatert befolkningsstudie. Alle Birkebeinere med antatt AF bosatt innenfor en totimersradius fra undersøkelsesstedet (n=134), Birkebeinere uten AF (n=123) og kontrollgrupper fra befolkningsstudien fra det samme geografiske området med (n=81) og uten AF (n=147) ble invitert. For å øke antallet i kontrollgruppen med AF ble alle mannlige pasienter i riktig alder som besøkte atrieflimmerpoliklinikken ved Diakonhjemmet sykehus i perioden mellom mai og september 2020 forespurt om å delta. Alle deltagerne svarte på et spørreskjema og gjennomgikk en grundig ekkokardiografisk undersøkelse, blodprøver, et 12-kanalers EKG samt en 24 timers Holter-registrering. AF diagnosen ble verifisert i henhold til gjeldende retningslinjer. I artikkel I og II ble deltagere med hjertesvikt (ejeksjonsfraksjon <35%), signifikant klaffesykdom, tidligere gjennomgått åpen hjertekirurgi, supraventrikulær takykardi annet enn AF og de med AF under undersøkelsen ekskludert. I artikkel III ekskluderte vi i tillegg de med pacet hjerterytme eller venstre grenblokk, ytterligere ni deltagere, fra analysen.

Resultater: 394 av de 520 inviterte (76%) deltok i studien. Artikkel I og II inkluderte 302 deltagere: 62 Birkebeinere med paroksysmal AF, 89 Birkebeinere uten AF, 89 kontroller uten AF og 62 kontroller med paroksysmal AF. Alle deltagerne var menn, gjennomsnittsalderen var 70.8 ± 6.7 år. Birkebeinerne hadde i gjennomsnitt fullført 16 årlige birkebeinerrenn og rapporterte et gjennomsnitt på 40-50 år med regelmessig utholdenhetstrening. Artikkel III inkluderte 293 deltagere: 57 birkebeinere med paroksysmal AF, 87 birkebeinere uten AF, 88 kontroller uten AF og 61 kontroller med paroksysmal AF. Til tross for treningsindusert kardial remodellering med større hjertekamre hos birkebeinerne ($p<0.001$), var det ingen signifikant forskjell i funksjonelle ekkokardiografiske parametre i noen av de fire hjertekamrene vurdert ved hjelp av *strain* mellom birkebeinerne og deltagerne fra kontrollgruppen. Individer med paroksysmal AF hadde i snitt signifikant lavere atrie-*strain*-parametre og økt mekanisk dispersjon i venstre atrium (vurdert ved standardavviket av tid til maksimal *strain*, SD-TPS)

sammenlignet med deltagere uten AF, uavhengig av treningshistorikk. Venstre atriums reservoir-*strain* (33.6% ± 4.8% vs. 28.3% ± 6.7% p<0.001), venstre atriums kontraktile *strain* (18.3% ± 4.0% vs. 15.0% ± 5.2% p<0.001), høyre atriums reservoir-*strain* (43.0%±7.9 vs. 39.9±7.7% p<0.001), høyre atriums kontraktile *strain* (21.5% ± 4.7% vs. 20.0% ± 5.9% p = 0.02) og SD-TPS (28.7±15.4 ms vs. 36.9±18.1ms p<0.001). Venstre atriums reservoir-*strain* viste den beste evnen til å identifisere atleter med paroksysmal AF (areal under kurven: 0.740 ±0.041). Hos de uten AF, var det en signifikant positiv assosiasjon mellom størrelsen av alle fire hjertekamre og antall år med selvrapportert regelmessig utholdenhetstrening (p for trend <0.001). Vi fant en større økning av høyre ventrikkels størrelse relativt til venstre ventrikkels størrelse ved økende antall år med rapportert utholdenhetstrening (p for trend <0.001), men med en proporsjonal remodellering av høyre ventrikkels innløp og utløp (p for trend = 0.08). Til tross for større hjertekamre hos de som rapporterte den lengste treningshistorikken, var det ingen signifikante forskjeller når det gjaldt funksjonelle parametere vurdert ved 2D-ekkokardiografi mellom de som aldri hadde trent regelmessig og de som rapporterte over 40 år med regelmessig utholdenhetstrening.

Konklusjon: Til tross for betydelig større hjertekamre hos de som rapporterte den lengste treningshistorikken, bevarte de eldre utholdenhetsutøverne i denne studien uten kjent hjerterytmeforstyrrelse normal funksjon i alle fire hjertekamre. Funksjonelle atrieparametre var redusert hos gruppene med paroksysmal AF uavhengig av treningshistorikk og fremstår som lovende markører for patologisk atrial remodellering hos personer som har bedrevet langvarig utholdenhetstrening. Venstre atriums reservoir-*strain* var i vårt materiale parameteren med best evne til å identifisere atleter med paroksysmal AF. Høyre ventrikkels strukturelle remodellering virker å være mer uttalt enn venstre ventrikkels remodellering etter langvarig utholdenhetstrening til tross for bevart funksjon og symmetrisk remodellering innad i selve høyre ventrikkel.

Articles in thesis

Article I

Sørensen E, Myrstad M, Solberg MG, Øie E, Tveit A, Aarønæs M.

Left atrial function in male veteran endurance athletes with paroxysmal atrial fibrillation

Eur Heart J Cardiovasc Imaging 2021;**23**(1):137-146.

Article II

Sørensen E, Myrstad M, Solberg MG, Øie E, Tveit A, Aarønæs M.

Right Heart Structure and Function in Lifelong Recreational Endurance Athletes with and without Paroxysmal Atrial Fibrillation

J Am Soc Echocardiogr 2022;**35**(12):1259-1268.

Article III

Sørensen E, Myrstad M, Solberg MG, Øie E, Platonov PG, Carlson J, Tveit A, Aarønæs M

Left atrial dyssynchrony in veteran endurance athletes with and without paroxysmal atrial fibrillation

Submitted

1 Introduction

1.1 Exercise and the definition of an athlete

Exercise is defined as planned, structured, and repetitive bodily movement performed to improve or maintain physical fitness.[1] *Cardiorespiratory endurance* relates to the ability of the cardiorespiratory system to supply fuel during sustained physical activity and to eliminate fatigue products.[1] Hence, *endurance exercise* aims to improve maximal physical capacity by increasing the maximum oxygen uptake through planned, structured, and repetitive bodily movement.

There is no worldwide consensus regarding the definition of an *athlete*. According to the European Society of Cardiology, an athlete is defined as *"an individual of young or adult age, either amateur or professional, who is engaged in regular exercise training and participate in official sports competition*".[2] This thesis defines *regular endurance exercise* as endurance exercise >30 min x >3 times/week with the intent to increase physical endurance capacity. *Prolonged endurance exercise* refers to regular endurance exercise continued over many years. There is no strict and uniform definition of a *veteran athlete*. Sometimes the term is used interchangeably with *master athlete*, defined as an athlete ≥ 35 years of age, other times, it refers to older master athletes, for example athletes over the age of 50.[2, 3] In this thesis, the term *veteran athlete* refers to earlier participants in the Birkebeiner cross-country ski race over 60 years of age.

1.2 Exercise and health

The benefits of physical activity in the general population, both regarding morbidity and mortality, are indusputable.[4, 5] As primary and secondary prevention, physical activity has proven to reduce the risk of cardiovascular disease significantly.[6, 7] Coinciding with physical inactivity being a leading cause of non-communicable diseases worldwide, the number of veteran recreational athletes exceeding the physical recommendation guidelines and partaking in endurance sports events is increasing.[2, 8, 9] Several studies have indicated a curvilinear association between physical activity and mortality with decreasing returns at the highest doses of exercise.[10, 11] Although endurance athletes even at the highest level seem to have a survival advantage compared to individuals from the general population, vigorous and prolonged endurance exercise might have negative consequences in some individuals,

and has been linked with an increased prevalence of arrhythmias, coronary plaques, and sudden death.[12-16]

1.3 The "athlete´s heart"

Prolonged and intense exercise induces structural, functional, and electrical cardiac remodeling referred to as the "athlete´s heart".[17] Since the advent of the Morganroth hypothesis more than four decades ago, the grade and type of exercise-induced cardiac remodeling (EICR) have been connected to the type of sport the athlete is performing.[18] An acknowledged approach to sports classification is the scheme developed by Mitchell et al. relating individual sports to the degree of static and dynamic demands during exercise.[19] This classification has been linked to the grade and type of cardiac remodeling but has been challenged during the last years by a more simplistic approach developed by Beaudry et al., anticipating EICR solely based on exercise intensity and duration.[20] Cross-country skiers often sustain high workloads at submaximal effort, hours at a time, several times a week, and cardiac enlargement in cross-country skiers was recognized as early as the 1890s by Salomon Henschen.[21] Cross-country skiing is classified as a highly dynamic sport in the Mitchell classification scheme and a sport with potentially considerable cardiac remodeling in the classification scheme proposed by Beaudry and colleagues.[19, 20]

To perform in an endurance sport like cross-country skiing, a high oxygen uptake is needed to support the high metabolic demands during exercise.[22] The Fick equation describes the relationship between cardiac output and VO_2[22]:

VO_2 *= (left ventricular end-diastolic volume – left ventricular end-systolic volume) x heart rate x arterio-venous oxygen difference.*

The maximal heart rate of athletes and sedentary men is similar, and an athlete's left ventricular (LV) end-systolic volume is no smaller than that of a non-athlete. [23, 24] This, combined with the fact that the cardiac output of endurance athletes can increase up to eightfold during exercise, makes the endurance athletes depend on larger end-diastolic volumes to obtain the stroke volumes needed to excel in an endurance sport like cross-country skiing.[20, 25]

As the heart rate increases during exercise, the diastole shortens relative to systole, requiring a very high flow across the atrioventricular valves.[26] This is made possible by increased atrial pressure and greater LV lusitropy.[27] In relation to this, the phenotype "athlete´s heart" is characterized by a symmetrical enlargement of all four cardiac chambers with preserved and even enhanced diastolic properties.[26, 28-30] (Figure 1)

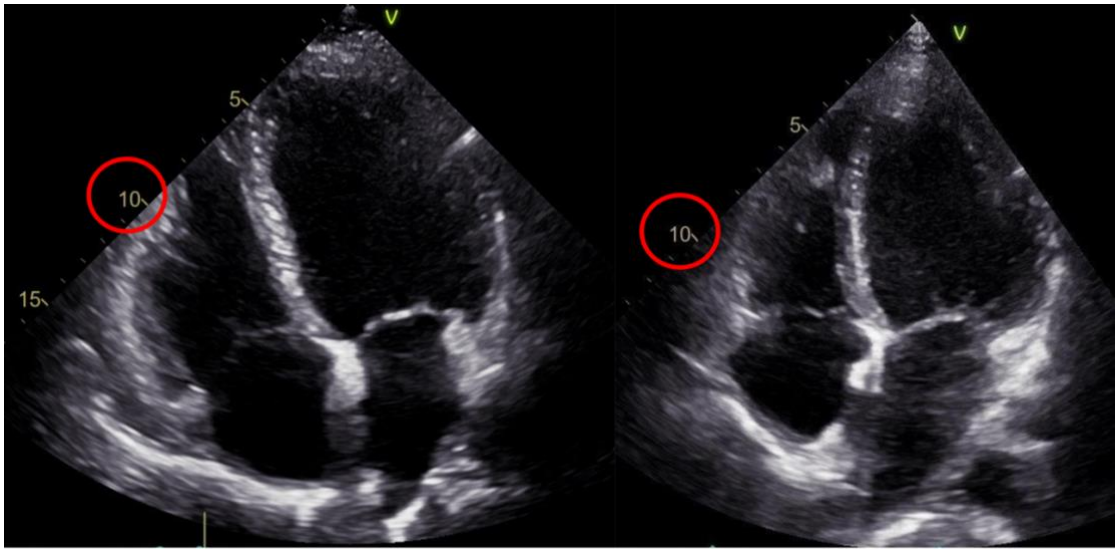

Figure 1. *Apical four-chamber view of a veteran recreational endurance athlete on the left and a non-athlete of similar age with paroxysmal atrial fibrillation on the right. Notice the symmetric exercise-induced cardiac remodeling in the recreational athlete (echocardiographic images reproduced with permission from the study participants).*

The "athlete´s heart" shares several common features with that of several cardiomyopathies, and the structural, functional, and electrical changes in the heart of an endurance athlete can be challenging to discern from pathological cardiac remodeling and might predispose some athletes to arrhythmias.[12, 31] The most common arrhythmia in endurance athletes is atrial fibrillation (AF).[32]

1.4 Atrial fibrillation

1.4.1 Definitions and classification

Willem Einthoven was the first to publish an electrocardiogram (ECG) showing AF in 1906, while the first description of "auricular fibrillation" was published in the British Medical Journal by Sir Tomas Lewis in 1909.[33, 34] The AF diagnosis relies on ECG documentation,

either by a standard 12-lead ECG or a single-lead ECG tracing of ≥30 seconds showing irregular RR-intervals and an absence of distinct repeating p-waves.[35] AF is the most common clinically relevant cardiac arrhythmia, with a known prevalence of 3.4% in the adult Norwegian population.[36] It is associated with an increased risk of death, stroke, dementia, and heart failure.[35, 37, 38] According to the European Society of Cardiology guidelines, we can distinguish between five types of AF:

1) First-time diagnosed AF
2) Paroxysmal AF – Terminating normally within 48 hours, but may continue up to 7 days
3) Persistent AF – AF episodes that last longer than seven days
4) Long-standing persistent AF – Continuous AF for ≥ one year, when it is decided to adopt a rhythm control strategy
5) Permanent AF – When rhythm control is no longer a goal

In patients experiencing both paroxysmal and persistent AF, the most frequently occurring type should be used for classification.[35] Over time, many patients will progress from short episodes to more persistent and, in the end, permanent AF.[39] In some patients, AF will remain paroxysmal over decades.[40] Advanced age, male sex, height, and genetic factors are all prominent non-modifiable risk factors. However, modifiable risk factors like hypertension, a sedentary lifestyle, obesity, smoking, and diabetes mellitus constitute as much as 50% of the total risk.[41] This emphasizes the importance of identifying the mechanisms leading to AF in every patient and better personalizing treatment strategies.

1.4.2 Atrial fibrillation and exercise

Light and moderate physical activity reduce the risk of AF, probably explained mainly by the beneficial effects of physical activity on major modifiable AF risk factors, such as diabetes mellitus, hypertension and obesity.[32, 42] Prolonged endurance exercise, on the other hand, seems to increase the risk of AF, indicating a J-shaped relationship between physical activity and AF.[32] Reports of a possible association between endurance exercise and AF emerged in the late 1980s and 90s, with Karjalainen et al. study of male elite orienteers in 1998 as a milestone publication.[43, 44] Subsequent small and large epidemiological studies have found

the same association, and extensive endurance exercise is now an established risk factor for AF in men.[35, 45-48] It has been demonstrated that participation in the Birkebeiner cross-country ski race is associated with an elevated risk of AF among older men and that prolonged regular endurance exercise in this group is associated with a graded increase in risk, supporting the findings of the J-shaped relationship.[49, 50] (Figure 2)

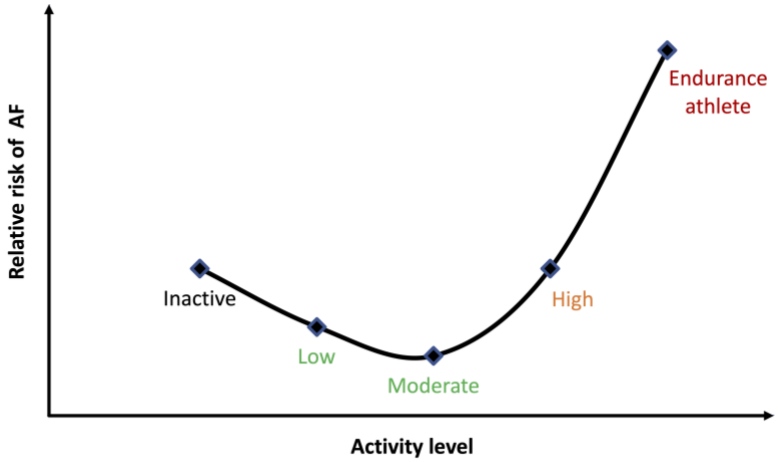

Figure 2. Association between the wide range of physical activity and atrial fibrillation. Figure modified from "The ambiguity of physical activity, exercise, and atrial fibrillation" with permission from the lead author.[32]

Endurance exercise induces structural, functional, and electrophysiological adaptations within the heart that could all potentially contribute to the increased risk of AF among endurance athletes.[12, 51, 52] Animal studies have demonstrated how prolonged intense exercise can trigger pro-inflammatory pathways, induce fibrosis, creating a substrate for AF.[53, 54] Autonomic dysfunction and a low resting heart rate have been demonstrated to be associated with AF, and prolonged endurance exercise modulates the autonomous nervous system and seems to reduce the intrinsic heart rate.[52, 55-57] In addition, some studies indicate a modest increase in ectopic beats among athletes, however, these findings are inconsistent.[58-61]

Most endurance athletes do not develop AF, and the reason why some individuals seem to be more vulnerable to pathological EICR is not yet clear. There is a scarcity of data describing cardiac structure and function in older veteran athletes, both with and without AF, that

could help increase the understanding of both physiological and pathological EICR in this group.

1.5 Exercise-induced cardiac remodeling and atrial fibrillation

1.5.1 Exercise-induced remodeling of the left atrium and atrial fibrillation

In the general population, left atrial (LA) dilation is an expression of pathology mainly caused by changes in the filling dynamics associated with abnormal relaxation of the LV, and several studies have established LA enlargement as an independent predictor of AF.[62-64] As part of EICR, the atria of young endurance athletes adapt rapidly to different training loads, which is viewed mainly as a physiological, dynamic, and potentially reversible mechanism.[65-68] Like LA volume, LA strain has proven to be an independent predictor of incident AF in the general population.[69] Despite differences in LA volumes, LA strain values seem to be similar in healthy young athletes and non-athletes, indicating preserved atrial function despite atrial enlargement.[70] Hence, LA strain has emerged as a promising marker when trying to separate adaptive from pathological atrial remodeling among athletes.[70-72] At the start of Birkebeiner II (the study on which all of the articles in this thesis are built), there were no studies describing atrial size and function in older veteran athletes with AF.

Atrial fibrosis is associated with a deterioration of atrial conduction and promotes re-entry circuits in the atrial walls.[73] Biopsy studies have established an association between atrial fibrosis and the presence and persistence of AF, both in individuals with and without a history of common cardiovascular comorbidities.[74, 75] LA mechanical dispersion (LA MD), as defined by the standard deviation of time to peak strain (SD-TPS), has been demonstrated to correlate with the degree of atrial fibrosis in AF patients, to be an independent predictor of AF in the general population, and has been linked to the recurrence of AF after catheter ablation.[76, 77] Watanabe et al. investigated patients with paroxysmal AF with LA voltage mapping. They found an association between low voltage zones and increased LA MD, despite similar indexed maximum LA volume ($LAVI_{max}$) in the groups with and without low voltage zones, indicating increased regional fibrosis in the LA wall of the patients with increased LA MD.[78] LA MD seems to increase with advancing age, speculated to be primarily due to age-associated atrial fibrosis.[79] A report has also linked prolonged endurance exercise to increased atrial fibrosis assessed by magnetic resonance imaging.[80] However, the

association between prolonged endurance exercise, LA MD and AF, and the ability of LA MD to identify veteran athletes with AF has yet to be investigated.

1.5.2 Exercise-induced remodeling of the right heart and atrial fibrillation

Most AF originates in the pulmonary veins, as demonstrated in the landmark paper by Haissaguerre et al., and studies regarding AF and atrial remodeling have primarily focused on the left side of the heart.[81, 82] In recent years, several studies have identified a link between right atrial (RA) remodeling and AF, especially in diseases primarily affecting the right side of the heart.[83-85] In an animal model Hiram et al. induced pulmonary hypertension in rats to develop right heart disease, demonstrating how this resulted in fibrosis and conduction abnormalities in the RA, producing a substrate for AF in these animals.[86] RA foci of AF and severe tricuspid regurgitation have also been demonstrated to be more common in patients with normal-sized LA and recurrence of AF after pulmonary vein isolation, indicating that substrate abnormalities in the RA are related to non-pulmonary vein AF triggers.[87] The right ventricle (RV) and RA are thin-walled and adapted to a low resting load.[88] During peak exercise, the load on the RV increases disproportionally to the LV, in theory making the right-hearted chambers more susceptible to EICR.[26, 88, 89] A study by Sanz-de la Garza et al. found that RA function increased after 14km of running, but then progressively declined after 35km. Dysfunction of the RA occurred earlier and was more profound than for the LA.[90] Data on RA size and function in veteran athletes after performing decades of endurance exercise is lacking. How and to what extent RA remodeling contributes to the increased risk of AF among these athletes is unknown.

2 Aims

2.1 Overall aim

To describe the specific cardiac traits of veteran recreational endurance athletes with and without AF exposed to prolonged endurance exercise, with a special focus on atrial remodeling.

2.2 Specific aims

2.2.1 Article I

To investigate structural and functional characteristics of the LA in relation to AF in veteran male athletes and to assess if LA strain by speckle tracking echocardiography is better than volumetric measurements to identify athletes with paroxysmal AF.

2.2.2 Article II

Investigate structural and functional characteristics of the right heart regarding prolonged endurance exercise, explore a possible dose-response relationship between exercise and right heart remodeling, and assess RA function in veteran athletes with and without AF.

2.2.3 Article III

To investigate LA MD in veteran athletes with and without AF to contribute to the understanding of electromechanical cardiac remodeling in this group.

3 Materials

3.1 The history of the Birkebeiner ski race and earlier Birkebeiner studies

3.1.1 The Birkebeiner cross-country ski race

The Birkebeiner cross-country ski race is an annual race founded on the legendary escape of the Birkebeiners Skjervald Skrukka and Torstein Skjevla in the year 1205 when they rescued the crown prince Håkon Håkonsson from the rivaling fraction the Baglers by carrying the prince over the mountains separating Østerdalen and Gudbrandsdalen. In 1932, the first Birkebeiner ski race honoring this escape was arranged, gathering 147 men following the route of Skrukka and Skjevla over the mountains. Today the Birkebeiner classical cross-country ski race is 54 km long, covering 1147 uphill altitude meters, starting in Rena in Østerdalen, finishing in Lillehammer, and is regarded as one of the most challenging cross-country ski races in the world (Figure 3). Every contestant carries a backpack weighing at least 3.5kg, representing the weight of the crown prince, Håkon Håkonsson.[91] The ski race is currently a part of the Ski-classics, a long-distance ski championship comprising the world's twelve most traditional and prestigious cross-country skiing events.[92]

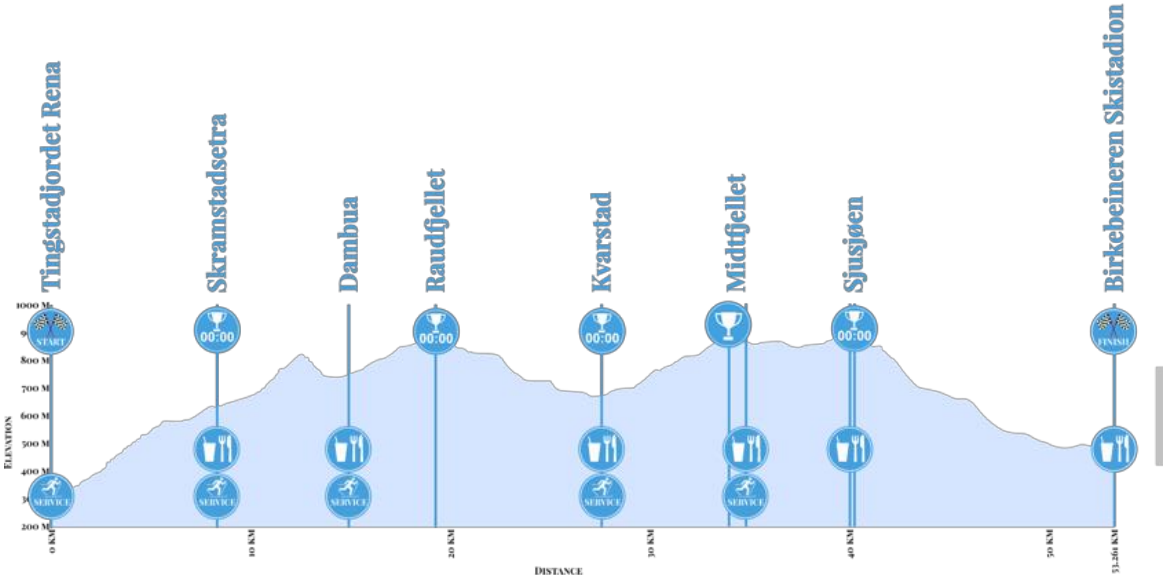

Figure 3. Track profile of the Birkebeiner classical cross-country ski race.[93]

3.1.2 Earlier Birkebeiner studies

Completing the Birkebeiner cross-country ski race requires continuous preparations, and a high level of cardiovascular fitness ($\dot{V}O_{2max}$) has been documented among the skiers.[94]

Hence, race participation could be considered a proxy for cardiovascular fitness. As a result, cardiovascular research on Birkebeiner participants has been ongoing for almost 50 years, starting in 1976, with H. Lie and J. Erikssen focusing on ECG aberrations, latent coronary heart disease, and cardiopulmonary fitness among the participants.[95, 96] A follow-up study of this cohort was performed by Grimsmo et al. in 2004-2006, being among the first to describe a high prevalence of AF among veteran skiers, linking this to LA enlargement.[97] A new longitudinal study of Birkebeiners ≥ 65 years of age was initiated in 2009, investigating associations of prolonged endurance exercise with aging, functional decline, and health outcomes.[98] To further investigate the associations between prolonged endurance exercise and AF, the Birkebeiner Atrial Fibrillation study was initiated in 2012.[49]

3.2 Birkebeiner II

The current thesis is based on data from Birkebeiner II, a clinical study that included a subset of participants from the Birkebeiner Atrial Fibrillation study.

3.2.1 The Birkebeiner Atrial Fibrillation study

Aiming to include the entire range of physical activity in the population, the Birkebeiner Atrial Fibrillation study comprised two independent cohorts:

1) Veteran skiers who participated in the Birkebeiner cross-country ski race in 1999 were born before 1960 and had a Norwegian postal address.[49]

2) Individuals who had participated in a population-based health survey (The Oslo Health study) in 2009 were ≥ 53 years at the time and had given consent to be contacted for further studies.[99]

A total of 2653 (76%) of the invited skiers and 2737 (68%) of the invited individuals from the population-based health study participated.

3.2.2 The Birkebeiner II study

Intending to investigate cardiac remodeling in relation to prolonged endurance exercise and AF, we invited a subset of male participants from The Birkebeiner Atrial Fibrillation study, veteran skiers with and without AF, and age-matched controls with and without AF from the population-based health study to attend a clinical study. Exclusion criteria were prior open-

heart surgery, heart failure (EF<35%), clinically relevant heart valve disease, or supraventricular tachycardia other than AF.
All skiers with a history of AF included in The Birkebeiner Atrial Fibrillation study living within a perimeter of 2 hours by car from Diakonhjemmet Hospital in Oslo, where the study was conducted (travel time was assessed by postal code) were invited to participate. Twenty-four of the invitees did not respond. The non-responders had a mean age of 73 years and, with few exceptions, resided in the periphery of the geographical area of inclusion. Of the remaining 110, 21 were excluded due to fulfilling exclusion criteria or because AF could not be verified. Hence, eighty-nine veteran skiers with a history of AF were included. Twenty-seven of the 89 skiers with AF that met for examination had AF at the time of examination, and 62 had sinus rhythm during the echocardiographic exam.

All veteran skiers included in the Birkebeiner Atrial Fibrillation study without a history of AF residing in the same geographical area as the skiers with AF were sorted randomly. Starting at the top of this list, we invited age-matched controls to the skiers with AF until n=89 skiers without a history of AF were included.

Participants in the Oslo Health study included in The Birkebeiner Atrial Fibrillation study were also divided into those with and without a known history of AF and randomly sorted in the same manner described above. Again, age-matched controls were invited until n=89 controls without a history of AF were included.
In the group of individuals from the Oslo Health study with a history of AF, we could only identify and recruit 54 age-matched controls with a verifiable history of AF, of which 27 had permanent AF. To reach the same number of participants in the non-athletic group with AF both in total (n=89) and with sinus rhythm during examination (n=62) as in the athletic AF group, we recruited participants from the outpatient clinic at Diakonhjemmet Hospital in Oslo. Every male patient of the proper age with paroxysmal AF visiting the AF outpatient clinic between May and September 2020 was consecutively invited to participate until the aim of participants was reached. All invited patients from the outpatient clinic agreed to participate in the study.

In Articles I and II, atrial functional measures, including atrial contractile function, were a central focus. Hence, all participants with AF during the echocardiographic exam were excluded from the analysis in these papers. In Article III, focusing on LA MD, participants with left bundle branch block or paced rhythm were also excluded from the analysis. (Figure 4)

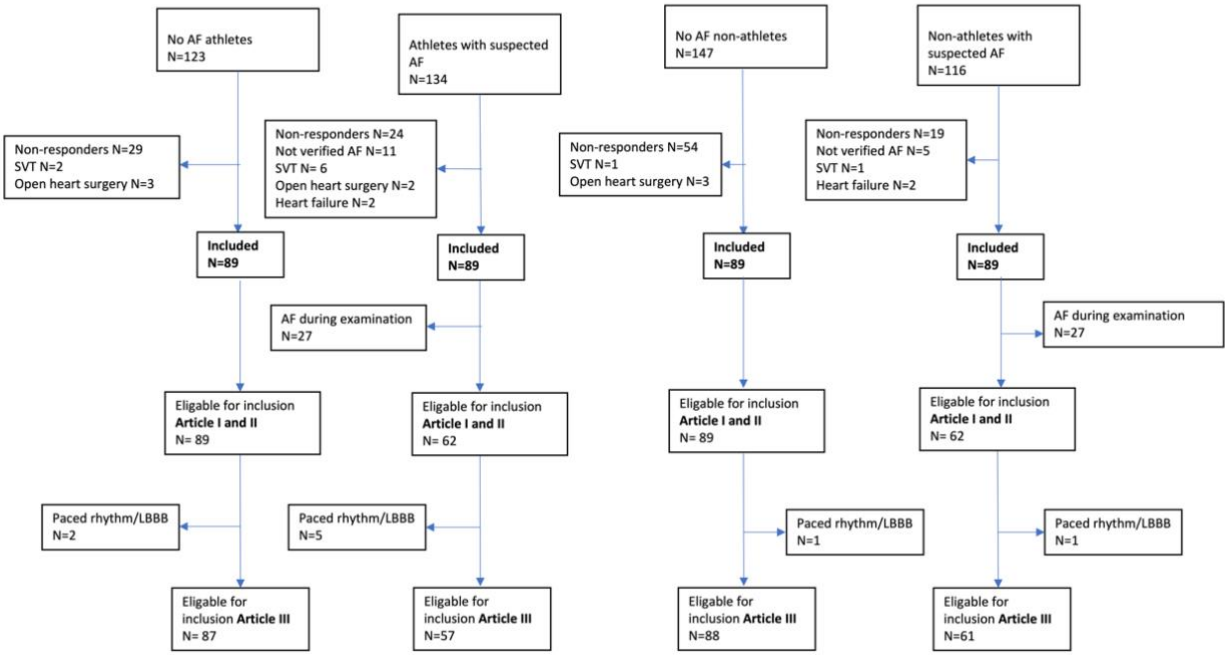

Figure 4. Recruitment of the study sample in Birkebeiner II and all three articles in this thesis. AF, atrial fibrillation; SVT, supraventricular tachycardia; LBBB, left bundle branch block.

4 Methods

4.1 Clinical measurements

Height was measured without shoes to the nearest cm, and weight in light clothes to the nearest kilogram. Body mass index was calculated based on these measurements. Blood pressure was measured thrice with participants sitting with cuff on arm after >5 min of rest. An average of three values was reported. Resting heart rate was measured by observing the heart rate on the ECG machine.

4.2 Data regarding exercise and medical history

Information on exercise habits, medical history, and medication use was gathered from a self-reported questionnaire included in this thesis's appendix. When designing the questionnaire for this study, we chose to build on the questionnaire used in The Birkebeiner Atrial Fibrillation study to allow comparing analyses. In addition, the main investigator interviewed all participants and gathered supplementary relevant information from medical journals when required.

4.2.1 Assessment of exercise load

Birkebeiner II was designed assuming that participation in the Birkebeiner cross-country ski race requires regular endurance sports practice. In all three articles in this thesis, the term veteran athlete refers to those from the cohort of veteran cross-country skiers recruited from the Birkebeiner Atrial Fibrillation study.

In Article II, we aimed to investigate the structural and functional characteristics of the right heart in relation to prolonged endurance exercise. In Article III, we aimed to investigate LA MD in relation to prolonged endurance exercise, exploring a possible dose-response relationship between exercise and cardiac remodeling. The primary exposure variable in these analyses was reported years of performing regular endurance exercise. To separate regular endurance exercise from more modest physical activity, the questionnaire contained a question pertaining regular endurance exercise with the purpose of increasing physical endurance capacity: *"Have you, at any time in your life, engaged in regular endurance exercise (exercise sessions for a minimum of 30 minutes at least 3 times per week to improve*

endurance capacity)?" This was reported on an eight-level ordinal scale: Never, <5, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59, and ≥ 60 years. The scale was condensed into four categories to obtain a meaningful number of participants in each category: Those who had never exercised regularly, those who had performed regular endurance exercise for 1-19 years, 20-39 years, and for a duration of ≥ 40 years.

4.2.2 Drug use and medical history

Drug use related to AF was assessed by the question: "*Do you use the following medications due to atrial fibrillation?"* With the following possible answers: Beta-blockers (e.g., Selo-zok, Metoprolol, Emconcor, Sotalol, Sotacor), calcium-channel blockers (e.g., Isoptin, Verapamil, Verakard), Cordarone, Tambocor/Flecainide, Multaq/Dronedarone, Digitoxin/Digoxin/Lanoxin, Albyl-E/Magnyl/Acetylsalisylic acid, Marevan/Warfarin, Pradaxa, Xarelto, Eliquis and Lixiana.

Medical history regarding relevant comorbidities was assessed by the question: "*Do you have, or have you ever had any of the following diseases?"* Myocardial infarction, angina, hyperthyroidism, diabetes, hypertension, heart failure, kidney failure, asthma, chronic obstructive pulmonary disease, stroke/TIA, high cholesterol, cardiac surgery (bypass-operation or heart-valve surgery), cerebral hemorrhage, and osteoporosis. CHA_2DS_2-VASc score was calculated based on the answers to these questions and the participant's age at the time of examination.[100] In addition to the questionnaire, all participants were interviewed regarding their medical history and status regarding implanted devices (pacemaker or implantable cardioverter defibrillator) and ablation history.

4.3 Verification and classification of atrial fibrillation

4.3.1 Verification of atrial fibrillation

The questionnaire included questions regarding the presence of AF, including where the participants had been diagnosed. To verify the history of AF, the main investigator reviewed medical records confirming the AF diagnosis by ECG according to guidelines.[35] The diagnosis could not be verified in 16 participants reporting a history of AF (11 veteran skiers and five controls). These were excluded from the study. To minimize the probability of unnoticed AF in the non-AF groups, we conducted a resting ECG and a 24-hour Holter ECG monitoring. We

did not find any cases of undetected AF during resting ECG or Holter monitoring in study participants without priorly known AF.

4.3.2 Classification of atrial fibrillation

The questionnaire contained a question regarding the type of AF. "*Do you have a) AF the entire time, b) AF that terminates spontaneously or with medication/electric cardioversion within seven days, c) AF that is sustained beyond seven days and then terminates spontaneously or with medication/electric cardioversion."*

All participants were interviewed by the main investigator regarding the answer to this question. One hundred and eleven participants answered b), i.e., paroxysmal AF verified by the patient´s medical record. Thirteen participants (five athletes and eight non-athletes) answered c), i.e., persistent or long-standing AF, none of which were considered to have long-standing AF based on their medical history. The 2020 European society of cardiology AF guidelines state that in patients experiencing both paroxysmal and persistent AF, the more frequently occurring type should be used for classification.[35] As it was challenging to differentiate paroxysmal from persistent AF in some participants, we defined all participants with ECG-verified non-permanent AF in sinus rhythm at the time of examination as having paroxysmal AF. In addition, the questionnaire included a question regarding the frequency of paroxysms of AF. "*How often do you experience AF?"* with the possible answers: Two or more times per week, approximately once a week, one to three times per month, or less than once a month.

4.4 Echocardiography

The main investigator recorded resting echocardiograms using the same digital ultrasound scanner in all participants (Vivid E9, GE Vingmed Ultrasound, Horten, Norway). According to recommendations, we obtained 2D-greyscale, tissue Doppler, and color Doppler images in parasternal and apical views.[101] Three to five consecutive loops were acquired and saved in cine loop format, including 200 milliseconds (ms) before and after all beats.

All analyses were performed offline (Echo PAC version 203, GE Vingmed Ultrasound, Horten, Norway) by the main investigator blinded to the patients' other data.

4.4.1 Conventional echocardiography

LV size parameters were obtained, calculated, and indexed to body surface area according to recommendations.[101] Mitral inflow parameters and pulsed wave tissue Doppler images were obtained from an apical four-chamber view assessing early and late trans-mitral inflow parameters and diastolic tissue velocities. E/A ratio and E/e' was computed from these values, E/e' was calculated from an average of septal and lateral e' velocities.[102]

Atrial 2D acquisitions were obtained using atria-focused apical views. LA volumes were calculated by the summation of discs in apical four- and two-chamber views, and RA volume by the summation of discs in an RA-focused apical view. An average from three consecutive loops was computed. Atrial stiffness was calculated by dividing E/e' by peak LA reservoir strain (LASr).[103] The ratio of maximum LA volume to LV end-diastolic volume (LA/LV) was computed to evaluate potentially unbalanced remodeling.[104]

Proximal RV outflow tract diameter was obtained from a parasternal short-axis view at end-diastole. RV basal and mid-cavity diameter and RV areas were obtained from an apical RV-focused view, and RV fractional area change was calculated.[101] Tricuspid annular plane systolic excursion was obtained by aligning the M-mode curser with the direction of RV longitudinal excursion from an apical approach. Early (E) and late (A) trans-tricuspid inflow parameters were recorded from an RV-focused apical view, and E/A ratio was computed from these values. Pulsed wave tissue-Doppler images were obtained, early diastolic (e′) and systolic excursion velocities (S`) were measured at the lateral tricuspid annulus, and E/e′ was calculated.[105] RV basal end-diastolic diameter/proximal RV outflow tract (RV inflow/outflow ratio) and RV basal end-diastolic diameter/LV end-diastolic dimension in parasternal long-axis view (RV/LV ratio) were computed to identify asymmetric remodeling of the ventricles.[106, 107]

4.4.2 Speckle tracking echocardiography

During the last couple of decades, new and more sensitive echocardiographic techniques assessing systolic function by deformation imaging using two-dimensional speckle-tracking have emerged.[108] The technique is based on tracking myocardial pixels, referred to as speckles, generated through an interaction between ultrasound waves and cardiac tissue. Deformation curves are generated based on the relative position of these speckles. The

grade of deformation is commonly reported by strain. Strain describes the deformation of an object normalized to its original size. A widely used way to describe this change is Lagrangian strain where a single reference length L_0 is defined, which against all subsequent deformation will be measured.[109] All strain measurements in this thesis were performed using Lagrangian strain.

$$S_L(t) = \frac{L(t) - L_0}{L_0}$$

For many years speckle tracking echocardiography was primarily performed on the LV, and there has been a lack of standardized parameters to be measured and software packages to use to obtain two-dimensional strain measurements of the atria and the RV. In 2018 the EACVI/ACE/Industry Task Force published a consensus paper standardizing these measurements, complementing the consensus document regarding speckle tracking analysis from 2015, giving researchers and clinicians advice on what parameters to use and how to measure them.[109, 110] All strain measurements in this thesis were obtained in accordance to these recommendations and stated in absolute values. LV global longitudinal strain (GLS) was computed from apical four-chamber, two-chamber, and apical long-axis views, using the 18-segment model. End-diastole was defined by the frame before mitral valve closure.
RV free wall longitudinal strain (RVFWSL) was obtained from an RV-focused apical four-chamber view, visualizing the RV apex throughout the entire cardiac cycle. The RV endocardial border was traced from the lateral tricuspid annulus level to the medial tricuspid annulus level. A region of interest was automatically defined and adjusted manually to fit the thickness of the RV wall. The software automatically divided the RV into six segments, scoring the tracking quality with the possibility of manual correction. The three septal segments were excluded from the analysis, and RVFWSL was computed as the average of the three segments of the RV free wall. All three segments had to be adequately tracked to be accepted for analysis. RVFWSL was defined as the peak negative strain during systole. The reported value is averaged over three heart cycles and stated in absolute numbers.[110]
LA strain was obtained from an LA-focused four-chamber apical view, and RA strain from an RA-focused view, with narrow image sectors at frame rates >60 frames per second. The

atrial borders were traced from one side of the annulus to the other along the endocardium. A region of interest was automatically defined, then adjusted manually to fit the thickness of the atrial walls. The software automatically divided the atria into six segments, scoring their tracking quality with the possibility of manual correction. A minimum of four segments had to be accepted for analysis.[110] All strain values were computed as the average of the accepted segments and averaged over three heart cycles. Zero strain reference was set at ventricular end-diastole. LA strain values are stated as LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct). RA strain values as RA reservoir strain (RASr), RA conduit strain (RAScd), and RA contractile strain (RASct) (Figure 5).

SD-TPS was calculated as the mean value of time to peak strain in the six LA segments. SD-TPS was calculated separately in three consecutive loops, and an average of these values is reported. In addition to crude SD-TPS in milliseconds (ms), SD-TPS was corrected by the cycle length and expressed as a percentage of the cardiac cycle ($\frac{SD-TPS(ms)}{Cycle\ length(ms)}\ X\ 100$).

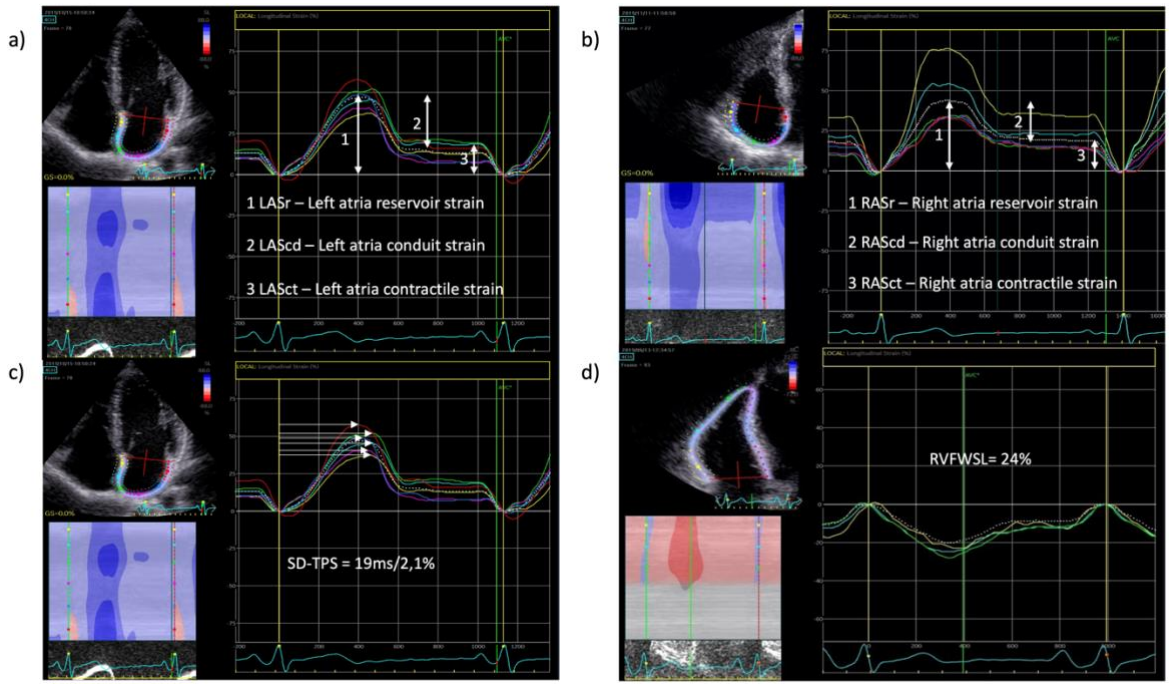

Figure 5. a) Left atria strain curves. The six segments were measured individually, and an average of accepted segments was computed. b) Right atria strain curves. The six segments were measured individually, and an average of accepted segments was computed c) Left atria strain curves. Left atrial mechanical dispersion was defined as the standard deviation of the time to peak strain. The white arrows indicate time to peak strain for the six different atrial segments. d) Right ventricular free wall longitudinal strain was obtained from a right ventricular-focused apical view. The three different segments were measured individually, and an average of the three segments was computed.

SD-TPS, standard deviation of the time to peak strain; RVFWSL, right ventricular free wall longitudinal strain

4.5 ECG and Holter monitoring

A 12-lead ECG was obtained, assessed by the main investigator, and exported in digital format for offline processing using the standard Glasgow algorithm with automatic identification of fiducial points, amplitudes, and intervals of the components of the PQRST-complex.[111] All participants underwent a seven-lead Holter monitoring (Medilog AR4Plus) from the time of examination until the following morning. All Holter files were assessed by the main investigator using the software Medilog Darwin Professional.[112]

4.6 Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation when normally distributed or as median (25^{th}-75^{th} percentile) for data not normally distributed. Categorical values are reported using frequencies and percentages.

In Articles I, II, and III, a two-way between-groups analysis of variance were conducted to explore the main effects of athletic status, AF status, and the interaction between AF status and athletic status regarding main echocardiographic parameters.
A one-way analysis of variance with polynomial contrasts was performed investigating a linear trend between cumulative years of reported endurance exercise and central echocardiographic variables from the right heart chambers in Article II and SD-TPS in Article III.

To assess independent associations between the atrial strain parameters LASr and LASct and AF in Article I, RASr and AF in Article II, and SD-TPS and AF in Article III, we performed a logistic regression for each parameter adjusting for height, weight, CHA_2DS_2-VASc-score, and relevant echocardiographic parameters in Article I and II, and height, weight, CHA_2DS_2-VASc-score, QRS width and relevant echocardiographic parameters in Article III.
In Article I, we performed a hierarchical logistic regression to evaluate the incremental value of LASr on top of clinical and relevant echocardiographic parameters at identifying athletes with AF. In Article III, we performed a hierarchical logistic regression to investigate the

incremental value of SD-TPS on top of height, weight, CHA_2DS_2-VASc score, QRS width, and relevant echocardiographic parameters including LASr.

Independent association between RV/LV ratio and cumulative years of exercise in the participants without AF was explored in a multiple regression analysis in Article II.

In Articles I and II, receiver operating curves (ROC) for atrial volumes and functional echocardiographic parameters were created. Areas under curves were calculated for these parameters' ability to identify athletes with AF.

In Articles, I, II, and III, intra and inter-rater variability analyses regarding echocardiographic measurements were conducted offline on anonymized recordings in 15 randomly selected participants using a two-way mixed model with absolute agreement between measures, supplemented by a coefficient of variation analysis in Article II. The main investigator did an intra-observer analysis with a two-week interval between measurements. Inter-rater analysis was conducted separated in time and place between the two raters. Analysis was performed on the same set of recordings from each participant. The raters could randomly select different pictures and loops for analysis and re-analysis.

4.7 Ethics

The Birkebeiner II study is approved by the Regional Committee for Medical and Health Research Ethics (2016/565/REK Vest) and complies with the Declaration of Helsinki. The study is registered at www.clinicaltrials.gov; NCT03741491

Informed written consent to participate in the study was obtained from all participants prior to data collection. The study did not include any experimental interventions. Only taking blood samples was an invasive procedure. All study participants underwent blood sampling, echocardiography, an ECG, and a 24-hour Holter recording. As all these examinations were performed as part of a study protocol and not medically indicated, we risked revealing abnormal findings in asymptomatic participants. Procedures for handling abnormal findings were developed to avoid reporting incident findings of no clinical relevance and follow up on abnormal findings in need of further examinations. The main investigator performed and

analyzed all exams, and participants with findings requiring further examination/follow-up were thoroughly informed.

4.8 Participant involvement

The Birkebeiner study has from 2009 involved a reference group with six participants, all ”Birkebeiners”, including two women. This reference group was continued as a part of the Birkebeiner II study, and they advised the organization of the present study. Research results and news from the Birkebeiner studies are presented in a newsletter to the participants.

5 Results

5.1 Article I: Left atrial function in male veteran endurance athletes with paroxysmal atrial fibrillation

In Article I, we investigated LA function in male veteran cross-country skiers with and without paroxysmal AF compared with men from the general population and sought to investigate if LA function assessed by atrial strain were better at identifying athletes with paroxysmal AF than volumetric measurements. Three-hundred and ninety-four out of the 520 invited individuals (76%) participated in the study. After excluding participants with clinically significant valvular disease, heart failure, previous open-heart surgery, supraventricular tachycardia other than AF or AF during the examination, we included 302 participants: 62 skiers with paroxysmal AF, 89 skiers without AF, 89 non-skiers without AF and 62 non-skiers with paroxysmal AF.

The athletes (mean age 70.8 $\pm$ 6.7 years) reported an average exposure to regular endurance exercise of 40-50 years and an average of 16 completed Birkebeiner races. The prevalence of cardiovascular risk factors among athletes was very low. Reported AF burden was low in both athletes and non-athletes, with approximately three out of four participants reporting paroxysms of AF less than once a month. Compared with the control group, the veteran athletes had larger $LAVI_{max}$ and minimum LA volume indexed ($LAVI_{min}$) but similar LA strain values. LA volumes differed within the athletic and non-athletic groups, with larger volumes in the AF groups. LA strain values were lower in both AF groups regardless of athletic status. LASr was the parameter with the best ability to identify the athletes with paroxysmal AF when in sinus rhythm (area under the curve (AUC): 0.740 $\pm$ 0.041).

Table 1. Left atrial echocardiographic values.

	Athletes		Non-athletes				
	AF	**No AF**	**AF**	**No AF**	**P-value athletes vs. non-athletes**	**P-value AF vs. No AF**	**P-value interaction athletic status and AF status**
LASr (%)	27.9 ± 6.4	33.5 ± 4.8	28.7 ± 7.0	33.8 ± 4.9	0.410	<0.001	0.673
LAScd (%)	13.4 ± 4.9	15.4 ± 4.0	13.3 ± 4.0	15.3 ± 4.5	0.788	<0.001	0.955
LASct (%)	14.6 ± 4.5	18.1 ± 4.1	15.5 ± 5.8	18.5 ± 4.0	0.215	<0.001	0.591
$LAVI_{max}$ (ml/m^2)	52.4 ± 15.2	45.9 ± 10.8	44.3 ± 11.9	38.2 ± 8.0	<0.001	<0.001	0.867
$LAVI_{min}$ (ml/m^2)	29.7 ± 12.3	22.9 ± 7.2	25.0 ± 10.0	18.3 ± 4.8	<0.001	<0.001	0.997

Values are expressed as mean±SD. A two-way between-groups analysis of variance was conducted. P-values for the main effects of athletic status and AF status and the interaction are presented in the table.
LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{min}$, minimum left atrial volume index; AF, atrial fibrillation

Table 2. Performance of left atrial echocardiographic parameters at identifying athletes with atrial fibrillation.

Variable	AUC	P-value
LASr	0.740 ± 0.041	0.000
LAScd	0.623 ± 0.049	0.012
LASct	0.706 ± 0.043	0.000
$LAVI_{max}$	0.626 ± 0.047	0.008
$LAVI_{min}$	0.688 ± 0.044	0.000

LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; $LAVI_{max}$, maximum left atrial volume indexed; $LAVI_{min}$, minimum left atrial volume indexed; AF, atrial fibrillation; AUC, area under the curve.

5.2 Article II: Right heart structure and function in lifelong recreational endurance athletes with and without paroxysmal atrial fibrillation

Article II focused on right heart remodeling based on years of reported regular endurance exercise and RA function in veteran athletes with and without AF. Exclusion criteria were identical to Article I, and the same 302 participants were included. Eighty-seven participants

had never practiced regular endurance exercise, whereas 50 participants had practiced regular endurance exercise for 1-19 years, 43 participants for 20-39 years, and 122 participants for more than 40 years. One hundred and thirty-three of the study participants were still engaged in regular endurance exercise at the time of examination.

RA volume and RV size increased with cumulative years of reported exercise ($p<0.001$), with a disproportionate increase in RV size compared with LV size regardless of AF status ($p<0.001$). There was no significant trend between years of reported exercise and RV inflow/outflow ratio when participants with AF were excluded ($p=0.076$). RA and RV function was similar in athletes reporting $\geq$ 40 years of regular endurance exercise and those who reported never to have performed regular endurance exercise.
RV/LV ratio remained positively associated with cumulative years of endurance exercise in a multiple regression model excluding participants with AF and adjusting for confounders (height, age, and weight), competing echocardiographic exposure variables (RVFWSL and maximum tricuspid regurgitation velocity), and relevant comorbidities (hypertension, diabetes mellitus, a history of myocardial infarction and asthma) ($p=0.018$).
When assessing RA and RV size and function based on athletic and AF status, we found RA and RV size to be larger in athletes ($p<0.001$), while RA and RV strain parameters were similar in athletes and non-athletes. AF was significantly associated with reduced RASr irrespective of exposure to exercise, but RA strain values had a lower AUC than LA strain values in identifying athletes with AF.

5.3 Article III: Left atrial dyssynchrony in veteran endurance athletes with and without paroxysmal atrial fibrillation

Article III focused on LA MD in veteran athletes. As for Article I and II, participants with AF during examination were excluded. In addition, individuals with pacemaker rhythm or a left bundle branch block in their ECG were excluded from the analysis, including 57 athletes with paroxysmal AF, 87 athletes without AF, 88 non-athletes without AF, and 61 non-athletes with paroxysmal AF.
There was no significant trend between SD-TPS and years of performing endurance exercise in participants without a history of AF ($p=0.846$). While LA volumes were associated with

both AF and athletic status, SD-TPS was associated with AF but not with athletic status. However, SD-TPS did not add independent incremental value at identifying athletes with AF in addition to clinical markers, QRS width, LA volume, and LASr (p=0.056).

Table 3. Left atrial echocardiographic values.

	Athletes		**Non-athletes**				
	AF	**No AF**	**AF**	**No AF**	**P-value athletes vs. non-athletes**	**P-value AF vs. No AF**	**P-value interaction athletic status and AF status**
SD-TPS (ms)	35.0 ± 16.9	27.8 ± 13.9	38.7 ± 19.1	29.6 ± 16.9	0.173	<0.001	0.642
$LAVI_{max}$ (ml/m^2)	51.8 ± 14.6	45.6 ± 10.4	44.5 ± 11.8	38.3 ± 8.0	<0.001	<0.001	0.997
$LAVI_{min}$ (ml/m^2)	28.8 ± 10.9	22.8 ± 7.0	25.1 ± 10.1	18.3 ± 4.8	<0.001	<0.001	0.707

Values are expressed as mean$\pm$SD. A two-way between-groups analysis of variance was conducted. P-values for the main effects of athletic status and AF status and the interaction are presented in the table.

SD-TPS = standard deviation of time to peak strain, $LAVI_{min}$ = minimum left atrial volume index, $LAVI_{max}$ = maximum left atrial volume index

6 Discussion

6.1 Methodological considerations

6.1.1 Study design

A cross-sectional design can sort out the associations between one or more independent variables upon a dependent variable at a given point in time. However, it cannot answer questions about causal relationships.[113] The cross-sectional design was chosen due to several factors. Even though AF is prevalent among veteran endurance athletes, most athletes do not develop AF. In the Birkebeiner Atrial Fibrillation study, there was a crude AF prevalence of 13.2% among male athletes >65 years of age.[50] EICR starts at a very young age, and many endurance athletes choose to stop performing regular endurance exercise during their early adult life.[114] The risk of AF increases with years of regular endurance exercise, as does EICR.[49, 115] Due to the abovementioned factors, we would need a very large cohort of endurance athletes and follow them with repetitive clinical exams over several decades to obtain enough end-points to get purposeful prospective results regarding EICR and AF. This would be of great interest but demands a large multicenter study with a vast budget and was way beyond the scope of this Ph.D. As earlier studies of the cohort from the Birkebeiner Atrial Fibrillation study, with an average of 40-50 years of performing regular endurance exercise and almost a hundred adjudicated cases of AF within reasonable travel distance from the study site, had been based on questionnaires only, the current study aimed to describe cardiac remodeling in relation to prolonged endurance exercise and AF, without claiming causal relationships regarding the mechanisms leading to AF in these athletes. We believe that even with the inherent weaknesses of the cross-sectional design, the lack of data describing cardiac size and function in older veteran endurance athletes with and without AF makes the description of the cardiac traits of this unique cohort an important addition to the understanding of EICR and AF among lifelong recreational endurance athletes.

6.1.2 Generalizability

Most participants in the Birkebeiner cross-country ski race are of North-European ancestry. This was also the case for all athletes included in Birkebeiner II. Hence, this study's results might not apply to athletes of other ethnic backgrounds. One hundred and ten of the 1449

women in the Birkebeiner Atrial Fibrillation study reported AF.[116] Most cases of AF (84%) occurred among women without any or short exposure to endurance exercise. Eighteen of the 310 women reporting cumulative endurance exercise for ≥20 years reported having AF. Only six of these could be verified. Left with six female athletes with adjudicated AF, of whom only two resided within the geographical borders of the present study, we decided to include men only.

6.1.3 Selection bias

As the study focuses on the effects of long-term endurance exercise, it may have seemed more appealing to the fittest members of the control cohort, resulting in a skewed selection of participants and diluting the effect of training in the athletic group.[113] To increase the number of participants in the control group with AF, it was supplemented with patients from an AF outpatient clinic which introduces selection bias. However, all participants recruited from the outpatient clinic resided in the same geographical area as our original control cohort, minimizing this effect.

6.1.4 Recall bias

In Articles II and III, we aimed to investigate the dose-response relationship between years of endurance exercise and cardiac remodeling. The participants reported years of regular exercise on an eight-level scale with a cut of at 60 years of exercise, as used in earlier Birkebeiner studies.[49] Thus, at least partly, the exposure occurred decades ago, and the answers were prone to recall bias risking misclassification.[117] The general population tends to overestimate their physical activity level when self-reporting.[118] If the veteran athletes in this study tend to over or underestimate their exposure to endurance exercise is not known.

6.1.5 AF measurements

AF can be asymptomatic, introducing the possibility of misclassifying individuals with asymptomatic AF to the non-AF groups.[119] Although we performed a 12-channel ECG and a one-day Holter monitoring as part of the study, we cannot exclude the possibility of misclassification among our participants as we did not perform longer-lasting heart-rhythm monitoring. In 2018 an AF screening study performed over two weeks in the same geographical area as the present study, in a similar age group (65 years of age), could only

identify 0.9% of undiagnosed AF, despite a higher median CHA_2DS_2-VASc-score of 3 among their participants.[120] This indicates a low prevalence of undiagnosed AF among the individuals included in the non-AF groups of our study. A strength of the Birkebeiner II study is that all AF diagnosis was verified according to guidelines.[35] Because the participants had no long-term continuous heart rhythm monitoring, we do not have objective control of the AF burden. Both athletes and non-athletes reported a low AF burden, with three out of four participants reporting less than one monthly episode of AF.

Even though the athletes included in Birkebeiner II had a very low cardiovascular comorbidity burden, AF prevalence increase with increasing age, prolonged endurance exercise is associated with an increase in coronary atherosclerosis, and one in four athletes included in the study had hypertension.[121] I.e., we do not know to what extent other risk factors than prolonged endurance exercise affected the development of AF among the athletes included in this study.

6.1.6 Considerations regarding echocardiographic analysis

The consensus document on atrial and RV strain by Badano et al. recommends using LA strain values from an optimized apical four-chamber view, mentioning biplane measurements as an option.[110] The main reason for recommending a single-plane view is feasibility. We chose to follow these recommendations. However, we observe that studies publishing normal values regarding LA strain still vary in the use of four-chamber or biplane LA-strain measurements.[122-124] Novel software with automated function imaging of the LA has made strain measurements more feasible. It will extend the clinical use of these parameters, increasing the importance of standardizing them.

Regarding LA MD, there are no guidelines on how to perform this measurement. Most studies calculate it as SD-TPS, which we adopted in this study.[125] The intra- and interrater coefficients regarding both structural and functional echocardiographic parameters in the articles included in this thesis were generally high. All measurements were performed in one lab, and even though there are guidelines and recommendations on how to perform these measurements, meta-analysis illustrates how normal-range for especially RA functional parameters still vary widely between studies and that there is a need for more detailed guidelines on how to measure these parameters and standardization of strain analysis software.[126] The main investigator went on several study visits to other echocardiography

labs to ensure the technique used to measure functional parameters complied with colleagues in Norway and abroad.

Endurance athletes have larger cardiac chambers and on average are slimmer than individuals from the general population. Therefore, there is a risk of introducing bias due to differences in image quality and a higher risk of foreshortening when obtaining echocardiographic images from the control group. We were aware of this risk when performing the echocardiographic examination and strove to avoid foreshortening both in the ventricles and atria, complying with guidelines and obtaining echocardiographic images focusing on one chamber at a time. In addition, to minimize the risk of atrial stunning affecting atrial function, none of the participants underwent cardioversion the last four weeks before the echocardiographic examination.

6.2 Discussion of the main results

6.2.1 Article I

In Article I, we found that LA size was highly affected by both athletic and AF status. On the other hand, LA function assessed by atrial strain was far less affected by athletic status than AF status in veteran cross-country skiers. LASr was the parameter demonstrating the best ability to identify athletes with paroxysmal AF when in sinus rhythm.

While data from younger healthy athletes had demonstrated only minute differences in LA strain values despite significant differences in LA volume, data regarding LA strain in veteran athletes are sparse.[70] Excluding the athletes with a history of AF, we found similar LA strain values in athletes and non-athletes, suggesting LA strain values to be similar in older veteran athletes and a more sedentary population of similar age, despite differences in atrial volume. This might come as a surprise, given that a larger atrium demands less deformation to produce the same stroke volume. Hence, LASr is partly defined by LA size in addition to the stiffness of the LA wall and the descent of the mitral plane towards the apex in systole represented by the LV GLS.[127] This observation is at least partly explained by a lower resting heart rate in the athletic population, giving the athletes fewer beats per minute to produce the same stroke volume, demanding a higher degree of deformation in each stroke than in the non-athletic population.

With increasing age, diastolic properties decline.[128] We found a significantly lower E/e' in athletes than non-athletes, but the differences in absolute values were modest. In addition, we observed a high LASct relative to LASr in both athletes and non-athletes compared to earlier studies in younger athletic individuals.[70, 104] During the study period of Birkebeiner II, age-specific values for atrial strain from population-based studies have been presented.[122, 123] These studies show how LASr correlates inversely with age, compensated by a rise in LASct, probably due to age-induced cardiac remodeling with reduced diastolic properties and lower atrial compliance.[122, 123] While endurance exercise seems to promote LV relaxation properties and slow the decline in diastolic properties among athletes, our data support the notion that exercise cannot prevent an age-induced decline in diastolic properties and atrial compliance in older veteran athletes.[29, 129]

$LAVI_{max}$ and $LAVI_{min}$ are associated with AF in non-athletic populations.[64, 130] We found a strong association between absolute atrial volumes and AF in both athletes and non-athletes, but as $LAVI_{max}$ and $LAVI_{min}$ were also strongly associated with athletic status, cardiorespiratory fitness needs to be taken into account when assessing LA volumes. As opposed to absolute volumes, LA strain values were less affected by athletic status but still lower in individuals with AF. This indicates LA strain measurements to be promising markers when wanting to discern physiological from pathological atrial remodeling in veteran athletes.

When it comes to the ability of atrial strain to identify athletes with paroxysmal AF when in sinus rhythm, the data material is scarce and somewhat conflicting. Comparing 27 veteran endurance athletes with AF and 30 athletes without AF with a mean age of 60 years, Hubert and colleagues found atrial strain values to have a strikingly high ability to identify athletes with paroxysmal AF, with LASr demonstrating the highest AUC of 0.957 ± 0.023.[71] A study by Trivedi et al. investigating a small group of younger more highly trained endurance athletes, however, could not identify any differences in LASr between athletes with and without paroxysmal AF.[104] In the present study, LASr was the parameter that demonstrated the best ability to identify athletes with paroxysmal AF but with a lower AUC than in the study by Hubert et al. According to the NORRE study, the lower normal limit of LASr >60 years of age was 22.7%.[123] Thirteen veteran athletes had strain values below this point, all suffering from

paroxysmal AF. Suggesting that a LASr value below this limit is a reason for further investigating the possible presence of undiagnosed paroxysmal AF in veteran athletes where there is no other apparent reason for this finding.

6.2.2 Article II

In Article II, we found a clear positive association between increasing size of the right-hearted chambers and years of reported endurance exercise with a disproportionate increase in RV size relative to LV size. Despite increasing size of the RA and RV with years of reported exercise, function assessed by strain was similar even in the group who reported ≥ 40 years of regular endurance exercise and those who never had performed regular endurance exercise. While absolute RA volumes were associated with both athletic and AF status, RASr was associated with AF status but not athletic status.

Many healthy endurance athletes have right-hearted chamber sizes exceeding the normal size for a non-athlete and even fulfilling minor and major echocardiography criteria for arrhythmogenic cardiomyopathy.[101, 107] EICR has traditionally been characterized by balanced athletic remodeling of all four cardiac chambers in contrast to the classical right-dominant arrhythmogenic cardiomyopathy phenotype, where right heart remodeling is more pronounced.[107, 131] As a consequence, strict "cut-off" values regarding RV size in athletes have been discouraged.[132] Instead of sheer size, the focus has been on function and disproportionate remodeling of the ventricles, where an RV/LV ratio >0.9 has been proposed as a possible cutoff to differentiate physiological from pathological cardiac remodeling in this group.[106, 133] However, Le Gerche and colleagues demonstrated how the thin-walled right-hearted chambers are exposed to higher wall stress and afterload during exercise than the left side, hypothesizing that greater RV loading may be matched by more pronounced RV remodeling over time.[89] As an overwhelming majority of studies regarding EICR have been conducted in younger athletes, there has been a lack of data on right heart remodeling among veteran endurance athletes.[134] Our findings with an increase in RV/LV ratio by years of reported endurance exercise support the hypothesis of more pronounced RV remodeling over time and supplement the findings of Teske and Oxborough et al. reporting a higher RV/LV ratio among veteran athletes.[135, 136] We identified an increase in RV/LV ratio by years of reported exercise among veteran endurance athletes with a mean age of 70 years,

without known arrhythmias, with preserved functional echocardiographic parameters at rest and with a proportionate remodeling within the RV itself, indicating this disproportionate remodeling to be a physiological response to prolonged exercise. However, we know there is a high prevalence of RV involvement in arrhythmias among endurance athletes.[137] We do not yet have sufficient data to conclude regarding the normal development of EICR among lifelong endurance athletes and their arrhythmia risk. When evaluating these athletes, it is essential with an integrated approach, including family history, symptoms, ECG, and multimodality imaging, not just focus on sheer size or extrapolating ratios based on echocardiographic data from younger athletes.[138]

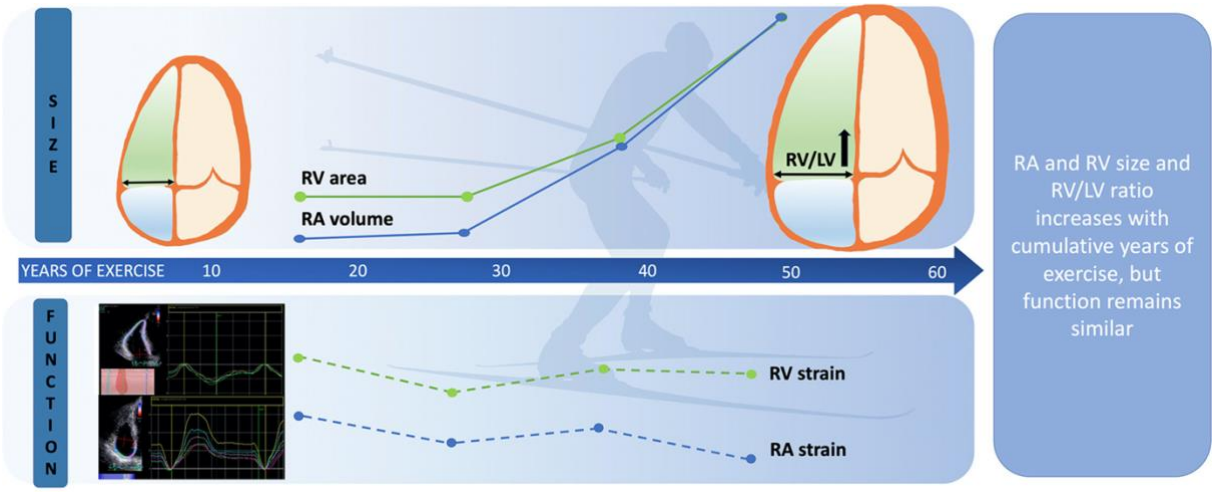

Figure 6. Graphical abstract from Article II reprinted with permission from Journal of the American Society of Echocardiography. RV, right ventricle; RA, right atria; LV, left ventricle.[139]

Several studies have reported RA dilation as part of EICR. [17, 107, 140] Our findings agree with the findings in these studies, demonstrating a positive association between years of performing endurance exercise and minimum as well as maximum RA volume. Normative data regarding RA strain in older individuals, both from the general population and among veteran athletes, are sparse. During the Birkebeiner II study, the World Alliance Societies of Echocardiography study presented age-specific normal values for RA function, indicating that RA function becomes more dependent on the contractile phase with increasing age.[141] Compared with values from a younger European cohort, we found a higher RASct regardless of athletic status in our study, supporting this notion.[142] Despite a clear association between

RA size and years of reported exercise, we could not identify a significant association between RA function and years of exercise, excluding the participants with AF. This indicates that healthy veteran athletes maintain normal RA function despite athletic remodeling. We identified a lower RASr in the AF groups regardless of athletic status, but RA strain measures had a lower ability to identify athletes with AF than LA strain measurements. This is a cross-sectional study, and even though the AF burden among the participants with known paroxysmal AF in this study was low, it is impossible to tell if the lower RA function in the AF groups causes or results from AF. Prospective studies are warranted to explore further the interplay between RA function and the development of AF.

6.2.3 Article III

In Article III, we found no significant association between athletic status and SD-TPS or reported years of exercise and SD-TPS in participants without AF, indicating that despite athletic remodeling with an increase in LA size, prolonged exercise per se did not increase LA MD assessed by echocardiography in these individuals. On the other hand, SD-TPS was associated with AF regardless of athletic status, indicating LA MD to be a promising marker of pathological atrial remodeling in endurance athletes. However, as SD-TPS did not add independent incremental value at identifying athletes with AF on top of clinical features, QRS width, LA volume, and LASr, the clinical utility of this marker in veteran endurance athletes regarding AF remains questionable.

Studies in non-athletic cohorts have demonstrated an independent incremental value of SD-TPS in predicting AF and the recurrence of AF after ablation.[76, 143] LA MD seems to increase with age, probably due to age-induced atrial myopathy.[79] As the mean age of the participants in Birkebeiner II was 70 years, it is most probable that age-induced atrial remodeling affects LA MD in the participants of this study. Prospective studies and studies including younger endurance athletes will have to answer whether LA MD can predict AF or identify athletes with paroxysmal AF at a younger age.

7 Conclusions

7.1 General conclusion

Atrial functional measures assessed by 2D speckle tracking echocardiography were associated with AF regardless of athletic status. Suggesting atrial functional parameters are more closely linked to AF than absolute volumetric atrial parameters in older veteran endurance athletes, with left atrial reservoir strain having the best ability to identify veteran athletes with AF while in sinus rhythm.

In participants without known AF, the size of all four cardiac chambers increased by years of reported endurance exercise, while functional measures assessed by 2D speckle tracking echocardiography were similar regardless of exposure to endurance exercise. Indicating cardiac function remains normal in healthy older recreational endurance athletes despite structural cardiac remodeling.

Right ventricular size increased disproportionately relative to left ventricular size by years of reported exercise, regardless of AF status and with preserved functional parameters. Indicating that increasing RV/LV ratio among older veteran athletes could be a physiological adaptation to lifelong endurance exercise.

7.2 Specific conclusions

7.2.1 Article I

LA volumes were associated with both athletic and AF status. LA function assessed by strain was associated with AF status but not with athletic status, indicating these functional measures to be promising markers when wanting to discern physiological from pathological atrial remodeling in veteran endurance athletes. LASr was the parameter demonstrating the best ability to identify athletes with paroxysmal AF.

7.2.2 Article II

RA and RV size progressively increased with years of reported exercise, with a disproportionate increase in RV relative to LV size, regardless of AF status and with preserved functional parameters. This indicates that increasing RV/LV ratio among older

veteran athletes could be a physiological adaptation to lifelong endurance exercise. RA function was associated with AF regardless of athletic status, suggesting RA functional parameters are more closely linked to AF than RA size in veteran endurance athletes.

7.2.3 Article III

LA MD was associated with AF regardless of athletic status, but not associated with years of performing endurance exercise, hence making it a potential tool when trying to distinguish pathological from physiological atrial remodeling in athletes. However, when including LASr in the model, LA MD did not add independent incremental value in identifying veteran athletes with AF, questioning its clinical utility in this group.

8 Future perspectives

8.1 Consequences of this thesis

Given that this is a cross-sectional study, we must be cautious when interpreting the results and not draw far-reaching conclusions based on this study alone. However, as there is a scarcity of echocardiographic data on older veteran athletes, both with and without AF, several of the observations made in this study are relevant to clinicians facing this group of athletes.

None of the athletes without known paroxysmal AF in this study had LASr <23%, the lower normal limit for individuals >60 years of age in the NORRE study.[123] This implies that LASr values below the age-expected normal value in older recreational athletes seem to be a marker of pathology and should be investigated until finding a reasonable explanation.

Even though some studies have identified a mild reduction in systolic RV, LV, and LA function at rest among the athletes with the highest degree of EICR, LV GLS and RVFWSL below the normal limit is an uncommon feature in younger athletes and cannot be considered a physiological response to exercise without further investigations.[70, 106, 132] Normal echocardiographic data regarding athletes >50 years of age are scarce. The data from this thesis imply that healthy older veteran endurance athletes seem to preserve normal cardiac function assessed by strain in all four cardiac chambers and that impaired cardiac function demand further investigation even in this group of athletes.

EICR is expected to be balanced between the right and left heart chambers, and a RV/LV ratio >0.9 on echocardiography has been suggested as a helpful marker regarding the limit of normality.[106, 144] Intense exercise puts a disproportionate load on the RV, and the data from the present study builds on the findings of Oxborough et al. suggesting a dose-response relationship between increasing RV/LV and years of exercise.[136] More data is needed to conclude whether or not this is a purely physiological response to prolonged exercise, but data from this thesis reminds clinicians that absolute cut-off values based on results from younger athletes might not apply to older veteran athletes.

8.2 Suggestions for future research

All three articles in this thesis focus on veteran athletes with non-permanent AF. This is also the case with similar cross-sectional studies regarding atrial function and AF among

athletes.[71, 104] Although many active endurance athletes seek rhythm control, we observed in the Birkebeiner II study that non-permanent AF progresses to permanent AF in many older veteran athletes, as is the case with other AF patients.[39] There is very little data on the long-term consequences of permanent AF in veteran athletes with EICR. This applies both to electrical, structural, and functional cardiac remodeling and would be of great interest to the clinicians advising these individuals regarding rhythm versus rate control strategy.

There is a need for prospective studies following athletes over decades to elucidate the mechanisms leading to adverse events and AF in some endurance athletes and to assess how prolonged endurance sport practice affects functional decline and morbidity in athletes with and without AF. In addition to randomized controlled trials to evaluate the effects of intense exercise on atrial function and AF burden, as well as the short and long-term impacts of detraining in athletes with AF. This is, of course, cumbersome tasks, but several large trials are now underway addressing these very questions, and time will tell if they manage to provide us with better answers to the athletes seeking advice regarding AF. [98, 145, 146]

Given the challenges researchers are facing when designing and carrying out adequately powered prospective studies regarding the mechanisms of AF in endurance athletes, there is still a need for well-designed animal studies like the studies from Aschar-Sobbi et al. and Hiram et al. exploring EICR in a controlled environment.[54, 86]

Historically the number of women performing endurance exercise over decades have been vastly outnumbered by men. Combined with a later average onset of AF in women, as well as a possible lower prevalence of AF among female athletes, this has resulted in an underrepresentation of female athletes in studies striving to study the association between prolonged endurance exercise and AF, and often too small sample sizes to provide clear cut answers. [116, 147] To remedy this, we must acknowledge the persistent sex differences in endurance sports participation, exposure, and outcomes, take advantage of the increasing number of female athletes prolonging their careers, and actively seek to include women in future studies.

Considering the limitations of the cross-sectional design, both Article II in this thesis and earlier Birkebeiner studies imply a dose-response relationship between years of performing

endurance exercise, the grade of cardiac remodeling, and the risk of AF.[49] This reminds us that not all athletes are the same and that we must be cautious when extrapolating results from one group of athletes to another. Future research needs to take this into account and perform studies both on young and old athletes, men and women, and recreational as well as professional athletes.

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Article I

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ORIGINAL PAPER

Left atrial function in male veteran endurance athletes with paroxysmal atrial fibrillation

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Aims To assess left atrial (LA) function in sinus rhythm in veteran athletes with a history of paroxysmal atrial fibrillation (AF) exposed to prolonged endurance exercise compared with veteran athletes without AF and controls with and without paroxysmal AF from a non-athletic population.

Methods and results Three hundred and two male participants from four groups, veteran recreational skiers with paroxysmal AF ($n = 62$), veteran skiers without AF ($n = 89$), and controls from a non-athletic population with ($n = 62$) and without paroxysmal AF ($n = 89$) underwent an echocardiographic examination in sinus rhythm to evaluate LA anatomy and function. The skiers (mean age 70.8±6.7 years) reported an average exposure to regular endurance exercise for 40–50 years. LA maximum and minimum volumes were larger in skiers ($P < 0.001$). LA volumes differed within the athletic and non-athletic groups with larger volumes in the AF groups ($P < 0.001$). We observed a considerable overlap in LA volumes among non-athletes with AF and athletes without AF. LA reservoir strain (33.6% ± 4.8% vs. 28.3% ± 6.7% $P < 0.001$) and contractile strain (18.3% ± 4.0% vs. 15.0% ± 5.2% $P < 0.001$) were lower in both AF groups regardless of athletic status. LA reservoir strain was superior to volumetric measurements at identifying participants with AF (area under the curve 0.740 ±0.041).

Conclusion Male veteran athletes had significantly larger LA volumes than non-athletes. In contrast, LA strain values were similar in athletes and non-athletes with paroxysmal AF, and significantly lower than in subjects without AF.

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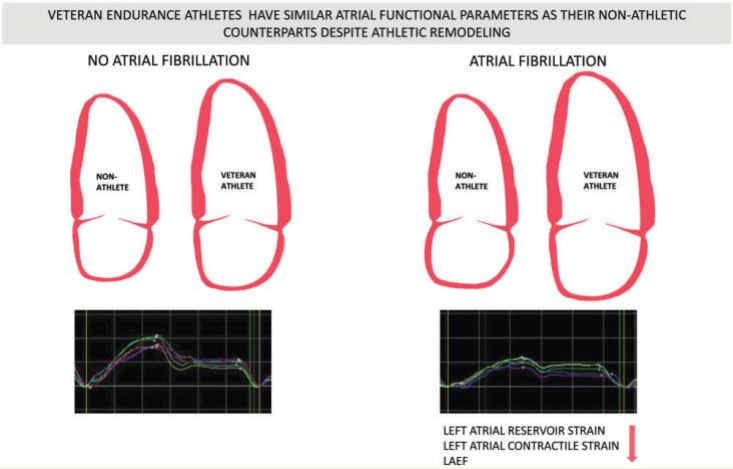
Graphical Abstract



Keywords atrial fibrillation • strain • athlete • atrium • diastolic function • exercise

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder, associated with an increased risk of stroke, heart failure, dementia, and death.[1,2] Moderate intensity exercise lowers the probability of AF, whereas prolonged endurance exercise seems to increase this risk.[3–5] Long-distance endurance races have become increasingly popular, and changes in exercise habits could cause an increased incidence of exercise-induced AF.[6]

Although not fully understood, the pathophysiology of AF in otherwise healthy athletes is likely to include exercise-related adverse cardiac adaptations, such as dilation of the atria, changes in autonomic activation, inflammation, and myocardial fibrosis.[3,7] Cardiac output increases with increasing exercise intensity.[8] Simultaneously, the relative duration of the diastole decreases, which in turn requires a high flow across the atrioventricular valves, made possible by increased atrial pressure and greater left ventricular (LV) lusitropy.[9] While younger athletes adapt to the increased demands during exercise by symmetrical enlargement of all four chambers with preserved and even enhanced diastolic properties ('athlete's heart'), diastolic function attenuate with increasing age, increasing LV filling pressures, and the load on the atria during exercise.[10,11] Improved understanding of the interplay between exercise-related cardiac remodelling and physiological remodelling promoted by aging is warranted. It may guide clinicians facing veteran athletes to distinguish physiological from pathological atrial remodelling and enable us to provide evidence-based exercise recommendations.

Over the last few years, novel echocardiographic techniques using speckle tracking to assess atrial function have emerged, and atrial function is established to be strongly associated with AF in the general population.[12,13] In athletes, however, data are limited and studies in younger elite athletes are not necessarily relevant to elderly recreational athletes.[14,15] This study is the first to investigate the atrial function and AF in a large group of elderly recreational athletes.

The main aim of this study was to investigate structural and functional characteristics of the atria in relation to AF in a cohort of male veteran endurance athletes exposed to endurance exercise over decades. The secondary aim was to assess if left atrial (LA) strain by speckle tracking echocardiography is better than volumetric measurements to identify the athletes diagnosed with paroxysmal AF.

Methods

Study population

To cover the whole range of physical activity in the population, The Birkebeiner (2012) study comprised two independent cohorts: Men who had participated in The Birkebeiner cross-country ski race (veteran recreational skiers), and men who had participated in a population-based health survey, (The Oslo Health study). Altogether 3545 men aged 53 years and older participated.[16] Aiming to investigate atrial function

related to exercise-induced AF, we invited 520 out of these to attend a cross-sectional study in 2019:134 skiers with a history of AF, 123 skiers without AF, and age and gender-matched control groups with ($n = 81$) and without ($n = 147$) a history of AF from the general population. To increase the size of the non-athletic control group with AF, every male patient at the proper age visiting the AF outpatient clinic at Diakonhjemmet Hospital between May and September 2020, were consecutively invited to participate until reaching the same number of participants as in the athletic AF-group.

The annual Birkebeiner ski race, with a course length of 54 km covering over a 1000 m uphill, has an average finishing time for the top 25% 70-year-old men of 4 h. It is regarded as one of the most challenging cross-country ski races globally and requires regular endurance exercise for preparation.

All participants answered a questionnaire and were physically examined. Regular endurance exercise was defined in the questionnaire as an exercise for ≥30 min ≥3 times a week with the purpose of increasing physical endurance capacity and reported on an 8-level ordinal scale. CHA_2DS_2-VASc score was estimated based on data from the questionnaire (age, sex, history of heart failure, hypertension, stroke, coronary heart disease, and diabetes mellitus).

We performed a resting electrocardiogram (ECG) and a 24-h Holter monitoring to assess undetected AF. A comprehensive echocardiographic examination in sinus rhythm was performed, assessing all phases of atrial function. The history of AF was verified by reviewing medical records, identifying paroxysmal AF according to guidelines.[17] As it was difficult to differentiate paroxysmal from persistent AF in 13 participants (5 athletes and 8 non-athletes), these were included as having paroxysmal AF.

The study was approved by the Regional Committee for Medical and Health Research Ethics (ref.nr: 2016/565) and complies with the Declaration of Helsinki. All participants gave informed written consent.

Transthoracic echocardiography

Resting echocardiograms were recorded by the main investigator (ES) in the left lateral decubitus position using the same digital ultrasound scanner in all participants (Vivid E9, GE Vingmed Ultrasound, Horten, Norway). We obtained 2D-greyscale, colour Doppler, and tissue Doppler images in two parasternal and three standard apical views according to recommendations.[18] Three to five consecutive loops were obtained and saved in cine loop format, including 200 ms before and after all beats.

Registrations were analysed offline (Echo PAC version 203, GE Vingmed Ultrasound, Horten, Norway) by a physician (ES) blinded for the patients' other data.

Parameters of LV size were obtained, calculated, and indexed to body surface area according to recommendations.[18]

LA 2D acquisitions were obtained from atria-focused apical views, and LA volumes were calculated by the summation of discs in apical four- and two-chamber views.[18] Maximum LA volume (LA_{max}) was measured tracing the LA inner border at end-systole on the frame before mitral valve opening, and minimum LA volume (LA_{min}) was measured at end diastole on the frame before mitral valve closing. Pre-atrial contraction volume (LA_{Pa}) was measured on the frame before atrial contraction. Atrial functional parameters were computed using the following formulas: LA ejection fraction (LAEF): $(LA_{max} - LA_{min}/LA_{max}) \times 100$; passive emptying fraction (p-LAEF): $(LA_{max} - LA_{Pa}/LA_{max}) \times 100$; LA active emptying fraction (a-LAEF): $(LA_{Pa} - LA_{min}/LA_{Pa}) \times 100$. Atrial volumes were indexed to body surface areas, and an average from three consecutive loops was computed.

Mitral inflow parameters *E*, *A*, and *E* deceleration time were assessed from an apical four-chamber view by pulsed-wave Doppler, and *E*/*A* ratio was computed from these values. Pulsed-wave tissue Doppler images were obtained, and values of early diastolic (e') velocities were assessed. E/e' was calculated from an average of septal and lateral e' velocities.[19]

Atrial stiffness was computed by dividing E/e' by peak LA reservoir strain.[20] The ratio of LA_{max} to LV end-diastolic volume (LA/LV) was computed to evaluate potentially unbalanced remodelling.[14]

Strain analysis

LV global longitudinal strain (GLS) was computed according to recommendations from apical four-chamber, two-chamber, and apical long-axis views, using the 18-segment model.[21] End-diastole was defined by the frame prior to mitral valve closure. GLS was defined as the peak negative strain during systole.

LA strain was obtained from apical four-chamber 2D views, optimized to avoid LA foreshortening, with a narrow image sector at frame rates > 60 fps. The LA border was traced from one side of the mitral annulus to the other along the endocardium. A region of interest was automatically defined, then adjusted manually to fit the thickness of the LA wall as recommended.[22] The software automatically divided the LA into six segments, scoring their tracking quality with the possibility for manual correction. All strain values were computed as the average of the accepted segments and averaged over three heart cycles. Zero strain reference was set at LV end-diastole. LA strain values are stated as LASr - LA reservoir strain, LAScd - LA conduit strain, and LASct - LA contractile strain (*Figure 1*).[22]

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) for normally distributed data. Other continuous variables are reported as median (25th–75th percentile). Categorical values are reported using frequencies and percentages. Two-way between groups analysis of variance was conducted to explore the main effects of athletic status, AF status, and the interaction between AF status and athletic status. To assess independent associations between the atrial strain parameters LASr and LASct and AF, we performed a logistic regression for each parameter. Each regression was adjusted for weight, height, CHA_2DS_2VASc score, GLS, LV mass index, $LAVI_{max}$, and E/e'. We performed a hierarchical logistic regression to evaluate the incremental value of LASr in identifying athletes with AF, LASct was excluded from this model due to collinearity.

Receiver operating curves (ROC) for atrial volumes and functional parameters were created, and areas under curves were calculated for these parameters' ability to identify athletes suffering from AF. A sensitivity analysis excluding ablated patients was performed. Reproducibility analyses were conducted offline on anonymized recordings in 15 randomly selected participants using a two-way mixed model with absolute agreement between measures. Intra-observer analysis was done by the main investigator (ES) with a 2-week interval between measurements. Inter-rater analysis was conducted by rater two (MS) separated in time and place from rater one. Analysis was performed on the same set of recordings from each participant. The raters could randomly select different pictures and loops for analysis and re-analysis. Tests with *P*-values <0.05 were considered statistically significant. All analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY, USA).

Results

Three hundred and ninety-four out of the 520 invited individuals (76%) participated in the study. After exclusion of participants with

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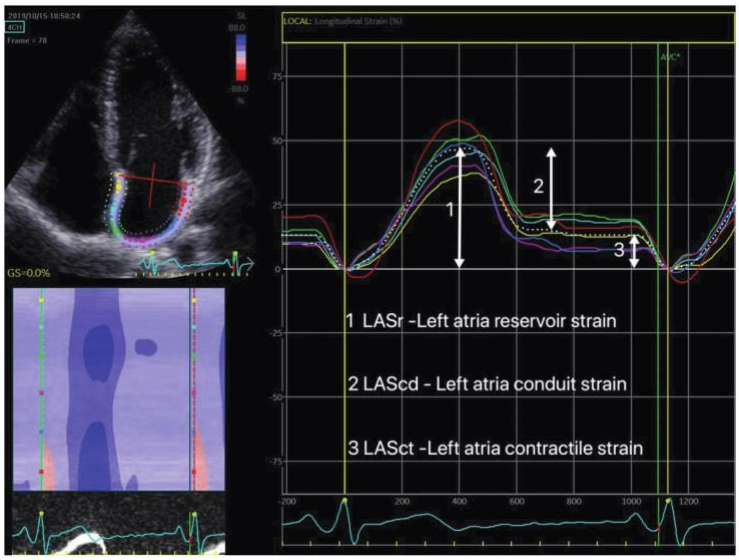

Figure 1 Left atria strain curves from apical four-chamber view. The six different segments were measured individually, and the average of accepted segments computed.

AF during the examination, supraventricular tachycardia other than AF, heart failure (EF < 35%), open-heart surgery, and clinically significant valvular disease, we included 302 participants; 62 athletes with paroxysmal AF, 89 athletes without AF, 89 non-athletes without AF, and 62 non-athletes with paroxysmal AF (*Figure 2*). We did not identify any cases of AF during resting ECG or Holter monitoring in study participants without priorly known AF.

Baseline characteristics

All participants were men with a mean age of 70.8 ± 6.7 years. Baseline characteristics are presented in *Table 1*. Athletes with and without AF reported a similar lifelong exposure to endurance sports, with an average of 40–50 years of regular endurance exercise and 16 completed Birkebeiner races. The prevalence of cardiovascular disease and risk factors in athletes was very low. AF burden was low in both athletes and non-athletes, with three out of four participants reporting less than one monthly episode of AF.

Blood pressure was similar in all groups. Individuals with AF were taller, independent of athletic status. Athletes had a lower mean body mass index. While a higher proportion of athletes had undergone AF ablation, antiarrhythmic drug use was more prevalent among non-athletes. *P*-values for the main effects of athletic status and AF status as well as the interaction effect of these parameters regarding baseline characteristics are reported in Supplementary material online, *Table S9*.

Atrial parameters

LA parameters are summarized in *Table 2*. There was no significant interaction between AF status and athletic status regarding atrial parameters. Athletes had larger atrial volumes than non-athletes ($P < 0.001$), but there were no significant differences in atrial function as assessed by strain nor LAEF between athletes and non-athletes. The AF-groups had larger atrial volumes, higher atrial stiffness, and lower atrial function as assessed both by atrial strain and dynamic volumetric parameters than the non-AF groups regardless of athletic status. LASr remained highly significantly associated with AF ($P < 0.001$) in all participants combined and in the athletic group alone after adjusting for height, weight, CHA_2DS_2VASc score, E/e', LV mass index, $LAVI_{max}$, and GLS. The sensitivity analysis excluding ablated participants demonstrated consistent results. Results are reported as Supplementary data online.

Evaluation of LA parameters in identifying AF in athletes

ROC curve analysis recognizes atrial strain parameters of the reservoir and contractile phase as best at identifying athletes suffering from AF. LASr demonstrated the highest area under the curve = 0.740 ± 0.041, slightly above dynamic volumetric measurements followed by absolute volumes (*Table 3*). *Figure 3* illustrates the independent and incremental value of LASr at identifying athletes with AF on top of clinical characteristics and standard echocardiographic parameters in a hierarchical logistic regression model. Height

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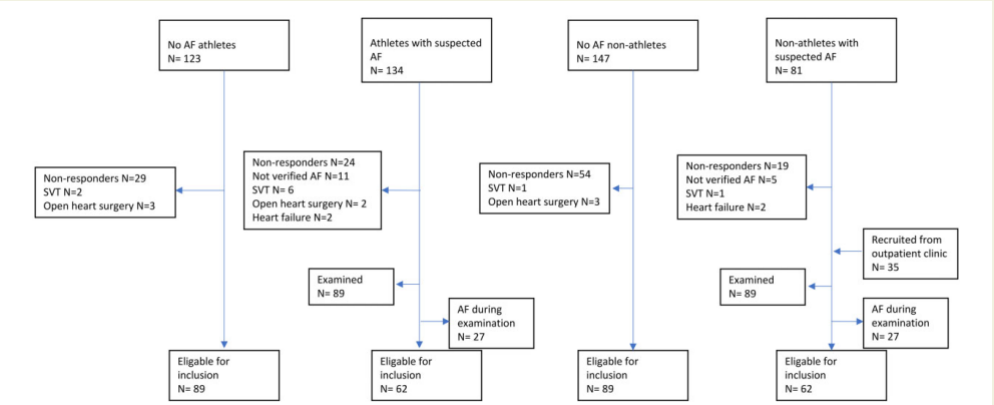

Figure 2 Recruitment of the study sample. AF, atrial fibrillation; SVT, supraventricular tachycardia.

Table 1 Baseline characteristics

	Athletes		Non-athletes	
	AF	No AF	AF	No AF
Age (years)	70.9±5.7	71.2±5.6	70.2±8.1	70.6±7.2
Weight (kg)	81.2±10.5	78.5±10.4	88.4±16.0	81.8±13.5
Height (m)	1.83±0.07	1.79±0.06	1.81±0.07	1.78±0.07
Body mass index (kg/m^2)	24.3±2.6	24.5±2.6	26.9±3.9	25.8±3.7
DBP (mmHg)	80±9	80±8	81±8	81±8
SBP (mmHg)	139±18	138±16	138±14	141±14
Heart rate (beats/min)	56±11	56±8	60±10	62±10
CHA_2DS_2-VASc score	1.6±1.1	1.5±1.1	1.9±1.4	1.6±1.4
Higher education, *n* (%)	52 (83.9)	73 (82.0)	50 (80.7)	69 (77.5)
Anti-hypertensive treatment, *n* (%)	17 (27.4)	25 (28.0)	25 (40.3)	32 (36.0)
Diabetes, *n* (%)	1 (1.6)	1 (1.1)	3 (4.8)	8 (9.0)
Current smoking, *n* (%)	1 (1.6)	1 (1.1)	3 (4.8)	1 (1.1)
Previous ablation, *n* (%)	22 (35.5)		14 (22.6)	
Beta-blocker, *n* (%)	12 19.4)		24 (38.7)	
Calsium-channel blocker, *n* (%)	1 (1.6)		4 (6.5)	
Amiodarone, *n* (%)	2 (3.2)		3 (4.8)	
Flecainid, *n* (%)	3 (4.8)		7 (11.3)	
Digoxin, *n* (%)	0 (0.0)		0 (0.0)	
Use of oral anticoagulants CHA_2DS_2-VASc score ≥ 2 (%)	19/30 (63%)		29/37 (84%)	
Use of oral anticoagulants CHA_2DS_2-VASc-score <2 (%)	13/32 (41%)		13/25 (52%)	
Number of completed Birkebeiner ski races	*Md* = 15(IQR 8–24)	*Md* = 18(IQR 9–27)		
Still participating in regular endurance exercise (%)	46 (75.8%)	68 (75.8%)	11 (17.7%)	8 (9.3%)

Values are expressed as mean±SD, *n* (%), or median (interquartile range).
DBP, diastolic blood pressure; SBP, systolic blood pressure.
CHA_2DS_2-VASc score estimated based on age, sex, CHF history, hypertension, stroke, coronary heart disease and diabetes mellitus.

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Table 2 Left atrium echocardiographic valuesP-value interaction athletic status and AF status

	Athletes		Non-athletes				
	AF	No AF	AF	No AF	*P*-value athletes vs. non-athletes	*P*-value AF vs. No AF	P-value interaction athletic status and AF status
LASr (%)	27.9±6.4	33.5±4.8	28.7±7.0	33.8±4.9	0.410	<0.001	0.673
LAScd (%)	13.4±4.9	15.4±4.0	13.3±4.0	15.3±4.5	0.788	<0.001	0.955
LASct (%)	14.6±4.5	18.1±4.1	15.5±5.8	18.5±4.0	0.215	<0.001	0.591
LAEF (%)	44.3±9.4	50.6±6.8	44.9±10.6	52.2±6.8	0.204	<0.001	0.546
$LAVI_{max}$ (mL/m^2)	52.4±15.2	45.9±10.8	44.3±11.9	38.2±8.0	<0.001	<0.001	0.867
$LAVI_{min}$ (mL/m^2)	29.7±12.3	22.9±7.2	25.0±10.0	18.3±4.8	<0.001	<0.001	0.997
LA passive emptying fraction (%)	29.0±8.6	29.7±8.1	26.1±9.6	30.2±8.8	0.247	0.020	0.090
LA active emptying fraction (%)	25.0±10.3	31.9±8.9	27.8±12.2	34.9±9.1	0.013	<0.001	0.970
LA stiffness	0.31±0.15	0.23±0.08	0.34±0.25	0.26±0.09	0.052	<0.001	0.948

Values are expressed as mean±SD. Two-way between groups analysis of variance was conducted. *P*-values for the main effects of athletic status and AF status as well as the interaction are presented in the table.
LA, left atrial; LAEF, left atrial ejection fraction; LAScd, Left atrial conduit strain; LASct, Left atrial contractile strain; LASr, Left atrial reservoir strain; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{min}$, minimum left atrial volume index.

Table 4 Left ventricular echocardiographic parameters

	Athletes		Non-athletes				
	AF	No AF	AF	No AF	*P*-value athletes vs. non-athletes	*P*-value AF vs. No AF	*P*-value interaction athletic status and AF status
GLS (%)	18.7±2.0	18.8±1.6	19.5±1.6	19.1±1.7	0.009	0.606	0.169
Ejection fraction (%)	54.4±3.5	56.2±3.7	56.8±3.5	57.1±3.8	<0.001	0.016	0.070
Peak mitral *E* wave vel (cm/s)	0.56±0.15	0.55±0.14	0.62±0.15	0.62±0.15	<0.001	0.842	0.750
Peak mitral *A* wave vel (cm/s)	0.53±0.16	0.60±0.16	0.58±0.16	0.68±0.16	<0.001	<0.001	0.525
E/A	1.1±0.37	0.94±0.22	1.2±0.54	0.95±0.25	0.427	<0.001	0.600
E/e′	8.1±2.4	7.5±2.3	8.5±2.3	8.7±2.3	0.003	0.417	0.156
Average e′ (cm/s)	7.2±1.8	7.7±1.8	7.5±1.7	7.4±1.5	0.789	0.509	0.177
EDecT (ms)	261±69	251±68	237±69	234±48	0.006	0.410	0.670
LVEDV indexed (mL/m^2)	84.9±17.5	78.6±16.8	69.1±9.5	68.2±10.0	<0.001	0.028	0.157
LVESV indexed (mL/m^2)	38.9±9.6	34.7±9.1	29.9±5.1	29.3±5.5	<0.001	0.008	0.068
LV mass index (g/m^2)	93.3±23.5	81.5±17.1	76.7±20.5	79.5±23.8	<0.001	0.075	0.004
Indexed LA/LV ratio	0.31±0.08	0.30±0.06	0.31±0.09	0.29±0.06	0.368	0.079	0.271
Stroke volume indexed (mL/beat/m^2)	46.0±8.9	44.0±8.4	39.2±5.5	38.9±5.8	0.005	0.967	0.189

Values are expressed as mean± SD. Two-way between groups analysis of variance was conducted. *P*-values for the main effects of athletic status and AF status as well as interaction are presented in the table.
AF, atrial fibrillation; EDecT, E deceleration time; EDV, end-diastolic volume; ESV, end-systolic volume; GLS, Global longitudinal strain; LA, Left atrium; LV, left ventricle.

and LV mass index provided significant incremental value, though only height was significant independent of other covariates.

Ventricular parameters

LV values are summarized in *Table 4*. There was no significant interaction between AF status and athletic status regarding ventricular parameters except for LV mass index. Volumes were larger in athletes compared with non-athletes, whereas *E/e′* was lower in athletes. LV mass index was higher in athletes than non-athletes and higher in athletes with AF than in athletes without AF. GLS was lower in athletes but unaffected by AF status.

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Table 3 Performance of atrial volumes and functional parameters at identifying athletes with AF

Variable	AUC	*P*-value
LASr	0.740±0.041	0.000
LAScd	0.623±0.049	0.012
LASct	0.706±0.043	0.000
LAEF	0.698±0.044	0.000
LA conduit fraction	0.504±0.048	0.928
LA pump fraction	0.679±0.045	0.000
$LAVI_{max}$	0.626±0.047	0.008
$LAVI_{Pa}$	0.601±0.048	0.034
$LAVI_{min}$	0.688±0.044	0.000

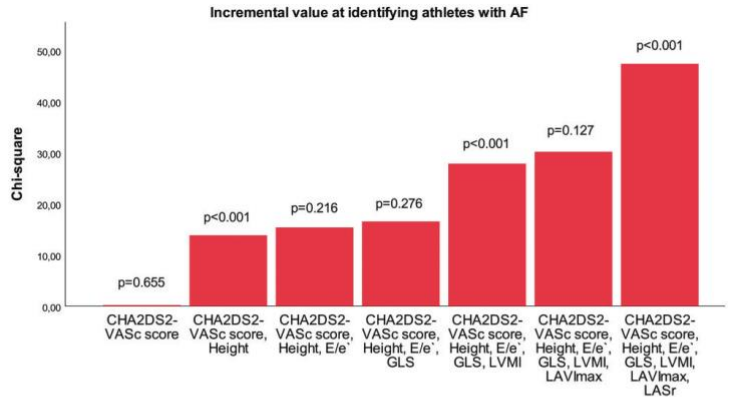
AUC, area under the curve; LAEF, left atrial ejection fraction; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; $LAVI_{max}$, maximum left atrial volume indexed; $LAVI_{min}$, minimum left atrial volume indexed; $LAVI_{Pa}$, left atrial preatrial contraction volume indexed.

Reproducibility

For $LAVI_{max}$ intra-observer intraclass correlation coefficient (ICC) was 0.985 (0.957–0.995) and inter-observer ICC was 0.984 (0.954–0.995). For $LAVI_{min}$ the corresponding numbers were 0.980 (0.922–0.994) and 0.959 (0.881–0.986). For LASr intra-observer ICC was 0.846 (0.543–0.948) and inter-observer ICC 0.893 (0.676–0.964). LAScd intra-observer ICC was 0.872 (0.614–0.956), inter-observer ICC 0.854 (0.557–0.951), and for LASct the intra-observer ICC was 0.869 (0.614–0.956) and the inter-observer ICC 0.820 (0.452–0.940). Other ICC results are reported as Supplementary data online.

Discussion

In this large cohort of male veteran recreational athletes with strong exposure to endurance exercise through several decades, we found enlarged left atria compared with non-athletes. Both athletes and



Variables in Model

	B	SE	Wald	df	Sig	Exp(B)	95% CI for Exp(B) Lower	Upper
LASr	-0.188	0.051	13.394	1	<0.001	0.828	0.749	0.916
E/e'	0.070	0.089	0.613	1	0.434	1.073	0.900	1.278
GLS (%)	0.158	0.140	1.273	1	0.259	1.171	0.890	1.540
$LAVI_{max}$ (ml/m²)	0.000	0.021	0.000	1	0.992	1.000	0.960	1.041
LVMI (g/m²)	0.016	0.013	1.556	1	0.212	1.017	0.991	1.043
Height (cm)	0.129	0.038	11.776	1	<0.001	1.138	1.057	1.225
CHA_2DS_2VASc score	0.071	0.211	0.112	1	0.738	1.073	0.709	1.625

Figure 3 Independent and incremental value of LASr at identifying athletes with AF on top of clinical characteristics (CHA_2DS_2-VASc score, height, and weight) and standard echocardiographic parameters (*E*/*e*', mitral inflow velocity and mitral annular early diastolic velocity; GLS, global longitudinal strain; $LAVI_{max}$, maximal left atrial volume indexed; LVMI, left ventricular mass index) in a hierarchical logistic regression model.

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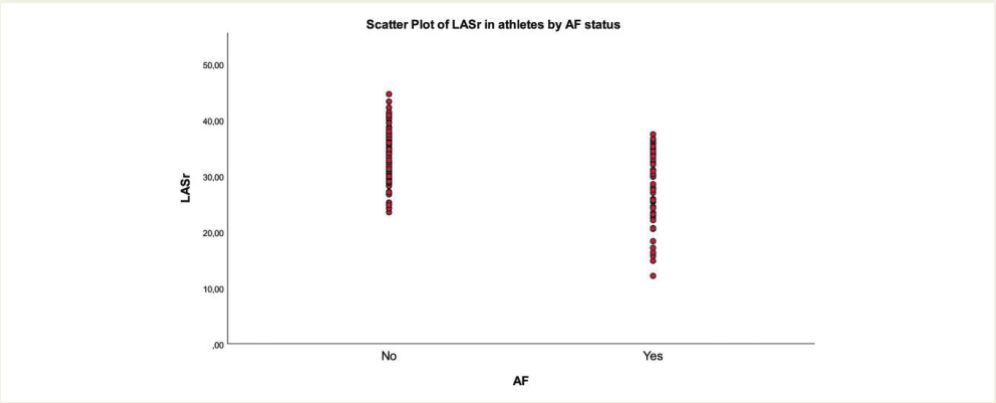

Figure 4 Scatter plot of left atrial reservoir strain (LASr) in athletes based on AF status.

non-athletes with paroxysmal AF had significantly reduced LA strain values compared with subjects without AF.

This is the first study exploring the relationship between atrial size, function, and AF in an elderly population of recreational athletes. The enlarged left atria in athletes compared with non-athletes suggests atrial remodelling due to prolonged exposure to exercise. This complies with the findings of Letnes *et al.*[23] that demonstrated how $LAVI_{max}$ increases with improved cardiorespiratory fitness, regardless of diastolic function, and how this effect augments with increasing age.

$LAVI_{max}$ and $LAVI_{min}$ are associated with AF in non-athletic populations, and we found a strong association between these parameters and AF status in athletes as well as non-athletes.[12,24] However, as $LAVI_{max}$ and $LAVI_{min}$ are also strongly associated with athletic status, cardiorespiratory fitness needs to be taken into consideration when evaluating left atrial volumes.

As opposed to absolute volumes, we found that functional parameters, both assessed by dynamic volumetric measurements and atrial strain, were less influenced by athletic status. This complies with studies of LA function in healthy athletes, showing minute differences between athletes and non-athletic controls with borderline significant lower reservoir strain and no difference in contractile strain, despite a highly significant difference in $LAVI_{max}$.[25]

Despite a higher indexed stroke volume, GLS was lower in athletes, reflecting that a larger ventricle demands less deformation to produce the same stroke volume. LV mass index was higher in athletes than non-athletes as expected and higher in athletes with AF than without AF, suggesting LV mass index as a potential co-marker of AF in athletes as seen in non-athletic populations.[26]

Diastolic properties decline with increasing age.[27] While exercise seems to promote LV relaxation properties and slow the age-related progression of diastolic dysfunction, our study supports the notion that long-term exercise does not prevent a gradual decline in resting diastolic function in athletes.[14,28,29] We identified significantly lower E/e' in athletes, but the numerical difference was slight with values close to their age-expected value.[30] In addition, we observed a high contractile strain relative to conduit and reservoir strain regardless of athletic status, concordant with findings in non-athletic populations, where age-induced atrial remodelling reduces early diastolic emptying and results in a compensatory increase in active LA function.[31,32] These findings imply that athletes cannot mitigate the impact of aging on diastolic properties and atrial compliance. To provide further insight as to whether these changes result in a lower atrial contractile reserve, studies examining atrial function in elderly athletes during exercise are warranted.

Two smaller studies have previously evaluated LA strain and AF in athletes.[14,15] In a group of younger elite athletes with AF, Trivedi *et al.*[14] found no differences in atrial strain between athletes with and without AF, but athletes with AF had normal diastolic function as opposed to their non-athletic control group with AF. Among 27 athletes with AF and a mean age of 60 years, Hubert *et al.*[15] found highly significant differences in all atrial strain parameters, with reservoir strain being the strongest identifier of AF. The age-induced cardiac remodelling in our elderly cohort may attenuate the favourable effect of exercise on diastolic properties in younger athletes, thus explaining much of the differences between the studies. The age-induced alterations in atrial strain parameters may also diminish the effect of athletic atrial remodelling and reduce the ability of atrial strain to identify AF compared to younger athletes. However, comparisons between different study populations are complicated, emphasizing the need for longitudinal studies in different athletic cohorts and caution when generalizing these results among different groups of athletes.

The majority of athletes without AF in our study surpass the upper limit of normality regarding $LAVI_{max}$ in guidelines despite having normal atrial function assessed by atrial strain.[18] This illustrates the difficulties of using $LAVI_{max}$ to identify pathological atrial remodelling in elderly recreational endurance athletes.

Even though atrial functional parameters and especially LASr prove a promising marker of atrial dysfunction in elderly endurance athletes with incremental value to clinical and conventional echocardiographic

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parameters in identifying athletes with AF, the values overlap between AF and non-AF athletes (*Figure 4*). Thus, it does not seem evident that LASr is suited to identify veteran athletes at risk of paroxysmal AF at an individual level. According to the NORRE study, the lower normal limit of LASr >60 years of age was 22.7%.[33] We found 13 athletes having strain values below this point, all suffering from paroxysmal AF. This suggests that a LASr value below this limit is a reason for further investigating the presence of undiagnosed AF in elderly athletes.

Strengths and limitations

To our knowledge, this is the most extensive study to date exploring the relationship between endurance exercise, AF, and atrial function. The study comprises a unique cohort of elderly recreational athletes with an average of 40–50 years of performing endurance exercise, making the results relevant to a large group of recreational athletes.

The study may have seemed more appealing to individuals interested in endurance exercise, hence likely to attract the fittest members of our control cohort, diluting the effect of training in the athletic group. To increase the number of participants in the control group with AF, we supplemented the control group with patients from an outpatient clinic. Finally, this is a single-centre study, consisting of men only, due to the low number of female participants in the Birkebeiner study with exercise-induced AF. Considering the increasing number of female recreational endurance athletes, future studies should strive to include women.

Conclusions

Male veteran athletes had significantly larger LA volumes than non-athletes. In contrast, LA strain values were similar in athletes and non-athletes with paroxysmal AF, and significantly lower than in subjects without AF. Our findings suggest that LA functional parameters are more closely linked to AF than volumetric parameters in veteran athletes.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Article II

Right Heart Structure and Function in Lifelong Recreational Endurance Athletes with and without Paroxysmal Atrial Fibrillation

Check for updates

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Background: Healthy young athletes adapt to the increased demands of endurance exercise with symmetric cardiac remodeling. Male veteran endurance athletes have an increased risk for atrial fibrillation (AF), and some athletes seem susceptible to changes mimicking arrhythmogenic cardiomyopathy. Intense exercise puts a disproportionate hemodynamic load on the right-sided heart chambers. Despite this, data describing right heart structure and function in older veteran athletes are scarce. The aim of this study was to investigate structural and functional characteristics of the right heart in veteran athletes with and without AF to contribute to the understanding of exercise-induced cardiac remodeling in this group.

Methods: Three hundred two male participants, of whom 151 were veteran skiers (62 with paroxysmal AF) and 151 were control subjects from the general population (62 with paroxysmal AF), underwent echocardiographic examinations in sinus rhythm to evaluate right atrial (RA) and right ventricular (RV) structure and function. While 87 of the participants had never exercised regularly, 50, 43, and 122 men had practiced regular endurance exercise for 1 to 20, 20 to 40, and >40 years, respectively.

Results: RA volume and RV size increased with cumulative years of exercise ($P < .001$), with a disproportionate increase in RV size compared with left ventricular (LV) size, regardless of AF status ($P < .001$). RA and RV function assessed by strain remained similar despite lifelong exposure to endurance exercise. AF was associated with reduced RA strain irrespective of exposure to exercise ($P < .001$).

Conclusions: RA and RV sizes and RV/LV ratio showed a dose-response relationship with cumulative years of endurance exercise, whereas RA and RV function did not, indicating that increasing RV/LV ratio may represent a physiologic adaptation to prolonged endurance exercise. AF was associated with reduced RA function, regardless of exposure to exercise, suggesting that RA functional parameters are more closely linked to AF than RA size in veteran athletes. (J Am Soc Echocardiogr 2022;35:1259-68.)

Keywords: Right atrium, Right ventricle, Athlete, Strain, Atrial fibrillation

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The health benefits of exercise are indisputable, and physical activity is inversely associated with mortality and cardiovascular disease.[1] Light and moderate physical activity reduces the risk for atrial fibrillation (AF), probably explained mainly by the beneficial effects of physical activity on major modifiable AF risk factors, such as hypertension, diabetes mellitus, and obesity.[2,3] On the other hand, extensive and prolonged endurance exercise increases the risk for AF in middle-aged and older men and seems to trigger structural changes mimicking arrhythmogenic cardiomyopathy in susceptible individuals.[3,4]

Vigorous physical activity, such as endurance exercise, demands high cardiac output and imposes increased stress on all cardiac structures.[5,6] To meet the demands of chronic endurance exercise, athletes experience structural and functional cardiac remodeling, referred to as "athlete's heart," characterized by a proportionate enlargement of all four chambers with preserved functional parameters.[7-10] The right ventricle and the atria are thin walled and adapted to a low resting load.[11] During peak exercise, right ventricular (RV) load increases dramatically and disproportionally compared with that of

Abbreviations
AF = Atrial fibrillation
CV = Coefficient of variation
ICC = Intraclass correlation coefficient
LA = Left atrial
LV = Left ventricular
RA = Right atrial
RAScd = Right atrial conduit strain
RASct = Right atrial contractile strain
RASr = Right atrial reservoir strain
$RAVI_{max}$ = Maximal right atrial volume index
$RAVI_{min}$ = Minimal right atrial volume index
RV = Right ventricular
RVFWSL = Right ventricular free wall longitudinal strain

the left ventricle.[6] This is due to a rise in pulmonary artery pressure as well as a greater increase in ventricular volumes and lesser compensation for wall stress through wall thickening than in the left ventricle.[5,6] The increased stress put on the right heart chambers during prolonged bouts of exercise can lead to a transient reduction in both right atrial (RA) and RV function.[12,13] Although recovery of function seems complete in younger athletes, it is not clear how repeated and cumulative exposure to endurance exercise over decades may affect right heart remodeling in older veteran athletes and if paroxysmal AF in veteran athletes is associated with impaired RA function.[13] Previous studies of right heart remodeling in relation to endurance exercise are conducted almost exclusively in younger athletes, with few attempts to assess dose-response relationships between prolonged exposure to exercise and right heart structure and function.[14-16] Furthermore, current recommendations do not include the athlete's age or cumulative years of exercise when evaluating right heart remodeling.[7]

There seems to be a positive dose-response relationship between cumulative years of endurance exercise and risk for AF, at least among men.[17,18] The role of right heart remodeling, however, in the development of AF in otherwise healthy endurance athletes is unclear, and the interplay among prolonged endurance exercise, aging, right heart remodeling, and AF has been scarcely studied.[19]

We aimed to investigate structural and functional characteristics of the right heart in relation to prolonged endurance exercise, explore a possible dose-response relationship between exercise and right heart remodeling, and assess RA function in a large group of recreational endurance athletes with AF and strong exposure to prolonged exercise.

METHODS

Study Population

To cover the entire range from inactivity to prolonged endurance exercise, the Birkebeiner Atrial Fibrillation study (2012) included 3,445 men aged ≥53 years, of whom 2,366 had participated in the annual 54-km Birkebeiner cross-country ski race; the remaining men had participated in a population-based health study.[18] Cross-country skiing is a highly dynamic endurance sport with high cardiovascular demand during competition, and the Birkebeiner cross-country ski race is one of the most challenging cross-country ski races globally, with a total of approximately 1,000 altitude meters.[20] Aiming to investigate cardiac remodeling in relation to prolonged endurance exercise and AF, we invited 520 men who had previously participated in the Birkebeiner Atrial Fibrillation study to attend a cross-sectional clinical study consisting of cardiac evaluation between January 2019 and October 2020. All veteran skiers with histories of AF living within a 2-hour perimeter from the study site were invited ($n = 134$), along with skiers without AF ($n = 123$) and control groups from the population-based health study in the same area with ($n = 81$) and without AF ($n = 147$). After exclusions, the groups with and without AF were age matched (Figure 1).

To increase the size of the nonathletic control group with AF, every male patient at the proper age visiting the AF outpatient clinic at Diakonhjemmet Hospital between May and September 2020 was consecutively invited to participate until reaching the same number of participants as in the athletic AF group (Figure 1). The methods of the study have been described in detail previously.[21]

All participants were physically examined and answered a questionnaire. Regular endurance exercise was self-reported and defined in the questionnaire as exercise for ≥30 min at least three times a week with the purpose of increasing physical endurance capacity and reported using an eight-level ordinal scale, in the same matter as used previously.[22]

To evaluate the dose-response relationship between years of endurance exercise and structural and functional cardiac remodeling, we condensed this scale into four categories: those who had never exercised regularly and those who had performed regular endurance exercise for 1 to 20, 20 to 40, and >40 years.

The study was approved by the Regional Committee for Medical and Health Research Ethics (2016/565) and complied with the Declaration of Helsinki. All participants gave informed written consent.

Transthoracic Echocardiography

Resting echocardiograms were recorded in the left lateral decubitus position using a commercially available digital ultrasound scanner (Vivid E9; GE Vingmed Ultrasound). We obtained images in two parasternal and three standard apical views according to recommendations.[23] Two-dimensional grayscale, color Doppler, and tissue Doppler imaging data were acquired. Three consecutive loops were obtained and saved in cine loop format, including 200 msec before and after all beats.

Images were analyzed offline (EchoPAC version 203; GE Vingmed Ultrasound) by a physician (E.S.) blinded to the patients' other data.

Parameters of left ventricular (LV) size were obtained, calculated, and indexed to body surface area according to recommendations. LV global longitudinal strain is stated as absolute values. Atrial two-dimensional acquisitions were obtained from atria-focused apical views, and atrial volumes were calculated by the summation of disks. Maximal RA volume was measured by tracing the atria inner border at end-systole on the frame before tricuspid valve opening. Minimal RA volume was measured at end-diastole on the frame before tricuspid valve closing. Atrial volumes were indexed to body surface areas, and an average from three consecutive loops was computed.[23]

Proximal RV outflow tract diameter was obtained from a parasternal short-axis view at end-diastole. RV areas and RV basal and midcavity diameters were obtained from an apical RV-focused view, and RV fractional area change was calculated.[23] Tricuspid annular plane systolic excursion was obtained by aligning the M-mode cursor with the direction of RV longitudinal excursion from an apical approach. Peak systolic velocity of the tricuspid annulus by pulsed-wave tissue Doppler imaging (S′) was obtained from an apical view. RV free wall longitudinal strain (RVFWSL) was obtained

HIGHLIGHTS

- RA and RV sizes increase with cumulative years of exercise; function remains similar.
- RV remodeling was more pronounced than LV remodeling in veteran endurance athletes.
- AF was associated with reduced RA function, regardless of exposure to exercise.

from an RV-focused apical view in compliance with recommendations and is stated as absolute values (Figure 2).[24] Early (E) and late (A) transtricuspid inflow parameters were recorded from an RV-focused apical view on pulsed-wave Doppler, and the E/A ratio was computed from these values. Pulsed-wave tissue-Doppler images were obtained, early diastolic (e′) velocities were measured at the lateral tricuspid annulus, and the E/e′ ratio was calculated.[25] The RV inflow/outflow ratio (RV basal end-diastolic diameter/RV outflow tract diameter) and RV/LV ratio (RV basal end-diastolic diameter/LV end-diastolic dimension in the parasternal long-axis view) were computed to identify asymmetric remodeling of the right ventricle.[7,26]

Atrial strain values were obtained from atria-focused apical views, optimized to avoid RA and left atrial (LA) foreshortening, at frame rates > 60 frames/sec. The atrial borders were traced from one side of the annulus to the other along the endocardium. A region of interest was automatically defined, then adjusted manually to fit the thickness of the atrial walls as recommended.[24] The software automatically divided the atria into six segments, scoring their tracking quality with the possibility for manual correction. All strain values were computed as the average of the accepted segments and averaged over three heart cycles. Zero strain reference was set at end-diastole. RA strain values measured were RA reservoir strain (RASr), RA conduit strain (RAScd), and RA contractile strain (RASct). LA strain values measured were LA reservoir strain, LA conduit strain, and LA contractile strain.[24]

Other Variables

Information on medical history, medication use, and exercise habits was gathered from self-reported questionnaires. A medical doctor (E.S.) performed anthropometric measurements, interviewed all participants, and gathered supplementary relevant information from medical journals when required. Height was measured without shoes to the nearest centimeter and weight in light clothes to the nearest kilogram. Blood pressure was measured with participants in a sitting position with cuff on arm after >5 min of rest, and an average of three measurements was reported.

Statistical Analysis

Continuous variables are reported as mean ± SD when normally distributed or as median (interquartile range) for data not normally distributed. Categorical values are reported using frequencies and percentages. To assess echocardiographic variables according to the four categories of cumulative years of endurance exercise, a one-way analysis of variance with polynomial contrasts investigating for a linear trend was conducted, both in all participants and after excluding participants with AF.

To assess the independent association between RV/LV ratio and years of cumulative exercise, we performed a multiple regression analysis with RV/LV ratio as dependent variable and confounders (age, height, and weight), competing echocardiographic exposure variables (maximal tricuspid regurgitant velocity and RVFWSL) as well as relevant comorbidities (hypertension, diabetes mellitus, history of myocardial infarction, and asthma) as independent variables.

To explore the interplay among RA function, AF, and exercise, we conducted a two-way between-group analysis of variance with athletic status (on the basis of participation in the Birkebeiner ski race) and AF status. In addition, to assess an independent association between the atrial strain parameter RASr and AF, we performed a logistic regression with AF as the dependent variable and weight, height, CHA_2DS_2-VASc score, RVFWSL, maximal RA volume index ($RAVI_{max}$), RV E/e′ ratio, and RASr as independent variables.

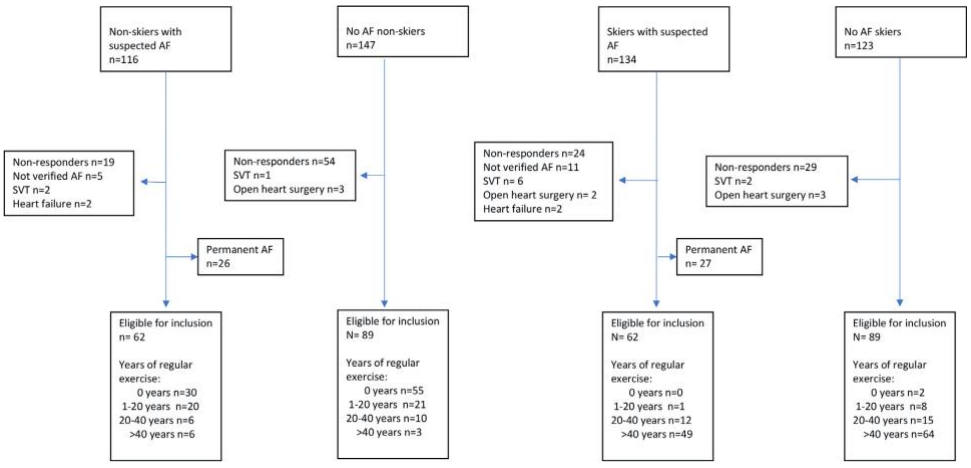

Figure 1 Recruitment of the study sample. *SVT*, Supraventricular tachycardia.

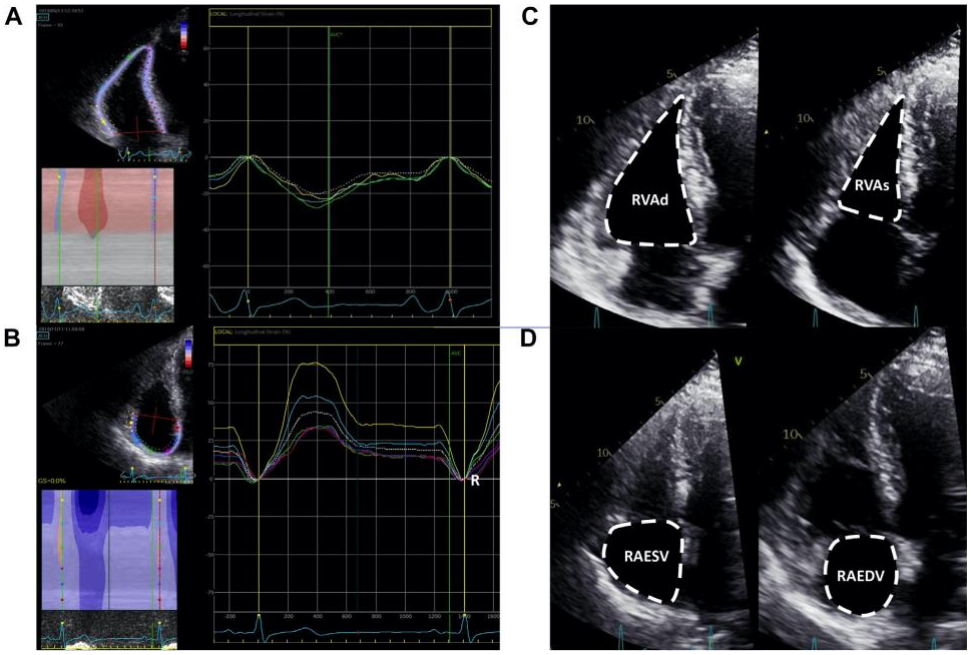

Figure 2 **(A)** RVFWSL was obtained from an RV-focused apical view. The three different segments were measured individually, and an average of the three segments was computed. **(B)** RA strain curves from an RA-focused view. The six different segments were measured individually, and the average of accepted segments was computed. **(C)** RV areas were manually traced along the endocardial border from an RV-focused apical view. **(D)** RA volumetric measurements on the basis of tracings from an RA*focused apical view using summation of disks. *RAEDV*, RA end-diastolic volume; *RAESV*, RA end-systolic volume; *RVAd*, RV end-diastolic area; *RVAs*, RV end-systolic area.

Receiver operating curves for RA and LA functional parameters were created, and areas under the curves were calculated for these parameters' ability to identify athletes with AF.

Intra- and interrater variability analyses were conducted offline on anonymized recordings in 15 randomly selected participants using a two-way mixed model with absolute agreement between measures and a coefficient of variation (CV) analysis. Intraobserver analysis was done by the main investigator (E.S.), with a 2-week interval between measurements. Interrater analysis was conducted by rater 2 (M.S.), separated in time and place from rater 1. Analysis was performed on the same set of recordings from each participant. The raters could randomly select different pictures and loops for analysis and reanalysis. Tests with P values $< .05$ were considered statistically significant. All analyses were performed using SPSS Statistics version 26 (IBM).

RESULTS

Three hundred ninety-four of the 520 invited individuals (76%) participated in the study. After exclusion of participants with heart failure (ejection fraction $< 35\%$), clinically significant valvular disease, previous open heart surgery, supraventricular tachycardia other than AF, or AF during examination, we included 302 participants: 62 recreational skiers with paroxysmal AF, 89 skiers without AF, 89 nonskiers without AF, and 62 nonskiers with paroxysmal AF. All study participants were men, with a mean age of 70.8 ± 6.7 years.

Eighty-seven of the participants had never practiced regular endurance exercise, whereas 50 participants had practiced regular endurance exercise for 1 to 20 years, 43 participants for 20 to 40 years, and 122 participants for >40 years. The skiers had completed an average of 16 Birkebeiner races, and 133 of the study participants were still engaged in regular endurance exercise.

Baseline Characteristics

Baseline characteristics are presented in Table 1. Those who had never exercised regularly were older, and those who had exercised between 1 and 20 years were younger than the other groups. Blood pressure and the prevalence of AF were similar in all groups, and the prevalence of cardiovascular risk factors was low in all groups. The group with >40 years of endurance exercise had a lower mean body mass index and fewer individuals using antihypertensive medications.

RA and RV Parameters

RA and RV parameters are presented in Table 2. RA and RV deformation imaging was feasible in 92% of the participants.

Table 1 Baseline characteristics

	Years of endurance exercise			
	0	1-20	21-40	>40
Number of participants	87	50	43	122
Age, y	71.7 ± 7.2	67.2 ± 7.2	69.6 ± 6.0	71.9 ± 5.6
Weight, kg	83.1 ± 13.9	88.6 ± 17.2	81.1 ± 10.1	78.9 ± 10.4
Height, m	1.78 ± 0.08	1.81 ± 0.06	1.80 ± 0.07	1.80 ± 0.07
Body mass index, kg/m^2	26.1 ± 3.8	26.8 ± 4.2	24.9 ± 2.4	24.2 ± 2.6
DBP, mm Hg	81 ± 9	82 ± 7	82 ± 8	80 ± 9
SBP, mm Hg	139 ± 14	141 ± 16	139 ± 16	139 ± 16
Heart rate, beats/min	61 ± 10	62 ± 9	58 ± 12	57 ± 10
AF	30 (34)	21 (42)	18 (42)	55 (45)
Higher education	69 (79)	37 (74)	36 (84)	102 (84)
Antihypertensive treatment	36 (41)	17 (34)	14 (33)	29 (24)
Diabetes	7 (8)	1 (2)	2 (5)	3 (3)
Current smoking	3 (3)	1 (2)	1 (2)	1 (1)
Previous ablation	5 (5.7)	7 (14.0)	5 (11.6)	19 (15.6)
Flecainide	3 (3.4)	3 (6.0)	0 (0.0)	4 (3.3)
Amiodarone	1 (1.1)	2 (4.0)	0 (0)	2 (1.6)
β-blocker	13 (14.9)	13 (18.0)	5 (11.6)	10 (8.2)
AF burden				
Experience AF two or more times per week	2 (6.9)	3 (14.3)	1 (5.6)	1 (1.9)
Experience AF approximately once a week	1 (3.4)	1 (4.8)	0	1 (1.9)
Experience AF one to three times a month	4 (13.8)	3 (14.3)	3 (16.7)	9 (16.4)
Experience AF less than one time a month	22 (75.9)	14 (66.7)	14 (77.8)	43 (79.6)
Exercise intensity				
Overweight of low-intensity exercise, %		42	47	39
Equal parts low- and high-intensity exercise, %		40	33	37
Overweight of high-intensity exercise, %		18	21	23
Number of completed Birkebeiner ski races	0 (0-0)	0 (0-0)	4 (0-12)	18 (10-26)
Still participating in regular endurance exercise	0 (0)	10 (20)	24 (56)	102 (84)
Age when starting regular endurance exercise, y		25.9 ± 15.0	26.3 ± 10.6	17.5 ± 6.9

DBP, Diastolic blood pressure; *SBP*, systolic blood pressure.
Data are expressed as mean ± SD, number (percentage), or median (interquartile range). AF burden is presented as a percentage of those with AF in each group.

There was a significant linear trend between cumulative years of endurance exercise and RA volumes (minimal RA volume and maximal RA volume) but not between RA functional parameters assessed by RASr, RAScd, and RASct and years of exercise (Figure 3A).

Cumulative years of exercise were associated with increasing RV end-diastolic and end-systolic areas, while RV functional parameters, assessed by RVFWSL, S′, and fractional area change, remained similar among groups. Prolonged endurance exercise was associated with a lower E/e′ ratio (Figure 3B, Table 2).

The sensitivity analysis excluding participants with AF demonstrated consistent results regarding RA and RV parameters, except for RV inflow/outflow ratio, for which the trend no longer displayed a significant linear association with years of exercise (Supplemental Table 1; *P* for linear trend = .076).

The linear trend between years of exercise and RV/LV ratio remained highly significant in the sensitivity analysis, excluding participants with AF (*P* for linear trend < .001). Furthermore, RV/LV ratio remained positively associated with years of exercise in a multiple regression model excluding participants with AF and adjusting for confounders (age, height, and weight), competing echocardiographic exposure variables (maximal tricuspid regurgitant velocity and RVFWSL), and relevant comorbidities (hypertension, diabetes mellitus, history of myocardial infarction, and asthma). These results are presented in Supplemental Table 2.

LA and LV echocardiographic values are presented in Supplemental Table 3.

RA Function According to Athletic and AF Status

RA and RV parameters according to AF status are summarized in Table 3. There was no significant interaction between athletic status and AF status regarding RA or RV parameters. Athletes had significantly larger RA volumes than nonathletes. RA functional parameters were higher in nonathletes than athletes in absolute numbers, but these

Table 2 RA and RV echocardiographic values in all participants

	Years of endurance exercise				*P* value for linear trend
	0	1-20	21-40	>40	
RASr, %	41.5 ± 7.6	44.1 ± 8.6	42.5 ± 8.2	40.6 ± 7.8	.263
RAScd, %	20.8 ± 5.2	22.4 ± 7.5	20.9 ± 6.3	20.1 ± 5.6	.244
RASct, %	20.7 ± 5.0	21.7 ± 5.8	21.6 ± 5.6	20.5 ± 5.1	.710
$RAVI_{max}$, mL/m^2	33.3 ± 13.1	33.6 ± 12.1	38.1 ± 11.9	44.9 ± 15.3	<.001
$RAVI_{min}$, mL/m^2	18.7 ± 9.1	19.4 ± 8.1	22.6 ± 7.2	26.6 ± 10.2	<.001
RVFWSL, %	27.5 ± 3.3	26.6 ± 3.3	27.0 ± 3.0	26.9 ± 4.0	.405
FAC, %	45.6 ± 4.5	45.4 ± 4.6	45.4 ± 5.3	44.5 ± 5.1	.098
RV S′, cm/sec	13.2 ± 2.2	13.1 ± 2.4	13.3 ± 2.4	13.5 ± 2.5	.228
RVAd indexed, cm^2/m^2	11.5 ± 1.9	11.5 ± 1.7	12.3 ± 1.9	13.8 ± 2.6	<.001
RVAs indexed, cm^2/m^2	6.2 ± 1.3	6.2 ± 1.1	6.7 ± 1.2	7.7 ± 1.9	<.001
RV basal diameter, mm/m^2	21.1 ± 3.2	2.0 ± 2.5	22.3 ± 2.7	23.7 ± 3.3	<.001
RV midventricular diameter, mm/m^2	14.4 ± 2.7	13.6 ± 1.9	14.6 ± 2.0	15.6 ± 2.4	<.001
RVOT, PSAX view, mm/m^2	16.7 ± 2.1	16.5 ± 2.0	17.1 ± 2.1	18.2 ± 2.6	<.001
RV/LV ratio	0.81 ± 0.12	0.78 ± .10	0.83 ± 0.11	0.86 ± 0.12	<.001
RV inflow/outflow ratio	1.27 ± 0.19	1.22 ± .15	1.31 ± 0.16	1.31 ± 0.19	.018
TR V_{max}, m/sec	2.3 ± 0.3	2.3 ± .2	2.3 ± 0.2	2.3 ± 0.3	.874
E, m/sec	0.37 ± 0.09	0.38 ± .08	0.35 ± 0.07	0.34 ± 0.09	.001
e′, cm/sec	9.2 ± 2.5	9.1 ± 2.3	9.4 ± 2.6	9.7 ± 2.4	.142
E/e′ ratio	4.4 ± 1.7	4.4 ± 1.6	3.9 ± 1.2	3.7 ± 1.2	<.001

FAC, Fractional area change; *PSAX*, parasternal short-axis; *RVAd*, RV end-diastolic area; *RVAs*, RV end-systolic area; *RVOT*, RV outflow tract; *TR* V_{max}, maximal tricuspid regurgitation velocity.
Data are expressed as mean ± SD. *P* value for linear trend was calculated in a one-way analysis of variance with polynomial contrasts.

differences were nonsignificant for all atrial strain values. Maximal RA volume and minimal RA volume were higher in the AF groups, and all atrial strain parameters were lower, regardless of athletic status. Although RV areas were larger in athletes, RV function did not differ between athletes and nonathletes, regardless of AF status.

RASr remained significantly associated with AF after adjusting for weight, height, CHA_2DS_2-VASC score, RVFWSL, $RAVI_{max}$, and E/e′ ratio. The results are presented in Supplemental Table 4. RA strain values had a lower area under the curve than LA strain values in identifying athletes with AF (Table 4).

Reproducibility

For RVFWSL, the intraobserver intraclass correlation coefficient (ICC) and CV were 0.974 and 2.2%, and the interobserver ICC and CV were 0.853 and 4.8%. For RASr, the intraobserver ICC and CV were 0.876 and 5.6%, and the interobserver ICC and CV were 0.837 and 7.4%. For RAScd, the intraobserver ICC and CV were 0.866 and 8.6%, and the interobserver ICC and CV were 0.857 and 12.6%. For RASct, the intraobserver ICC and CV were 0.869 and 7.7%, and the interobserver ICC and CV were 0.849 and 9.6%. Other reproducibility results are reported in Supplemental Tables 5 and 6.

DISCUSSION

In this large cohort of male veteran recreational skiers, RA and RV sizes increased with cumulative years of regular endurance exercise, with a disproportionate increase in RV relative to LV size. Despite athletic remodeling with larger chamber sizes, RA and RV functional parameters assessed by strain were similar in endurance athletes and those who had never performed regular endurance exercise. Both athletes and nonathletes with paroxysmal AF had significantly reduced RA strain parameters compared with subjects without AF.

RV adaptations in professional athletes are well documented.[14] Despite increased RV size, RV systolic function usually does not differ between athletes and nonathletes or among different sporting disciplines in younger athletes.[26-28] Our results agree with these findings and suggest that even lifelong endurance exercise does not significantly alter RV function.

Physiologic athletic remodeling is expected to be balanced between left and right heart chambers.[8,26] Disproportionate cardiac remodeling with an RV/LV ratio > 0.9 on echocardiography is mentioned in current recommendations as a useful limit for separating physiologic from pathologic RV remodeling in athletes.[7] In a meta-analysis proposing new reference values regarding the right heart in athletes, only one of 64 studies consisted of athletes with a mean age > 50 years.[14] In this meta-analysis, Teske *et al.*[29] found significantly higher RV/LV ratios among veteran athletes (mean age, 51 years) than among young elite athletes (mean age, 27 years). Oxborough *et al.*[27] also reported increased RV/LV ratios in healthy athletes with a mean age of 38 years, including athletes up to 71 years of age. Our results supplement this knowledge by suggesting that cumulative years of exercise may be independently associated with an increasing RV/LV ratio in older recreational endurance athletes. This supports the notion that increasing RV/LV ratio could represent a physiologic adaptation to prolonged endurance training and that the disproportionate

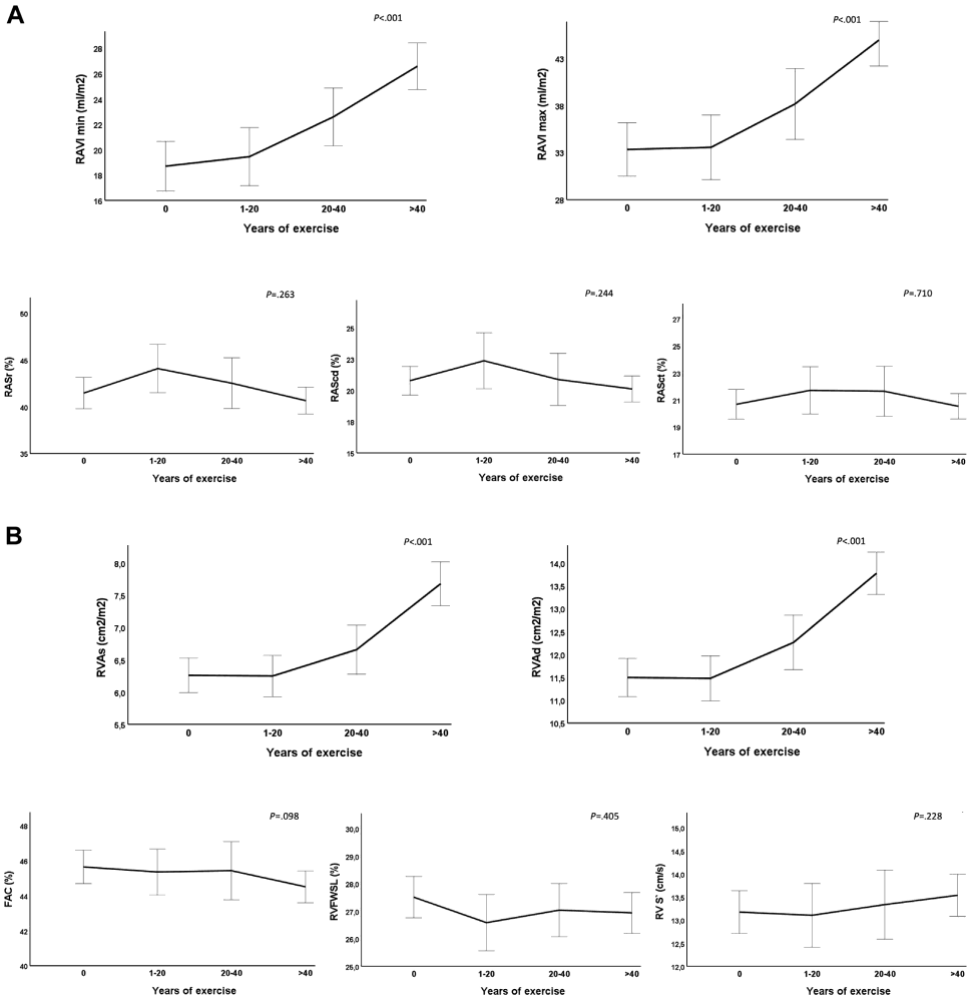

Figure 3 **(A)** Mean values of RA volumes and functional parameters according to years of exercise. *P* values for linear trends in a one-way analysis of variance (ANOVA) with polynomial contrasts. Error bars denote 95% CIs. **(B)** Mean values of RV areas and functional parameters according to years of exercise. *P* values for linear trends in a one-way ANOVA with polynomial contrasts. Error bars denote 95% CIs. *FAC*, Fractional area change; *RVAd*, RV end-diastolic area; *RVAs*, RV end-systolic area.

load put on the right ventricle during exercise results in greater RV than LV enlargement.[6] The association between increasing RV inflow/outflow ratio and cumulative years of exercise did not remain significant after excluding participants with AF, indicating a proportionate remodeling within the RV itself in healthy veteran athletes. This follows studies in younger athletes and is contrary to cardiac remodeling in arrhythmogenic cardiomyopathy, in which RV outflow tract remodeling is predominant.[7]

The results of the present study remind us of the importance of not generalizing findings in one group of athletes to other athletes. Further studies in older veteran endurance athletes are warranted to discriminate better between physiologic and pathologic cardiac remodeling in this group.

Even though most studies in athletes have focused on the left side of the heart and the right ventricle, several studies have reported dilation of the right atrium in endurance athletes as part of the athletic remodeling referred to as "athlete's heart."[10,14,16,26] In agreement with these studies, we found cumulative years of endurance exercise to be associated with an increase in $RAVI_{max}$ and minimal RA volume index ($RAVI_{min}$). Few studies have focused on RA function in athletes, but

Table 3 RA and RV echocardiographic values on the basis of athletic and AF status

	Athletes		Nonathletes		*P* value, athletes vs nonathletes	*P* value, AF vs no AF	*P* value, interaction of athletic status and AF status
	AF	No AF	AF	No AF			
RASr, %	38.9 ± 7.9	42.4 ± 7.9	40.9 ± 7.4	43.6 ± 7.9	.090	.001	.718
RAScd, %	19.1 ± 5.7	21.0 ± 5.8	20.6 ± 5.4	21.9 ± 6.5	.080	.024	.724
RASct, %	19.8 ± 6.4	21.4 ± 4.7	20.3 ± 5.4	21.7 ± 4.6	.576	.018	.888
$RAVI_{max}$, mL/m^2	44.1 ± 13.9	41.9 ± 15.8	37.6 ± 16.4	32.3 ± 9.5	<.001	.022	.341
$RAVI_{min}$, mL/m^2	26.5 ± 9.0	24.7 ± 10.3	22.0 ± 11.3	17.8 ± 6.0	<.001	.006	.263
RVFWSL, %	27.1 ± 4.1	26.5 ± 3.9	27.3 ± 3.0	27.5 ± 3.2	.179	.561	.375
FAC, %	44.7 ± 4.8	44.5 ± 5.3	45.6 ± 4.9	45.8 ± 4.4	.063	.985	.758
RV S′, cm/sec	13.6 ± 12.6	13.0 ± 2.7	13.9 ± 2.0	13.2 ± 2.2	.389	.027	.819
RVAd indexed, cm^2/m^2	13.5 ± 2.8	13.4 ± 2.4	12.1 ± 1.9	11.2 ± 1.7	<.001	.040	.106
RVAs indexed, cm^2/m^2	7.5 ± 1.9	7.5 ± 1.8	6.6 ± 1.2	6.1 ± 1.1	<.001	.116	.151
RV basal diameter, mm/m^2	23.3 ± 3.4	23.4 ± 3.4	21.1 ± 3.2	20.7 ± 2.7	<.001	.693	.511
RV midventricular diameter, mm/m^2	15.6 ± 2.4	15.3 ± 2.1	14.4 ± 2.6	14.1 ± 2.4	<.001	.305	.878
RVOT, PSAX view, mm/m^2	17.9 ± 2.3	18.3 ± 2.7	16.7 ± 2.2	16.5 ± 1.7	<.001	.727	.228
RV/LV ratio	0.84 ± 0.11	0.86 ± 0.13	0.79 ± 0.11	0.81 ± 0.11	.001	.973	.175
E, m/sec	0.33 ± 0.08	0.34 ± 0.07	0.39 ± 0.10	0.36 ± 0.08	<.001	.266	.170
e′, cm/sec	9.7 ± 2.6	9.1 ± 2.5	10.0 ± 2.4	9.0 ± 2.3	.004	.625	.558
E/e′ ratio	3.7 ± 1.3	4.1 ± 1.5	4.1 ± 1.4	4.3 ± 1.6	.088	.170	.628
TR V_{max}, m/sec	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.3	2.3 ± 0.2	.400	.416	.622

FAC, Fractional area change; *PSAX*, parasternal short-axis; *RVAd*, RV end-diastolic area; *RVAs*, RV end-systolic area; *RVOT*, RV outflow tract; *TR V_{max}*, maximal tricuspid regurgitation velocity.
Data are expressed as mean ± SD. Two-way between-groups analysis of variance was conducted. *P* values for the main effects of athletic status and AF status, as well as the interaction, are presented.

current data indicate that RASr and RASct in young, healthy athletes are comparable with but probably somewhat lower than in the general population.[30,31]

As opposed to absolute volumes, we found RA function assessed by RA strain to be less influenced by prolonged endurance exercise, and we could not identify a significant linear trend between RA strain parameters and years of exercise.

Current chamber quantification guidelines do not present normative data for RA strain.[23] Compared with values from a younger European cohort, we found slightly lower RAScd and higher RASct regardless of years of performing endurance exercise.[32] This agrees with a sizable multiethnic study demonstrating how RA function depends more heavily on the contractile phase with increasing age.[33]

Table 4 Performance of atrial volumes and functional parameters at identifying athletes with AF

Variable	AUC	*P*
LASr	0.752 ± 0.042	.000
LAScd	0.644 ± 0.050	.004
LASct	0.706 ± 0.045	.000
RASr	0.617 ± 0.048	.015
RAScd	0.582 ± 0.049	.095
RASct	0.596 ± 0.052	.065

LAScd, LA conduit strain; *LASct*, LA contractile strain; *LASr*, LA reservoir strain.

Similar findings have been done regarding the left atrium, in which LA reservoir strain and LA conduit strain decrease with increasing age and LA contractile strain increases, implying that age-induced atrial remodeling affects recreational athletes and nonathletes in the same manner.[21,34]

Prolonged endurance exercise increases the risk for AF, but the mechanisms governing this increased risk remain elusive.[17,22] Studies have demonstrated how RA function deteriorates before LA function after intense bouts of exercise, giving rise to the theory that prolonged endurance exercise might pathologically alter RA function in athletes, favoring the development of atrial arrhythmias.[12] Several conditions affecting primarily the right side of the heart, including chronic obstructive pulmonary disease, congenital heart disease, and pulmonary embolism, increase the risk for AF.[35-37] The underlying mechanisms are not well understood. However, animal studies have demonstrated how pulmonary hypertension can produce a substrate for AF in the right atrium and increase fibrous tissue content in the left atrium, suggesting that fibrosis can be caused directly by hemodynamic stress in the right atrium and remote signaling to the left atrium.[38] $RAVI_{max}$ and $RAVI_{min}$ are independently associated with AF in the general population.[39] We found $RAVI_{max}$ and $RAVI_{min}$ to be associated with AF in both athletes and nonathletes but even more strongly associated with athletic status. Both $RAVI_{max}$ and $RAVI_{min}$ were higher in athletes without AF than in nonathletes with AF, emphasizing the importance of taking athletic status into account when evaluating RA size.

To our knowledge, the only study to date assessing RA function in athletes with AF demonstrated the association between RA function

and AF to be lower than the association between AF and LA function.[40] We found RASr to be significantly lower in individuals with AF regardless of athletic status, and the association remained significant in a logistic regression model adjusting for relevant confounders. However, LA reservoir strain demonstrated a higher ability to identify athletes with paroxysmal AF than RASr. Hence, current data do not indicate RA function to be profoundly reduced compared with LA function in older endurance athletes with paroxysmal AF. The skiers in our study had a mean age of 70 years, and as AF is perceived as a biatrial disease, pathologic changes in the right atrium probably affect the left atrium over time and vice versa, leaving minor differences between LA and RA functional parameters. Longitudinal studies of endurance athletes are warranted to unravel the timeline along which atrial function deteriorates in athletes developing exercise-induced AF and if changes in RA dysfunction precede those in the left side of the heart.

Strengths and Limitations

This is the most extensive study to date exploring the relationship between prolonged endurance exercise, right heart structural and functional remodeling, and AF and the first study to demonstrate a dose-response relationship between years of endurance exercise and structural and functional right heart remodeling in older recreational athletes. The study comprises a unique cohort of athletes with decades of exposure to endurance exercise, making the results relevant to a large group of older recreational athletes.

This is a cross-sectional study, and given the design's inherent limitations, we can only describe associations between endurance exercise and cardiac remodeling. Another limitation of our study is the lack of deformation imaging during exercise.

As persons with AF and histories of prolonged exercise in the control group may have been more likely to participate in the study, and because only persons living in a certain geographic area were invited to attend, selection bias may have influenced the results.

We analyzed structural and functional right heart changes on the basis of the number of years performing endurance exercise to remedy this. Finally, this is a single-center study, consisting of men only, because of the small number of female participants in the Birkebeiner study with exercise-induced AF. As an increasing number of women are performing prolonged endurance exercise, future studies should strive to include women.

CONCLUSION

RA and RV sizes, but not RA and RV functional parameters, showed a dose-response relationship with cumulative years of endurance exercise in veteran recreational endurance athletes. RV remodeling seemed to be more pronounced than LV remodeling in men exposed to prolonged endurance exercise. AF was associated with reduced RA function, regardless of exposure to endurance exercise, and RA strain seems to be more closely related to AF in veteran athletes than absolute atrial volumes.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2022.06.008.

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Article III

Title Page

Title: Left atrial dyssynchrony in veteran endurance athletes with and without paroxysmal atrial fibrillation

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Ethics approval statement: The study complies with the Declaration of Helsinki and is approved by the Regional Committee for Medical and Health Research Ethics (ref.nr: 2016/565).

Patient consent statement: All participants gave written consent.

Clinical trial registration: The study is registered at ClinicalTrials.gov (NCT 03741491)

Abstract:

Background: Prolonged endurance exercise increase the risk of atrial fibrillation (AF) in men. Functional parameters may help separate physiological from pathological atrial remodeling in athletes. LA mechanical dispersion (LA MD) is associated with AF in the general population, but the associations between prolonged exercise, LA MD and AF are not known.

Purpose: To describe LA MD in veteran athletes with and without paroxysmal AF (pAF) and to investigate LA MD's ability to identify veteran athletes with pAF.

Methods: Two hundred and ninety-three men, skiers with (n=57) and without (n=87) pAF, and controls with (n=61) and without pAF (n=88) underwent an echocardiographic exam in sinus rhythm. LA reservoir strain (LASr) was measured, and LA MD defined as the standard deviation of time-to-peak strain (SD-TPS).

Results: Skiers (mean age 70.9±5.7 years) reported an average of 40-50 years of endurance exercise. LA volumes were associated with pAF and athletic status ($p<0.001$). SD-TPS was associated with pAF ($p<0.001$) but not athletic status ($p=0.173$). We found no significant trend between years of exercise and SD-TPS in individuals without AF ($p=0.846$). SD-TPS did not add incremental value in identifying athletes with pAF in addition to clinical markers, QRS width, LA volume, and LASr ($p=0.056$).

Conclusion: LA MD was associated with pAF regardless of athletic status but not related to years of endurance exercise, suggesting LA MD could be a promising marker of pathological atrial remodeling in athletes. However, we found no incremental value of LA MD identifying athletes with pAF when LASr was included in the model.

Keywords: Atrial fibrillation, strain, left atrium, exercise, Athletes heart

Abbreviations: AF, atrial fibrillation; LA, left atrium; $LAVI_{max,}$ maximal left atrial volume indexed; LA MD, left atrial mechanical dispersion; SD-TPS, standard deviation of time-to-peak strain; LASr, left atrial reservoir strain; LV, left ventricle/left ventricular; GLS, global longitudinal strain; XC, cross-country;

Introduction:

Exercise is beneficial for a wide range of diseases and associated with lower cardiovascular morbidity and mortality.[1, 2] When it comes to atrial fibrillation (AF), however, the effect of exercise is ambiguous. While exercise of low and moderate intensity and duration lowers the risk of AF, prolonged endurance exercise is associated with an increased risk of AF in men.[3-6] To accommodate the increased demands of exercise, endurance athletes experience structural, functional, and electrical cardiac remodeling referred to as the "athlete's heart".[7] While cardiac remodeling is a physiological response to exercise, the athlete's heart shares several common features with pathologically remodeled hearts, and to separate physiological from pathological atrial remodeling in athletes is a challenging task.[8, 9] Current knowledge indicates that functional measures obtained by speckle-tracking echocardiography could be more helpful than mere size when trying to differentiate physiological from pathological atrial remodeling in veteran endurance athletes. However, data is sparse and somewhat conflicting.[9-12] Studies assessing atrial function in athletes with AF have focused on left atrial (LA) strain values.[10-13] Speckle-tracking echocardiography can also be used to measure the timing of atrial contraction. LA mechanical dispersion (LA MD), defined by the standard deviation of time-to-peak strain (SD-TPS), is a marker of electromechanical atrial function. It is reported to be a novel predictor of AF in the general population, linked to the recurrence of AF after catheter ablation, and associated with stroke among AF patients.[14-17] Watanabe et al. found an association between increased LA MD and low voltage zones recognized by voltage mapping in paroxysmal AF patients indicating regional fibrosis in the LA wall.[18] There has also been a report of increased atrial fibrosis assessed by magnetic resonance imaging (MRI) in a group of healthy veteran endurance athletes, linking long-term endurance exercise to increased atrial fibrosis.[19] Still, the impact of long-term endurance exercise on LA MD, the interplay between AF, endurance exercise, aging, and LA MD, and the ability of LA MD to identify athletes with paroxysmal AF in sinus rhythm have yet to be investigated.

The main aim of this study was to investigate LA MD in veteran endurance athletes with and without AF and to evaluate the ability of LA MD to identify veteran athletes with paroxysmal AF when in sinus rhythm.

Material and methods:

Study population:

Cross-country (XC) skiing ranks among the sports with the highest cardiovascular demands and profound cardiac remodeling.[20] The Norwegian Birkebeiner XC ski race is one of the world's most demanding XC ski races, with a course length of 54 km, covering approximately 1000 altitude meters. Previous studies have demonstrated how participation in the Birkebeiner XC ski race is associated with athletic cardiac remodeling and an increased risk of AF.[4, 13, 21] To cover the whole range of physical activity in the population, the Birkebeiner Atrial Fibrillation study (2012) comprised two independent cohorts; one cohort consisting of persons who had completed the Birkebeiner XC ski race, and another cohort of individuals that had participated in a population-based health survey (The Oslo Health study).[4] With the aim to investigate athletic cardiac remodeling in relation to AF, we invited 520 former participants in the Birkebeiner Atrial Fibrillation study to participate in a cross-sectional clinical study performed between January 2019 and October 2020. All veteran skiers with AF living within a 2-hour perimeter from the study site were invited. Participants with supraventricular tachycardia other than AF, prior open-heart surgery, heart failure (EF <35%), or clinically significant valvular disease were excluded. Veteran skiers without AF, age-matched to the included skiers with AF, were invited until reaching the same number of included skiers with and without a history of AF. Age-matched participants from the non-athletic cohort with and without a history of AF were consecutively invited until reaching the same number of included individuals in all four groups. Because the original study cohort lacked age-matched non-athletic controls, the group of non-athletes with AF was supplemented by male patients visiting the AF outpatient clinic at Diakonhjemmet Hospital between May and September 2020. All patients were screened, and men of the proper age were consecutively invited to participate. Participants with AF during the examination, paced rhythm, or left bundle branch block were excluded from the current analysis (Figure 1). The methods of the study have been described in detail earlier.[10]

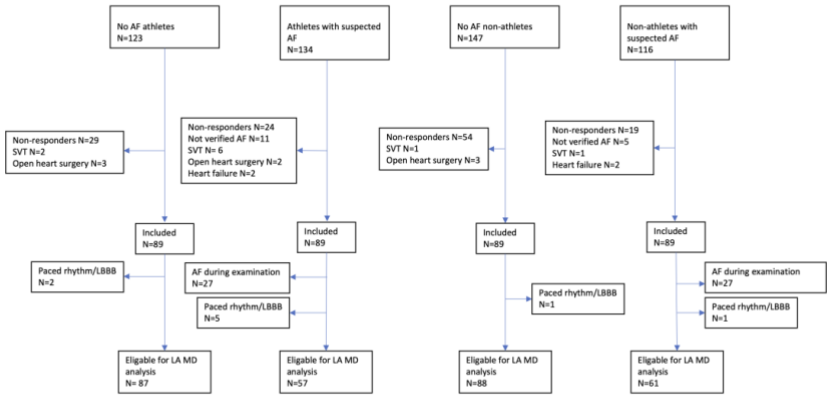

Figure 1
Recruitment of the study sample. AF = atrial fibrillation, SVT = supraventricular tachycardia, LA MD = left atrial mechanical dispersion, LBBB = left bundle branch block

All participants answered a questionnaire and underwent physical examination by the main investigator (ES). Data from the questionnaire (age, sex, history of heart failure, hypertension, stroke, coronary heart disease, and diabetes mellitus) were used to estimate the CHA_2DS_2-VASc score as a marker of cardiovascular risk.[22] History of regular endurance exercise was self-reported in the questionnaire on an eight-level ordinal scale by all participants. To evaluate the dose-response relationship between years of endurance exercise and LA MD, we condensed this scale into four categories in the same matter used previously.[13]

A 12-lead electrocardiogram (ECG) was obtained and exported in digital format for offline processing using standard Glasgow algorithm with automatic identification of fiducial points, intervals and amplitudes of the components of the PQRST-complex.[23] We affirmed the history of AF by review of medical journals, adjudicating AF according to guidelines.[24] In 13 participants (5 athletes and 8 non-athletes), it was challenging to differentiate paroxysmal AF from persistent AF, these were included as having paroxysmal AF.

The study complies with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (ref.nr: 2016/565). All participants gave written consent.

Transthoracic echocardiography:

Resting echocardiograms were recorded in the left lateral decubitus position by the main investigator (ES) using the same digital ultrasound scanner in all participants (Vivid E9, GE Vingmed Ultrasound, Horten, Norway). We obtained 2D-greyscale, tissue Doppler, and color Doppler images in parasternal and apical views according to recommendations.[25] Three to five consecutive loops were obtained and saved in cine loop format, including 200 milliseconds (ms) before and after all beats.

The main investigator (ES) performed all analysis offline (Echo PAC version 203, GE Vingmed Ultrasound, Horten, Norway), blinded to the patients' other data.

Conventional parameters of left ventricular (LV) size were obtained, calculated, and indexed to body surface area according to recommendations.[25] We obtained LA 2D acquisitions from atria-focused apical views. LA volumes were calculated by the summation of discs in apical four- and two-chamber views.[25] Atrial volumes were indexed to body surface areas, and an average from three consecutive loops was computed.

Strain analysis:

We assessed strain parameters by speckle-tracking echocardiography. LV global longitudinal strain (GLS) was computed from apical four-chamber, two-chamber, and long-axis views using the 18-segment model.[26] GLS was defined as the peak negative strain during systole.

LA strain was obtained from LA-focused apical four-chamber 2D views at frame rates >60 frames per second. The LA border was traced along the endocardium from one side of the mitral annulus to the other, and a region of interest was automatically defined, then adjusted manually as recommended to fit the thickness of the LA wall.[27] The software divided the LA into six segments, scoring tracking quality with the possibility of manual correction. Zero strain reference was set at LV end-diastole, defined by the frame prior to mitral valve closure. LA strain values were computed as the average of accepted atrial segments averaged over three heart cycles and stated as LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct).[27] SD-TPS was calculated as the mean value of the time-to-peak strain in the six atrial segments. SD-TPS was calculated separately

in three consecutive loops, and an average of these values is reported. In addition to crude SD-TPS in ms, SD-TPS was also corrected by the cycle length and expressed as a percentage of the cardiac cycle SD-TPS (%) = ($\frac{SD-TPS(ms)}{Cycle\ length(ms)}\ X\ 100$). A higher value of SD-TPS reflects a higher degree of LA MD (Figure 2).

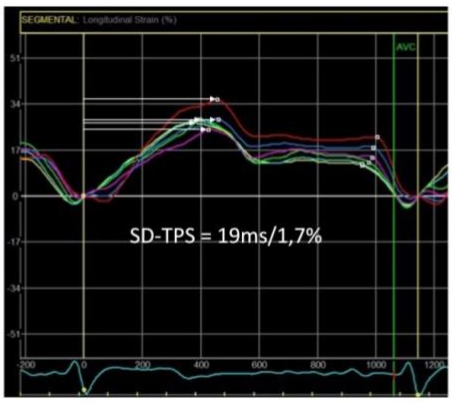

Figure 2
Left atrial strain curves obtained from an atria-focused apical 4-chamber view. Left atrial mechanical dispersion was defined as the standard deviation of the time to peak strain (SD-TPS). The white arrows indicate time to peak strain for the six different atrial segments. An average from three consecutive loops was computed.
SD-TPS = standard deviation of the time to peak strain

Statistical analysis:

Normally distributed continuous variables are reported as mean ± standard deviation, other continuous variables are reported as median (25^{th}-75^{th} percentile). Categorical variables are reported using frequencies and percentages.

Reproducibility analyses were conducted offline on 15 randomly selected anonymized recordings using a two-way mixed model with absolute agreement between measures. The main investigator (ES) performed intra-observer analysis with a two-week interval between measurements. Rater two (MGS) conducted inter-rater analysis, separated in time and place from rater one, on the same set of recordings from each participant. The raters could select different pictures and loops randomly for analysis and re-analysis.

To explore the interplay between AF, athletic status, and echocardiographic values, we conducted a two-way between-groups analysis of variance with athletic status and AF status

as independent variables, a sensitivity analysis excluding participants with prior AF ablation was also performed. In addition, a one-way analysis of variance with polynomial contrasts investigating for a linear trend between SD-TPS and years of regular exercise was performed in all participants without a history of AF to explore the associations between prolonged endurance exercise and LA MD.

To assess the association between AF and SD-TPS, we performed a logistic regression analysis with AF as the dependent variable, adjusting for weight, height, CHA_2DS_2-VASc score, GLS, QRS width, and indexed maximal LA volume ($LAVI_{max}$) in all participants and in athletes. We also performed a hierarchical logistic regression adding LASr to the model to evaluate the independent incremental value of SD-TPS in identifying athletes with AF.

Tests with *P*-values <0.05 were considered statistically significant. All analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY).

Results:

Of 520 invited individuals, 394 (76%) met for examination. After exclusions, 57 athletes with paroxysmal AF, 87 athletes without AF, 88 non-athletes without AF, and 61 non-athletes with paroxysmal AF were included (Figure 1).

Baseline characteristics: All participants were men, with a mean age of 70.7 ± 6.7 years. Athletes with and without AF reported a median of 40-50 years of performing regular endurance exercise and a median of 16 completed annual Birkebeiner XC-races. Eighty-six participants had never practiced regular endurance exercise, whereas 49 participants had practiced regular endurance exercise for 1 to 20 years, 43 participants for 20 to 40 years, and 115 participants for >40 years. An overview of reported years of performing regular endurance exercise among athletes and non-athletes is reported as supplementary data (Table S1). Almost 80% of the athletes still participated in regular endurance exercise at the time of examination, the last 20% stopped participating in the Birkebeiner cross-country ski race at a median age of 60 years. Athletes had a very low comorbidity burden, a lower BMI and a lower resting heart rate than non-athletes. Blood pressure was similar between all four groups. Individuals with AF were taller than those without AF. The AF burden was low in both AF groups, with more than three out of four individuals experiencing paroxysms of AF less than once a month. While a higher proportion of athletes had performed AF ablation,

the use of antiarrhythmic drugs was higher among non-athletes (Table 1). Statistical comparisons of baseline characteristics are reported as supplementary material (Table S2).

Table 1 Baseline characteristics

	Athletes		**Non-athletes**	
	AF	**No AF**	**AF**	**No AF**
Age (years)	70.5 ± 5.7	71.3 ± 5.7	70.1 ± 8.1	70.6 ± 7.2
Weight (kg)	80.4 ± 10.3	78.6 ± 10.5	88.7 ± 16.0	82.1 ± 13.5
Height (m)	1.83 ± 0.07	1.79 ± 0.06	1.81 ± 0.07	1.78 ± 0.07
Body mass index (kg/m^2)	24.0 ± 2.5	24.6 ± 2.6	26.9 ± 4.0	25.8 ± 3.7
DBP (mmHg)	80 ± 9	80 ± 8	81 ± 8	81 ± 8
SBP (mmHg)	138 ± 19	138 ± 16	138 ± 14	141 ± 14
Heart rate (beats/min)	55 ± 11	56 ± 8	60 ± 11	62 ± 10
CHA_2DS_2-VASc score	1.5 ± 1.0	1.5 ± 1.1	1.8 ± 1.4	1.6 ± 1.4
Higher education, *n* (%)	49 (86.0)	72 (81.8)	49 (80.3)	67 (77.0)
Anti-hypertensive treatment, *n* (%)	13 (22.8)	25 (28.4)	24 (39.3)	32 (37.0)
Diabetes, *n* (%)	1 (1.7)	1 (1.1)	3 (4.9)	5 (5.7)
Current smoking, *n* (%)	1 (1.8)	1 (1.1)	3 (4.9)	1 (1.1)
Previous ablation, *n* (%)	20 (35.1)		14 (23.0)	
Beta-blocker, *n* (%)	9 (15.8)		23 (37.7)	
Calsium-channel blocker, *n* (%)	1 (1.8)		4 (6.6)	
Amiodarone, *n* (%)	1 (1.8)		2 (3.3)	
Flecainide, *n* (%)	2 (3.5)		7 (11.5)	
Digoxin, *n* (%)	0 (0.0)		0 (0.0)	
Use of oral anticoagulants CHA_2DS_2-VASc score ≥ 2 (%)	15/26 (58%)		30/36 (83%)	
Use of oral anticoagulants CHA_2DS_2-VASc-score <2 (%)	12/31 (39%)		13/25 (52%)	
Number of completed Birkebeiner ski races	$Md = 14$ (IQR 8, 23)	$Md = 18$ (IQR 10, 26)		
Still participating in regular endurance exercise (%)	45 (78.9%)	68 (77.3 %)	11 (18.0%)	8 (9.2%)
Age at last Birkebeiner race among those no longer participating in regular endurance exercise (years)	$Md = 60$ (IQR 53, 65)	$Md = 60$ (IQR 53, 64)		

Values are expressed as mean±SD, n (%), or median (interquartile range)

DBP=Diastolic blood pressure, SBP=Systolic blood pressure. CHA_2DS_2-VASc score estimated based on age, sex, CHF history, hypertension, stroke, coronary heart disease and diabetes mellitus.

Echocardiographic parameters: LA echocardiographic parameters are presented in Table 2, and LV echocardiographic values are presented as supplemental material (Table S3).

Table 2 Echocardiographic values

	Athletes		Non-athletes				
	AF	**No AF**	**AF**	**No AF**	**P-value athletes vs. non-athletes**	**P-value AF vs No AF**	**P-value interaction athletic status and AF status**
SD-TPS (ms)	35.0 ± 16.9	27.8 ± 13.9	38.7 ± 19.1	29.6 ± 16.9	0.173	<0.001	0.642
SD-TPS (%)	3.2 ± 1.6	2.6 ± 1.4	3.8 ± 2.0	3.1 ± 2.0	0.008	0.003	0.732
$LAVI_{max}$ (ml/m^2)	51.8 ± 14.6	45.6 ± 10.4	44.5 ± 11.8	38.3 ± 8.0	<0.001	<0.001	0.997
$LAVI_{min}$ (ml/m^2)	28.8 ± 10.9	22.8 ± 7.0	25.1 ± 10.1	18.3 ± 4.8	<0.001	<0.001	0.707
LASr (%)	28.4 ± 6.1	33.6 ± 4.9	28.7 ± 7.1	33.7 ± 4.9	0.731	<0.001	0.941
LAScd (%)	13.9 ± 4.7	15.4 ± 4.1	13.3 ± 4.0	15.3 ± 4.5	0.788	<0.001	0.955
LASct (%)	14.7 ± 4.6	18.1 ± 4.1	15.5 ± 5.9	18.5 ± 4.1	0.273	<0.001	0.630
LAEF (%)	44.9 ± 8.8	50.5 ± 6.9	44.9 ± 10.7	52.2 ± 6.7	0.400	<0.001	0.361
LA stiffness	0.30 ± 0.14	0.23 ± 0.08	0.34 ± 0.25	0.26 ± 0.09	0.052	<0.001	0.948

Values are expressed as mean±SD. A two-way between-groups analysis of variance was conducted. P-values for the main effects of athletic status and AF status as well as the interaction are presented in the table. Atrial stiffness was computed by dividing E/e' by LASr.

SD-TPS = standard deviation of time to peak strain, LASr = left atrial reservoir strain, LAScd = left atrial conduit strain, LASct = left atrial contractile strain, $LAVI_{max}$ = maximum left atrial volume index, $LAVI_{min}$ = minimum left atrial volume index

There was no significant interaction between athletic status and AF status regarding atrial parameters. LA size was associated both with athletic status and AF status. SD-TPS stated in ms was associated with AF status but not athletic status. When correcting SD-TPS by the R-R interval, we found SD-TPS (%) to be associated with both athletic and AF status. LASr, LAScd, and LASct were lower in the AF groups regardless of athletic status. A sensitivity analysis excluding participants with a history of AF ablation demonstrated consistent results, these results are presented as supplementary data (Table S4). As opposed to $LAVI_{max,}$ we could not identify any significant trend between years of performing endurance exercise and SD-TPS in individuals without a history of AF (p=0.893) (Figure 3).

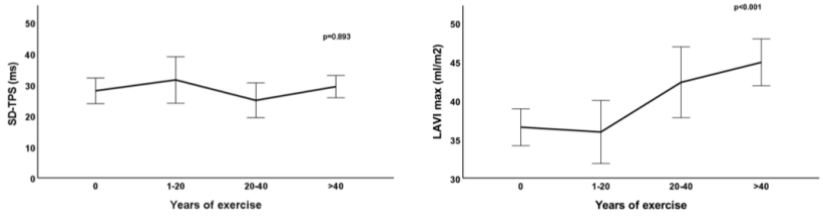

Figure 3
Mean values of left atrial mechanical dispersion defined by standard deviation of the time to peak strain and left atrial maximal volume according to years of exercise with 95% CI error bars. P-value for a linear trend in a one-way analysis of variance (ANOVA) with polynomial contrasts.
SD-TPS = standard deviation of the time to peak strain, $LAVI_{max}$ = maximal left atrial volume indexed

SD-TPS remained significantly associated with AF after adjusting for height, weight, CHA_2DS_2-VASc score, $LAVI_{max}$, GLS, and QRS width in all participants and the athletic group alone (Table S5 and S6). However, SD-TPS did not remain significantly associated with AF in athletes when LASr was included in the model (p=0.06) (Table S7). Hence, in a hierarchical logistic regression model, SD-TPS did not add independent incremental value in identifying individuals with AF on top of clinical characteristics, CHA_2DS_2-VASc score, QRS width, standard echocardiographic values, and LASr (Figure 4).

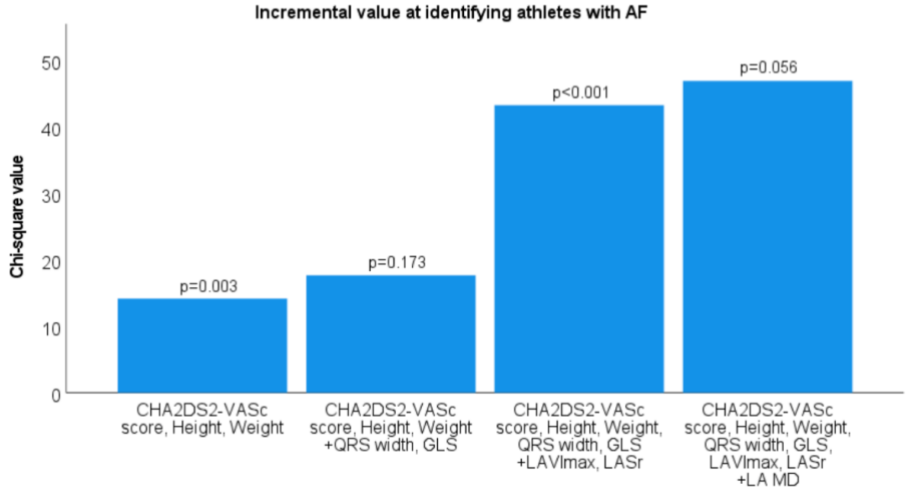

Figure 4
Independent incremental value of SD-TPS at identifying athletes with AF on top of clinical characteristics (CHA_2DS_2-VASc score, height, and weight), left ventricular parameters (QRS width and GLS) and left atrial parameters ($LAVI_{max}$ and LASr) in a hierarchical logistic regression model.
ST-TPS = standard deviation of the time to peak strain, GLS = global longitudinal strain, $LAVI_{max}$ = maximal left atrial volume indexed, LASr = left atrial reservoir strain

Athletes had larger left ventricles and slightly lower GLS and E/e` than non-athletes. There were no significant interactions between AF and athletic status regarding LV values except for LV mass index. GLS was not significantly affected by AF status.

Reproducibility:

For SD-TPS intra-observer intraclass correlation coefficient (ICC) was 0.935 (0.812-0.978), and the inter-observer ICC was 0.932 (0.803-0.977). $LAVI_{max}$ intra-observer ICC was 0.985 (0.957-0.995) and inter-observer ICC 0.984 (0.954-0.995). For $LAVI_{min,}$ the corresponding numbers were 0.980 (0.922-0.994) and 0.959 (0.881-0.986). For LASr, intra-observer ICC was 0.846 (0.543-0.948) and inter-observer ICC 0.893 (0.676-0.964). LAScd intra-observer ICC was 0.872 (0.614-0.956), inter-observer ICC 0.854 (0.557-0.951), and for LASct the intra-observer ICC was 0.869(0.614-0.956) and the inter-observer ICC 0.820 (0.452-0.940).

Discussion: The main finding of this study is that LA MD was associated with paroxysmal AF regardless of athletic status and not associated with years of performing endurance exercise, despite extensive cardiac remodeling among those reporting the longest history of endurance exercise. However, LA MD had no independent incremental value in identifying veteran athletes with a history of AF on top of clinical markers, other relevant echocardiographic variables, and LASr.

Due to promising results in its ability to identify patients with paroxysmal AF when in sinus rhythm, association with atrial fibrosis on MRI, and ability to identify electrical remodeling regardless of LA size, LA MD has emerged as an interesting marker when evaluating LA remodeling in athletes.[18, 28, 29] The present study is the first to investigate the associations between LA MD, prolonged endurance and AF in a large group of veteran endurance athletes.

Most studies of LA MD have defined the parameter as SD-TPS corrected by the R-R interval (%) instead of the crude SD-TPS value in ms.[14, 17, 28, 30] Endurance athletes experience exercise-induced bradycardia and as expected, the athletes in the present study had a lower resting heart rate than the non-athletic group.[31] Hence, we introduced an association between athletic status and LA MD when correcting SD-TPS by the R-R interval. Consequently, we chose to focus on SD-TPS in ms in this study and suggest stating the crude SD-TPS values in ms as well as SD-TPS (%) when investigating LA MD in endurance athletes.

An MRI study by Peritz et al. suggested an association between long-term endurance exercise and atrial fibrosis among a small group of healthy athletes, and LA MD has been demonstrated to associate with LA fibrosis on MRI.[19, 29] We found no association between years of reported endurance exercise and LA MD in this study, despite increasing atrial volumes by years of exercise, indicating that athletic remodeling per se has little effect on LA MD measured by echocardiography.

We found a highly significant association between paroxysmal AF and LA MD irrespective of athletic status, suggesting LA MD assessed by SD-TPS could be a promising marker of pathological atrial remodeling in endurance athletes, less affected by physiological exercise-induced cardiac remodeling than absolute volumetric measurements. However, SD-TPS did not add an independent incremental value in identifying veteran athletes with AF when including LASr in the model. This questions the clinical utility of LA MD in veteran athletes,

especially considering novel software with automated function imaging of the LA, making LA strain measurements more feasible without including LA MD measurements as an option. Several studies in non-athletic cohorts have demonstrated LA MD to have an independent incremental value at identifying individuals with AF on top of LASr and to predict the recurrence of AF post ablation.[14, 16] Current knowledge indicates that LA MD increases with increasing age in healthy individuals.[32] As the mean age in this study is 70 years, we must assume age-induced alterations in electromechanical function are present and affect LA MD. As LA MD is perceived to increase as associated with the pathophysiology of healthy aging, prospective studies and studies in younger endurance athletes will have to answer whether LA MD is an independent predictor of AF in endurance athletes and if it adds incremental value to LASr when trying to identify younger athletes with AF.

Strengths and limitations: This is the first study to explore the relationship between endurance exercise, AF, and LA MD, and it comprises a unique cohort of veteran XC skiers with an average of 40-50 years of performing endurance exercise.
The study may have seemed more appealing to individuals interested in endurance exercise, attracting the fittest members of the non-athletic control cohort, and possibly diluting the effect of training in the athletic group. Finally, this is a single-center study, and due to the low number of female participants in the Birkebeiner study with exercise-related AF, men only were included.

Conclusion: LA MD was associated with paroxysmal AF regardless of athletic status but not associated with years of performing endurance exercise despite considerable atrial remodeling in those reporting the longest history of endurance exercise. These results suggest LA MD could be a relevant marker of pathological atrial remodeling in endurance athletes. However, LA MD did not add incremental value to LASr identifying veteran athletes with AF, questioning its clinical utility in this group.

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Appendix I

Questionnaire Birkebeiner II in English

Birkebeiner II

- **Use a blue or black pen**

ABOUT YOU

1. Gender Female Male
2. Age Years
3. Height cm
4. Weight kg
5. Who do you live together with?

Live alone Spouse/partner Other people >18 years Other people <18 years

HEALTH

6. How is your current health?

Poor Fair Good Excellent

7. Do you suffer from, or have you ever suffered from the following illnesses?
   (Insert a cross and age when it first occurred)

	Yes	No	Age when first occurred	Confirmed by doctor Yes	No
Myocardial infarction					
Angina pectoris					
Hyperthyroidism					
Diabetes					
Heart valve surgery					
Coronary artery bypass surgery					
High blood pressure					
High cholesterol					
Stroke					
Cerebral hemorrhage					
Asthma					
COPD					
Osteoporosis					
Heart failure					
Kidney Failure					

8. If you suffer from a heart disease, how does it impact your ability to function?

   No restrictions. Regular physical activity causes no unusual fatigue, shortness of breath, or chest pain.

   Slight restriction on physical activity, however, unaffected when resting. Regular physical activity causes fatigue, shortness of breath, or chest pain.

   Significant restrictions on physical activity. Even minor physical exertion causes fatigue, shortness of breath, or chest pain.

   Impossible to perform any type of physical activity. Periodically shortness of breath or chest pain when resting.

9. Do you use, or have you ever used the following medications? (Insert cross)

	Yes, now	Previously, but not now	Never
Blood-pressure lowering medication			
Cholesterol-reducing medication			
Inhalation medication for asthma or chronic obstructive pulmonary disease (COPD)			

10. Have you ever experienced continual muscle or skeletal pain for at least three months?

    Yes No

11. Have you used anti-inflammatory medications over an extended period at least once (Voltaren, Diclofenac, Brexidol, Naproxen, Naprosyn, Vioxx, Celebra, Ibux, Ibuprofen, or similar)?

    Yes No

    At least 2 consecutive weeks
    At least 4 consecutive weeks
    At least 8 consecutive weeks
    At least 3 consecutive months
    At least 6 consecutive months

TOBACCO

12. Do you smoke, or have you previously smoked daily (cigarettes)?

    Yes, now Yes, previously Never

13. If yes, how many cigarettes do/did you usually smoke per day? Number:
14. How many years have you smoked/did you smoke daily? Number:
15. Do you use, or have you ever used snuff

    Yes, now Yes, previously Never
16. How many years have you used/did you use snuff? Number:

ALCOHOL

17. Are you a complete teetotaller?

    Yes, now Yes, always No

    If you have always been teetotal, go directly to question 22.
18. Approximately how often have you consumed alcohol in the past year?

    (non-alcoholic and low-alcoholic beer are not included)

    Insert a cross in the appropriate box:

4-7 times per week	2-3 times per week	Approx. once per week	2-3 times per month	Approx. once a month	A few times during the past year	Not during the past year	Never

19. How many glasses of the following drinks do you usually consume in two weeks?

    Beer Number:

    Wine Number

    Spirits Number:
20. When you have consumed alcohol, how many glasses and/or drinks have you usually had? Number:
21. Approximately how many times during the past year have you had at least five glasses/drinks during 24 hours?

Stress

22. Insert a cross for the alternative that best describes your situation (only one cross for the "At home" and one cross for the "At work" column). By stress, we mean that one feels tense, nervous, anxious, or has problems with sleeping due to circumstances at home or at work.

	At home	At work
Have never experienced stress		
Have sometimes experienced stress		
Have experienced stress during the last 5 years		
Have experienced several periods of stress during the past 5 years		
Have experienced persistent stress in the past year		
Have experienced persistent stress in the past 5 years		

PHYSICAL ACTIVITY AND EXERCISE

23. State the movement and physical activity you engage in during your leisure time. Use an average if the activity level varies significantly, e.g., between summer and winter. The question applies to the last 12 months.
(Insert a cross in the most appropriate box)

Reading, sitting still, or other sedentary activities
Walking, cycling, or a different manner of movement 2-4 hours per week
Recreational exercise, heavier garden work, or the like. (Note that the activity must be for at least 4 hours per week)
Strenuous exercise or competitive sport on a regular basis and several times per week

24. Have you, at any time in your life, engaged in regular endurance exercise (exercise sessions for a minimum of 30 minutes at least 3 times per week to improve endurance capacity)?
Yes No
If yes, proceed to question 25, if No go directly to question 33

25. How old were you when you started regular endurance exercise? Age:

26 How many years in total have you engaged in regular endurance exercise intending to increase your endurance capacity?

Less than 5 years	5-9 years	10-19 years	20-29 years	30-39 years	40-49 years	50-59 years	More than 60 years

27. What type of endurance exercise have you performed the most?
    Mostly sessions with low intensity (heart rate <75% of max heart rate, or able to conduct a conversation)
    Mostly sessions with high intensity (heart rate >75% of max heart rate, e.g., interval training)
    About half of the sessions at low intensity and half at high intensity
28. On average, how many times per week have you exercised at high intensity during the past year?
29. On average, how many times per week have you exercised at low intensity during the past year?
30. Do you still engage in regular endurance exercise?
    Yes No
31. How many times have you engaged in endurance exercise during your lifetime, even though you had a noticeable cold, infection, or fever?
    Never Once 2-3 times 4-5 times More than 5 times
32. How many times during your lifetime have you competed in endurance sports events even though you had a noticeable cold, an infection, or fever?
    Never Once 2-3 times 4-5 times More than 5 times

PARTICIPATION IN THE BIRKEBEINER RACE

33. Have you ever competed in the Birkebeiner ski race?
    Yes No
    If yes, proceed to question 34
    If no, go directly to question 40
34. How many times have you competed in the Birkebeiner ski race? Number:
35. How many times have you achieved the Birkebeiner medal (Merket)? Number:
36. How old were you the first time you competed?

IF YOU HAVE STOPPED COMPETING IN THE BIRKEBEINER SKI RACE:

37. How old were you when you competed for the last time? Age:
38. What was the most important reason for you no longer competing?
    Atrial fibrillation
    Heart attack
    Other illnesses
    No longer motivated
    Had no desire due to being in poorer physical condition than previously
    Other

39. Do you still compete in sporting competitions other than the Birkebeiner ski race?
    Yes No

ATRIAL FIBRILLATION

40. Have you noticed instances of sudden changes in pulse or heart rhythm during the past year?
    Yes No
41. Do you believe yourself that you have or have had atrial fibrillation
    Yes No Don't know
42. If yes, have you been diagnosed as suffering from atrial fibrillation by a doctor?
    Yes No Don't know
43. If yes, where?
    Regular doctor Hospital Doctor
    Name of the hospital……..
44. Do you suffer from persistent or paroxysmal atrial fibrillation
    Have atrial fibrillation the entire time
    Have atrial fibrillation that terminates spontaneously or with medication/electric cardioversion within seven days
    Have atrial fibrillation that is sustained beyond seven days and then terminates spontaneously or with medication/electric cardioversion
45. How often do you experience incidences of atrial fibrillation?
    2 or more times per week
    About once per week
    1-3 times per month
    Less than once a month
46. When do you experience incidences of atrial fibrillation?
    During exercise/physical exertion
    After exercise/physical exertion
    At night
    In connection with stress
    During or after consuming alcohol
    After large meals
    In connection with infections/fever
    Without any apparent connection with any of the abovementioned options
47. When did you experience your first incidence of atrial fibrillation?
    Month and year (e.g.03.76)
48. When were you diagnosed with suffering from atrial fibrillation?

Month and year (e.g., 03.76)

49. Do you use any of the following medications due to atrial fibrillation?

	Use	Have used
Beta-blockers daily (e.g., Selo-zok, Metoprolol, Metoprolol, Sotalol, Sotacor, Emconcor)		
Beta-blockers, in the event of an attack		
Calcium-channel blockers daily (e.g., Isoptin, Verapamil, Verakard)		
Calcium-channel blockers, in the event of an attack		
Cordarone daily		
Cordarone, in the event of an attack		
Tambocor/Flecainid daily		
Tambocor/Flecainid, in the event of an attack		
Digoxin/Digitoxin/Lanoxin		
Albyl-E/Magnyl/Acetylsalisylic acid		
Multaq/Dronedarone		
Marevan		
Pradaxa		
Xarelto		
Eliquis		
Lixiana		

50. Does anyone in your family suffer from atrial fibrillation? (insert cross)

Mother Father Sibling Child

51. How many times during your life (until you started suffering from atrial fibrillation) have you used anti-inflammatory medication more than once a day for at least a week at a time? (Voltaren, Diclofenac, Brexidol, Naproxen, Naprosyn, Vioxx, Celebra, Ibux, Ibuprofen or similar)?

Never Less than 5 times 5-15 times More than 15 times Don't know

EDUCATION AND INCOME

52. What is the highest level of education you completed?

9 years of elementary school

High school graduate/upper secondary school

Less than 4 years of college/university education

4 years or more of college/university education

53. How many years of education have you completed?

Include all the years you went to school or studied Number:

54. What was your total gross income in the past year?
    (Pensioners: What was your combined gross income before you retired?)
    NOK:

Appendix II

Questionnaire Birkebeiner II in Norwegian

Birkebeiner II

• **Bruk blå eller sort kulepenn**

OM DEG

1. Kjønn **Kvinne** ☐ **Mann** ☐

2. Alder ☐☐ **år**

3. Høyde ☐☐☐ **cm**

4. Vekt ☐☐☐ **kg**

5. Hvem bor du sammen med?

Ingen	Ektefelle/ Samboer	Andre personer 18 år og eldre	Personer under 18 år
☐	☐	☐	☐

HELSE

6. Hvordan er helsen din nå?

Dårlig	Ikke helt god	God	Svært god
☐	☐	☐	☐

7. Har du eller har du hatt følgende sykdommer:
(sett kryss og alder første gang.)

	Ja	Nei	Alder første gang	Bekreftet av lege Ja	Nei
Hjerteinfarkt	☐	☐	☐☐	☐	☐
Angina	☐	☐	☐☐	☐	☐
Høyt stoffskifte/hypertyreose	☐	☐	☐☐	☐	☐
Sukkersyke/diabetes	☐	☐	☐☐	☐	☐
Operasjon av hjerteklaff	☐	☐	☐☐	☐	☐
Bypass-operasjon i hjertet	☐	☐	☐☐	☐	☐
Høyt blodtrykk	☐	☐	☐☐	☐	☐
Høyt kolesterol	☐	☐	☐☐	☐	☐
Hjerneslag/TIA	☐	☐	☐☐	☐	☐
Astma	☐	☐	☐☐	☐	☐
KOLS	☐	☐	☐☐	☐	☐
Benskjørhet/Osteoporose	☐	☐	☐☐	☐	☐
Hjerneblødning	☐	☐	☐☐	☐	☐
Hjertesvikt	☐	☐	☐☐	☐	☐
Nyresvikt	☐	☐	☐☐	☐	☐

8. Hvis du har hjertesykdom, hvordan virker dette på ditt funksjonsnivå?

Ingen begrensninger. Vanlig fysisk aktivitet gir ingen uvanlig tretthet, tungpust eller brystsmerter.	☐
Lett begrensning av fysisk aktivitet, men ubesværet i hvile. Vanlig fysisk aktivitet gir tretthet, tungpust eller brystsmerter.	☐
Betydelige begrensninger i fysisk aktivitet. Selv små fysiske anstrengelser gir tretthet, tungpust eller brystsmerter.	☐
Umulig å utføre noen som helst fysisk anstrengelse. Periodevis også tungpust eller brystsmerter i hvile.	☐

9. Bruker du eller har du brukt: ***(sett kryss)***

	Ja, nå	Før, men ikke nå	Aldri
Blodtrykkssenkende medisiner	☐	☐	☐
Kolesterolsenkende medisiner	☐	☐	☐
Inhalasjonsmedisin mot astma eller kols	☐	☐	☐

10. Har du i minst 3 måneder sammenhengende hatt muskel- eller skjelettsmerter? Ja ☐ Nei ☐

11. Har du brukt betennelsedempende medisiner over en lengre periode minst en gang i livet (Voltaren, Diclofenac, Brexidol, Naproxen, Naprosyn, Vioxx, Celebra, Ibux, Ibuprofen el. lignende)? Ja ☐ Nei ☐

Minst 2 uker sammenhengende	☐
Minst 4 uker sammenhengende	☐
Minst 8 uker sammenhengende	☐
Minst 3 måneder sammenhengende	☐
Minst 6 måneder sammenhengende	☐

TOBAKK

12. Røyker du daglig eller har du tidligere røyket daglig (sigaretter)?

Ja, nå	Ja, tidligere	Aldri
☐	☐	☐

13. Hvis ja, hvor mange sigaretter røyker eller røykte du vanligvis daglig? *Antall:* ☐☐

14. Hvor mange år har du til sammen røyket daglig? *Antall:* ☐☐

15. Bruker du eller har du brukt snus?

Ja, nå	Ja, tidligere	Aldri
☐	☐	☐

16. Hvor mange år har du til sammen brukt snus? *Antall:* ☐☐

ALKOHOL

17. Er du total avholdsmann/-kvinne?

Ja, nå ☐ Ja, har alltid vært ☐ Nei ☐

Hvis du alltid har vært avholdsmann/-kvinne gå direkte til spørsmål 22.

18. Omtrent hvor ofte har du i løpet av det siste året drukket alkohol?
(Lettøl og alkoholfritt øl regnes ikke med).
Sett kryss i passende rute.

4-7 ganger i uka	2-3 ganger i uka	Ca. 1 gang i uka	2-3 ganger pr. mnd.	Omtrent 1 gang pr. mnd.	Noen få ganger siste år	Ikke siste år	Aldri
☐	☐	☐	☐	☐	☐	☐	☐

19. Hvor mange glass drikker du vanligvis i løpet av 2 uker av:

Øl	*Antall:*	
Vin	*Antall:*	
Brennevin	*Antall:*	

20. Når du har drukket alkohol, hvor mange glass/og eller drinker har du vanligvis drukket? *Antall:*

21. Omtrent hvor mange ganger i løpet av det siste året har du drukket så mye som minst 5 glass/drinker i løpet av ett døgn? *Antall:*

STRESS

22. Sett kryss for det alternativet som passer best for din situasjon (kun ett kryss for kolonnen *"Hjemme" og ett kryss for kolonnen "På jobb".*) Med stress mener vi at man kjenner seg spent, nervøs, engstelig eller har problemer med søvnen på grunn av forhold hjemme eller på jobb

	Hjemme	På jobb
Har aldri opplevd stress	☐	☐
Har opplevd stress noen ganger	☐	☐
Har opplevd stress i løpet av de 5 siste årene	☐	☐
Har opplevd flere stressperioder de 5 siste årene	☐	☐
Har opplevd vedvarende stress det siste året	☐	☐
Har opplevd vedvarende stress de siste 5 årene	☐	☐

FYSISK AKTiVITET OG TRENING

23. Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer mye, for eksempel mellom sommer/vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare de 12 siste månedene.
(Sett kryss i den ruten som passer best)

Leser, sitter stille eller annen stillesittende beskjeftigelse	☐
Spaserer, sykler eller beveger deg på annen måte 2–4 timer i uken	☐
Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken	☐
Driver mosjonsidrett, tyngre hagearbeid eller lignende (Merk at aktiviteten skal vare minst 4 timer i uken)	☐
Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uken	☐

24. Har du noen gang i livet drevet regelmessig utholdenhetstrening (treningsøkter med varighet på minst 30 minutter minst 3 ganger i uken med mål om å bedre utholdenhet)?

Ja ☐ Nei ☐

Hvis ja, fortsett med spørsmål 25
Hvis nei, gå direkte til spørsmål 33

25. Hvor gammel var du da du begynte med regelmessig utholdenhetstrening? *Alder:*

26. Hvor mange år tilsammen har du drevet regelmessig utholdningstrening flere ganger i uken med mål om å bedre utholdenheten?

Under 5 år	5-9 år	10-19 år	20-29 år	30-39 år	40-49 år	50-59 år	Mer enn 60 år
☐	☐	☐	☐	☐	☐	☐	☐

27. Hva slags type utholdenhetstrening har du drevet mest med?

- Flest økter med lav intensitet (puls <75% av maks puls, eller i stand til å føre en samtale) ☐
- Flest økter med høy intensitet (puls >75% av maks puls, for eksempel intervalltrening.) ☐
- Omtrent halvparten av øktene med lav intensitet og halvparten med høy intensitet ☐

28. I snitt hvor mange ganger i uken har du trent med høy intensitet det siste året? ☐☐

29. I snitt hvor mange ganger i uken har du trent med lav intensitet det siste året? ☐☐

30. Driver du fortsatt med regelmessig utholdenhetstrening?

Ja ☐ Nei ☐

31. Hvor mange ganger i løpet av livet har du trent utholdenhetstrening selv om du har vært merkbart forkjølet, hatt en infeksjon eller hatt feber?

Aldri ☐ Mindre enn 5 ganger ☐ 5-15 ganger ☐ Mer enn 15 ganger ☐

32. Hvor mange ganger i løpet av livet har du deltatt i konkurranse i utholdenhetsidrett selv om du har vært merkbart forkjølet, hatt en infeksjon eller feber?

Aldri ☐ En gang ☐ 2-3 ganger ☐ 4-5 ganger ☐ Mer enn 5 ganger ☐

DELTAKELSE I BIRKEBEINERRENNET

33. Har du deltatt i Birkebeinerrennet på ski?

Ja ☐ Nei ☐

Hvis ja, fortsett med spørsmål 34
Hvis nei, gå direkte til spørsmål 40

34. Hvor mange ganger har du gått Birkebeinerrennet? *Antall:* ☐☐

35. Hvor mange ganger har du gått til Merket? *Antall:* ☐☐

36. Hvor gammel var du første gang du deltok? *Alder:* ☐☐

HVIS DU HAR SLUTTET Å DELTA I BIRKEBEINERRENNET:

37. Hvor gammel var du da du deltok siste gang? *Alder:* ☐☐

38. Hva var den viktigste årsaken til at du sluttet å delta?

- Atrieflimmer ☐
- Hjerteinfarkt ☐
- Annen sykdom ☐
- Ikke motivert lenger ☐
- Orket ikke på grunn av dårligere fysisk form enn før ☐
- Annet ☐

39. Deltar du fortsatt i andre mosjonskonkurranser enn Birkebeinerrennet?

Ja ☐ Nei ☐

ATRIEFLIMMER

40. Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?

Ja ☐ Nei ☐

41. Mener du selv at du har eller har hatt atrieflimmer (forkammerflimmer/hjerteflimmer)?

Ja ☐ Nei ☐ Vet ikke ☐

Hvis nei gå til spørsmål 52

42. Hvis ja, har du fått stilt diagnosen atrieflimmer hos lege?

Ja ☐ Nei ☐ Vet ikke ☐

43. Hvis ja, hvor?

Fastlege ☐ lege på sykehus. ☐

Navn på sykehus.....

44. Har du permanent eller anfallsvis atrieflimmer?

- a) har atrieflimmer hele tiden (permanent) ☐
- b) har/har hatt anfall som går over av seg selv eller med medisiner/elektrosjokk innen 7 dager ☐
- c) har/har hatt anfall som har vart over 7 dager og gått over av seg selv eller med medisiner/elektrosjokk ☐

45. Hvor ofte har du i snitt anfall?

2 eller flere ggr pr uke	omtrent 1 gang per uke	1-3 ganger pr. mnd	Sjeldnere enn 1 gang pr. Mnd
☐	☐	☐	☐

46. Anfallene opptrer oftest:

under trening/fysiske anstrengelser	☐
etter trening/fysiske anstrengelser	☐
om natten	☐
i forbindelse med stress	☐
under eller etter inntak av alkohol	☐
etter større måltider	☐
i forbindelse med infeksjoner/feber	☐
uten tydelig sammenheng med noen av alternativene ovenfor	☐

47. Når hadde du ditt første anfall med atrieflimmer?
Mnd. og år (f. eks. 03.76) ☐☐.☐☐

48. Når ble diagnosen atrieflimmer stilt?
Mnd. og år (f. eks. 03.76) ☐☐.☐☐

49. Bruker du følgende medikamenter på grunn atrieflimmer? *(Sett kryss)*

	Bruker	Har brukt
Betablokker daglig *(F.eks Zelo-Zok, Metoprolol, Sotalol, Sotacor, Emconcor)*	☐	☐
Betablokker ved anfall	☐	☐
Kalsiumblokker daglig *(F.eks Isoptin, Verapamil, Veracard)*	☐	☐
Kalsiumblokker ved anfall	☐	☐
Cordarone daglig	☐	☐
Cordarone ved anfall	☐	☐
Tambocor/Flecainid daglig	☐	☐
Tambocor/Flecainid ved anfall	☐	☐
Digitoxin/Digoxin/Lanoxin	☐	☐
Albyl-E/Magnyl-E/Acetylsalisylsyre	☐	☐
Multaq/Dronedarone	☐	☐
Marevan	☐	☐
Pradaxa	☐	☐
Xarelto	☐	☐
Eliquis	☐	☐
Lixiana	☐	☐

50. Har du noen familiemedlemmer med atrieflimmer/hjerteflimmer, annen rytmeforstyrrelse eller plutselig uventet død?

Ja	Nei
☐	☐

51. Hvor mange ganger i løpet av livet (fram til du fikk atrieflimmer) har du brukt betennelsesdempende medisiner flere ganger daglig i minst en uke av gangen (Voltaren, Diclofenac, Brexidol, Naproxen, Naprosyn, Vioxx, Celebra, Ibux, Ibuprofen el. lignende)?

aldri	mindre enn 5 ganger	5-15 ganger	mer enn 15 ganger	Vet ikke
☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

52. Hvilken utdanning er den høyeste du har fullført

9 år grunnskole eller mindre	☐
artium/videregående skole	☐
mindre enn 4 år høgskole/universitetsutdanning	☐
4 år eller mer på høgskole/universitet	☐

53. Hvor mange års skolegang har du gjennomført
Ta med alle år du har gått på skole eller studert.
Antall: ☐☐

54. Hva var din samlede brutto inntekt siste (Pensjonister: Hva var din samlede brutto inntekt FØR DU BLE PENSJONIST)?

Kr. ☐☐☐☐☐☐

IKKE SETT KRYSS HER ☐
(fylles ut av mottaker.)