Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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Immediate effects of vigorous exercise on atrial fibrillation burden

Master's thesis in Exercise physiology
Supervisor: Bjarne Martens Nes
February 2023

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Lastly, I would like to thank my friends and family, who supported me throughout this wonderful process.

Infographic

The immediate effects of vigorous exercise on Atrial Fibrillation (AF) burden

This study looked at the immediate effects of exercise on AF burden. AF burden is the amount of time spent in AF as a percentage of total time.

One of the most common cardiac arrhythmias

AF is an irregular heart rhythm, in which the atria contracts irregularly and comes out of sync with the ventricles.

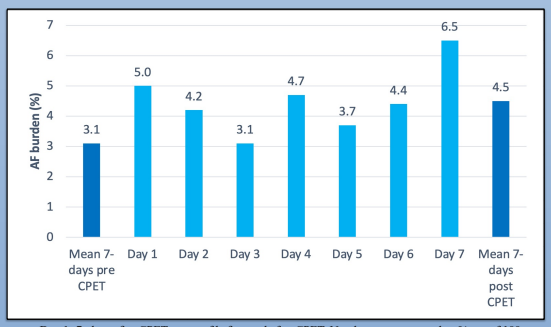
Hypothesis: One exercise session reduces AF burden the following day compared to the previous week.

Exercise stimuli

The participants underwent a VO2max test, and we monitored every AF episode and duration 7 days before and after the test using a implantable loop recorder.

Results

The average % of AF burden the week before exercise was slightly lower than the day after exercise, but not significant. The average of the 7-days before and after exercise was also similar (difference of 1.4%), but not significant.



Day 1.-7, days after CPET, mean of before and after CPET, Numbers are presented as % out of 100, CPET = Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day.

Conclusion

Vigorous exercise does not seem to impact AF burden or be a common trigger of AF episodes. Participants did not experience any adverse events after exercise. Indicating that exercise is safe for patients with AF. However, further research is needed.

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Abstract

Background

There is limited data on the immediate effects of exercise on atrial fibrillation (AF) burden.

Objective

We wanted to examine the immediate effects of vigorous exercise on AF burden.

Methods

Participants were inactive adults (>18 and <80 years) diagnosed with paroxysmal or persistent AF. We observed AF burden, defined as percent time-in-AF, the following days after one bout of maximal treadmill exercise, and compared it to the preceding seven days.

Results

A total of 48 patients were included in the study. During the 14-days of data collection, 22 participants recorded at least one AF episode while 26 did not experience any AF. When comparing the mean of the 7-day period before CPET (3.1%) to day 1 after exercise (5.0%), the difference was 1.9 (p=0.31). When excluding those without any AF, mean daily AF burden before (6.8%) compared to day 1 after CPET (10.8%), was 4.0 (p=0.31).

Conclusion

One single bout of vigorous exercise did not seem to reduce AF burden the next day. However, exercise did neither increase AF burden, and while awaiting further data, both moderate and vigorous exercise could be recommended to AF patients, in line with the general PA recommendations.

Sammendrag

Bakgrunn

Det er en begrenset mengde forskning på de umiddelbare effektene av trening på atrieflimmer (AF) mengde.

Mål

Vi ønsket å utforske de umiddelbare effektene høy intensiv trening har på AF mengde.

Metode

Deltakerne var inaktive voksne (>18 og 80< år) med diagnosen paroxysmal eller persistent AF. Vi observerte AF mengden, definert som prosentvis total tid-i-AF, dagene etter en treningsøkt på tredemølle med maksimal innsats, og sammenlignet det med de foregående syv dagene.

Resultat

Vi hadde totalt 48 deltakere inkludert i studien. I løpet av en 14-dagers periode med datainnsamling, hadde 22 deltakere minst en AF-episode, mens de resterende 26 hadde ingen AF. Når vi sammenlignet de foregående syv dagene før (3.1%) opp mot dagen etter trening (5.0%), var forskjellen 1.9% (p=0.31). Når vi ekskluderte de med ingen AF, var forskjellen for de syv dagene før (6.8%) og dagen etter trening (10.8%) 4.0% (p=0.31).

Konklusjon

En treningsøkt med høy intensitet virket ikke å redusere AF mengden den påfølgende dag. Trening økte heller ikke AF mengden, og i påvente av større studier bør både moderat og høy intensitets trening anbefales for AF pasienter.

Introduction

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common sustained cardiac arrhythmias, and is a supraventricular arrhythmia characterized by low-amplitude baseline oscillations and an irregular ventricular rhythm on electrocardiograms (Bonow et al., 2011). AF is an irregular heart rhythm, in which the atria contracts irregularly and comes out of sync with the ventricles because of electrical signals starting in the wrong place and misfire. These signals spread in a rapid and disorganised way and could cause the atria to quiver and don't contract completely.

If AF is left untreated, it can change the shape and size of the heart through remodelling. There is a possibility that remodelling could cause permanent changes to the heart in a short timeframe. During AF the heart works harder than normal, causing the heart tissue to be damaged and potentially heart size can increase. When this remodelling happens, through a period of continuous AF, the AF is facilitating its maintenance. If remodelling is allowed to continue these structural changes may happen along with a progression from one stage of AF to another (i.e., from paroxysmal to persistent or from persistent to permanent). This comes from the gradual increasing development of AF burden. AF burden is defined as the amount of time spent in AF as a percentage of total time (Boriani et al., 2014). AF is usually classified into three stages according to the pattern of the AF burden. AF which terminates spontaneously within seven days is called paroxysmal, and if AF continues over seven days it is called persistent AF (Bonow et al., 2011). The last form of AF is called permanent and is defined in the latest guidelines as AF that is accepted by the patient and physician, where no further attempts to restore or maintain sinus rhythm will be undertaken (Pelliccia et al., 2020).

AF can go undetected in some people, but most experience burdensome symptoms. These could include chest pain, the feeling of a fast or pounding heartbeat, dizziness, fatigue, light-headedness, reduction in exercise ability, shortness of breath and feeling of weakness. Hence, AF is often associated with impaired quality of life (QoL).

Occurrence and prevalence of AF

In Europe, approximately 8.8 million adults over 55 years had AF in 2010, with estimations of that number doubling by 2060 (Krijthe et al., 2013). Overall lifetime risk of developing AF

has been estimated to be 1 in 6 overall, and 1 in 4 at 55 years of age, along with an increase in prevalence of AF with higher age (Heeringa et al., 2006, Lloyd-Jones et al., 2004). The estimated increase could possibly be explained largely by an aging population, since age is highly associated with development of AF (Boriani et al., 2015). An older population also means higher prevalence of other cardiovascular diseases and cardiovascular risk factors, which also affect the risk of developing AF (Pelliccia et al., 2020). Regarding sex differences, men have a higher AF prevalence than women and women with AF are usually older and have a higher prevalence of hypertension than men. Women are also symptomatic more often than men, along with greater symptom severity (Pelliccia et al., 2020).

Presence of AF also increases the risk of several other diseases, including risk of stroke (Pelliccia et al., 2020), left ventricular (LV) dysfunction or heart failure (Santhanakrishnan et al., 2016), cognitive decline (Alonso & Arenas de Larriva, 2016), dementia (Silva et al., 2019), hospitalization (Meyre et al., 2019), and premature death (Andersson et al., 2013). The risk of stroke increases five-fold with AF although the actual risk is also depended on other stroke risk factors/modifiers (Pelliccia et al., 2020). During AF, blood can pool in the heart and from there cause a clot to form. When the blood coagulates and forms clots, they can travel through the left arteries and all the way to the brain and cause ischemic strokes. AF is therefore a considerable risk factor for stroke and may be accountable for 25% of all strokes, which is why anticoagulation is one of the most important treatments for AF (Pelliccia et al., 2020).

Risk factors and "triggers"

Besides aging, an unhealthy lifestyle, accumulation of risk factors, and other underlying cardiovascular diseases could contribute to atrial remodelling and development of AF (Pelliccia et al., 2020). Such risk factors include obesity, alcohol and caffeine use, physical inactivity, hypertension, depression (Feng et al., 2020), and diabetes. Risk of developing AF progressively increases according to body mass index (Pelliccia et al., 2020). Obesity have been shown to increase risk of developing AF (Nalliah et al., 2015) both among those considered metabolically healthy and those with additional risk factors. A positive association of severity of obesity with AF risk, regardless of metabolic status, is also found (Feng et al., 2019). Obesity is estimated to increase by 33% and 130% in severe obesity over the next two decades and may therefore contribute to increased AF incidence (Finkelstein et al., 2012).

Control of these risk factors and avoidance of factors or behaviors known or suspected to initiate an AF episode (triggers) are recommended to maintain rhythm control in AF patients (Pelliccia et al., 2020). We do know that the pulmonary vein (PV) is a main AF trigger site for patients with AF (Santangeli et al., 2016), but little is known about extrinsic factors and behaviors that may trigger AF episodes in patients with paroxysmal or persistent AF. Based on self-report, physical exertion and exercise are among the most commonly reported AF triggers together with alcohol, psychic stress, caffeine, sleep, lack of sleep, tiredness and infection (Groh et al., 2019, Hansson et al., 2004).

Physical activity (PA) and AF

PA in prevention of AF

There are some contradictory studies with regards to PA and risk of AF. The European Society of Cardiology (ESC) guidelines put forth the notion of a U-shaped relationship between habitual exercise and AF, where both high exercise volumes and inactivity, respectively, increase AF risk (Pelliccia et al., 2020). The European guidelines for AF management therefore state that "patients should be encouraged to undertake moderate-intensity exercise and remain physically active to prevent AF incidence or recurrence, but maybe avoid chronic excessive endurance exercise (such as marathons and long-distance triathlons, etc)" (Pelliccia et al., 2020). Several studies show a higher AF prevalence in former or active male master athletes, as well as men training high-intensity endurance sports (Myrstad et al., 2013, Morseth et al., 2018, Myrstad et al., 2014). However, regular moderate to vigorous PA have been shown to prevent AF, and both PA and higher cardiorespiratory fitness (CRF) have a positive impact on both risk reduction of AF and CRF. Higher CRF is associated with a significantly lower risk of AF (Elliott et al., 2018).

PA in management and treatment of AF

Moderate-intensity PA is recommended to prevent AF recurrence, but there is a lack of evidence on dose, type, and intensity of PA (Pelliccia et al., 2020) and there is still a concern that high volumes or intensities of exercise may increase the amount of AF. Recently a study found that a specific exercise-based intervention over 6 months reduced arrhythmia recurrence alongside improvements on symptom severity for patients with AF (Elliott et al., 2023). This is in line with other studies which suggest a significant role of exercise training in reducing AF burden in addition to improving disease-specific QoL, reducing resting heart

rate, and increasing general physical activity levels (Reed et al., 2022, Chung et al, 2020). Exercise training also improves exercise capacity in patients with AF, with improvements in peak oxygen uptake (VO_{2peak}). High intensity interval training over 12 weeks provided a 10% increase in VO_{2peak} in a previous study (Malmo et al., 2016), along with improvements in AF burden, functional capacity and general QoL.

Buckley et al looked at the association of exercise-based cardiac rehabilitation with progression of paroxysmal to sustained AF. They reported that exercise-based cardiac rehabilitation was associated with significantly 26% lower odds of progression from paroxysmal to sustained AF at 2-years follow-up compared to controls (Buckley et al., 2021). Buckley et al proposed that: "the beneficial impact of exercise training on physiological cardiac remodelling and an AF substrate has a direct impact on AF burden and recurrence and an indirect impact on AF morbidity" (Buckley et al., 2022). They also state a beneficial impact on vascular structure and function. The ESC guidelines recommend regular PA, partly due to the observed positive effect on AF burden and recurrence in some studies, which could stem from a reduction in other risk factors for AF. These factors could be reduced blood pressure, changes in heart volume and size, weight loss and so forth (Chung et al., 2020). If this is the case, it is implicit that sustained exercise over time is needed to achieve these benefits.

Furthermore, AF patients have a high burden of cardiovascular comorbidity. As exercise is an established treatment for most CVDs, it is highly probable that exercise will reduce comorbidity and cardiovascular events in AF patients as indicated by recent observational data (Garnvik et al, 2020 and Ahn et al., 2021).

Overall, accumulating research indicate that there is a positive effect of exercise for patients with AF. There are also indications that there could be positive immediate and chronic (exercise over time with effect on risk factors) effects on patients with AF.

Immediate effects of exercise on AF burden

As mentioned, physical exertion and exercise are frequently reported to provoke AF episodes. Still, AF onset during an exercise test, a vigorous short-term exercise session, are reported to be rare (<1%) when initiated in sinus rhythm (Keteyian et al., 2019). Moreover, a recent study

of 1410 participants using implantable loop recorders to detect AF showed that a 1 hour decrease in daily PA during the last week was associated with 24% increased odds of AF onset the next day (Bonnesen et al., 2021). This could imply a possible immediate or short-term AF-specific protective effect of regular PA, rather than a triggering effect (Buckley et al., 2022). Moreover, in those with lower activity levels overall a 1-hour reduction in participants' PA increased odds of AF onset further to 60%. Oppositely, the most physically active participants seemed somewhat protected during these reductions in PA, meaning that they had lower odds of AF after periods of physical inactivity (Bonnesen et al., 2021).

Also, in a previous 16-week RCT comparing high intensity aerobic interval training and control, a reduced AF burden was observed already after the first week of exercise (Malmo et al. 2016). One may therefore speculate that exercise is protective beyond changes in cardiovascular risk factors that would probably take longer to manifest. Interestingly, a small exploratory study found indications of using exercise as a way of reverting AF to sinus rhythm in some individuals (Gates et al., 2009). That study highlights a possible important point regarding a potential trigger for AF. Both sympathetic and parasympathetic nervous activity could have a triggering effect and exercise is known to increase parasympathetic activity. Reducing parasympathetic modulation have been shown to results in varying effects on atrial electrophysiological properties, which can vary from increase, decrease and no change at all in AF rate (Husser et al., 2007). This is however based on small data samples which warrants further investigating.

Overall, there is limited data on the immediate effects of exercise on AF burden. As mentioned earlier, there is a concern regarding vigorous exercise training with AF. Findings from Bonnesen et al support the notion of a protective short-term effect and the small study done by Gates et al further hints at the possibility of immediate effects of exercise in reverting AF to sinus rhythm. This highlights the need for further data on the topic, not just to see if there are any immediate reduction in AF, but to see if high vigorous exercise is safe to perform for patients with AF.

Aims and objectives

This pilot study aims to examine the immediate effects of vigorous exercise on AF burden and may provide further insight into whether patients with AF should perform or avoid vigorous exercise. The study objective is to observe the AF burden the following days after one bout of maximal treadmill exercise, compared to the preceding days, among patients diagnosed with paroxysmal or persistent AF. AF burden is defined as the amount of time spent in AF as a percentage of total time (Boriani et al., 2014). The hypothesis is that one single bout of vigorous exercise reduces AF burden the next day compared to the preceding week, with a gradual return to baseline level over the following inactive days.

Methods

Overall study design

The NEXAF (the Norwegian Exercise in Atrial Fibrillation trial) study is a prospective multicentre randomized controlled trial comparing clinical and patient-reported outcomes of a 12-months exercise intervention to usual care (control). The co-primary endpoints of the trial are total time-in-AF during the intervention period and health related quality of life determined by the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire after 12 months. NEXAF was registered in a clinical trials registry in February 2022 (ClinicalTrials.gov, Identifier: NCT05164718) and was approved by the Regional Ethics Committee in April 2021 (REK 213848).

Sub-study design

This paper is a pilot study of a pre-planned sub-study from NEXAF on the immediate effects of vigorous exercise on AF burden.

Population

The study population consists of inactive adults with a diagnose of paroxysmal or persistent AF from hospital records. The subjects were recruited from the NEXAF trial. A total of 48 patients were included in this pilot study from February to October 2022. Among them, 41 patients were included at St. Olavs Hospital, Trondheim, and 7 at Bærum Hospital, Vestre Viken.

Inclusion and exclusion criteria

The inclusion criteria were patients aged >18 and <80 years diagnosed with paroxysmal or persistent AF, who self-reported <75 min/week of vigorous and/or <150 min/week of moderate exercise the last three months. They should also own and be able to use a smartphone and live within a reasonable distance to the nearest study centre.
The exclusion criteria were permanent AF or unstable coronary heart disease, ejection fraction <40%, at least moderate to severe mitral or aortic pathology, implanted pacemaker or implanted cardiac defibrillator, alcohol, or drug abuse, cognitive, psychiatric, or physical impairments hindering exercise, residing in nursing homes or other institutions, or participating in conflicting intervention studies.

Duration

The NEXAF study has a total follow-up time of 12 months, while this study used 7-day measurements of time-in-AF the week before and after maximal exercise testing pre intervention (baseline). This study only uses baseline data including ILR (implantable loop recorder) data 7 days before and after baseline CPET, collected from February-October 2022.

Outcomes

The primary outcome of this study is time-in-AF from mean of the last 7 days before a maximal exercise test compared to the mean of the first day after the test. Immediate effects (24-h to 7 days) after exercise will be evaluated by post-exercise time-in-AF by an implantable loop recorder (ILR), Confirm Rx, Abbott). The secondary outcomes are differences in time-in-AF over the mean of the 7 days after the exercise test, and average number of AF episodes during the same time frames.

AF monitoring

All patients had an implantable loop recorder (ILR, Confirm Rx, Abbott) inserted subcutaneously a minimum of 4 weeks before baseline testing. A loop recorder, or ILR, provides automatic and continuous recording of total time and duration of all AF episodes during the 12-months follow-up. Information from the ILR were sent daily to a secure database through an app installed on the patient's smartphone. Datafiles containing information on all AF episodes from each patient were extracted from the manufacturers database and formatted for statistical analyses. Only data from the seven days prior to and after cardiopulmonary exercise testing (CPET), respectively, were used for this study. The data from the ILR was not validated by an electrocardiogram (ECG), and all was detected AF episodes were hence accepted as AF.

Cardiopulmonary exercise test (CPET)

The patients underwent a maximal exercise test using an individualized incremental treadmill protocol to voluntary exhaustion. After a 10-minute warm-up, there was a 3-minute submaximal steady state measurement. The speed (1 km/h) and/or incline (2%) was then increased every minute until exhaustion. During the test, maximal heart rate, ventilation parameters, subjective exertion (Borg 6-20) along with work economy and VO_{2peak} were all

recorded. During the whole test, a standard 12-lead ECG was used and monitored by a physician. All CPETs were performed with the patient in sinus rhythm.
After end of CPET patients were randomized to either the exercise group or control group. Regardless of randomization outcome, patients were informed to refrain from moderate to vigorous exercise the next 7 days due to this sub-study on immediate effects.

Other measurements

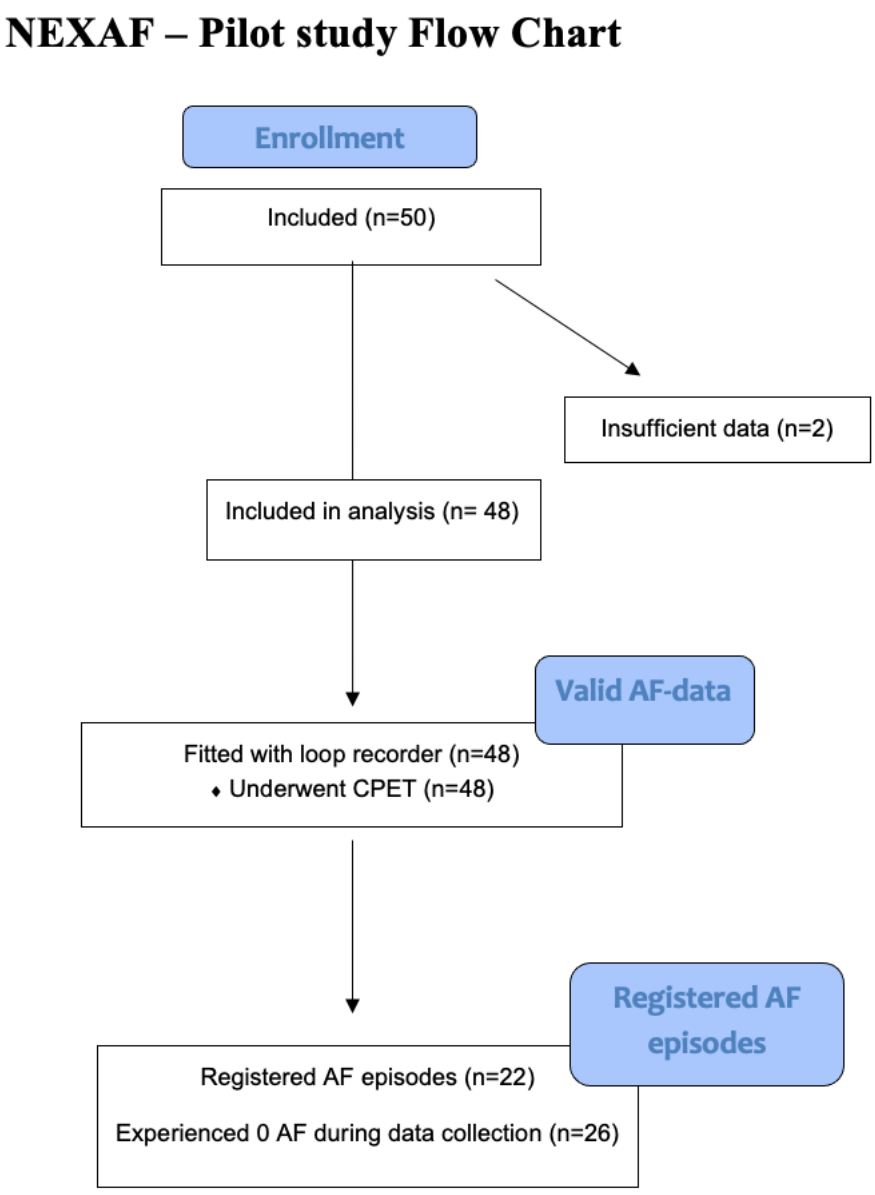
We also measured several clinical characteristics. Height was measured without shoes to the nearest 1 0.1 cm. Using bioimpedance, (InBody 770) we measured weight, fat and muscle mass and fat percent. Measurements were taken without shoes or socks, in light clothing and after an overnight fasting. Waist circumference was measured in a standing position to the nearest 1 cm midway between the lower rib margin and the iliac crest.

In addition, we performed blood sampling at rest after at least 12 hours fasting and analyses from serum samples on total cholesterol (mmol/L), HDL and LDL cholesterol (mmol/L), triglycerides (mmol/L), Hs-CRP (mg/L), Creatinine (micromol/L), eGFR (mL/min/1,73m^2), and glucose (mmol/L).

Systolic and diastolic blood pressure (BP) (mmHg), and resting heart rate, were measured in sitting position by an automatic oscillometer in a quiet setting. Systolic- and diastolic blood pressure were then measured on both arms, with a repeated measurement on the arm with the highest blood pressure. The mean of the 1st and 2nd measurement, regardless of arm, was used.

Furthermore, we collected data on disease diagnoses were gathered from hospital records and medication characteristics were collected from either hospital journals/hospital records or gathered from patient interviews after instructions to provide a list of their medications. Data on diagnoses included classification of subtype of AF (paroxysmal vs. persistent) based on their arrythmia history, previous ablation and cardioversion, and years since first diagnosis of AF. On medications, the following types were registered; betablockers, antiarrhythmics, anticoagulation, platelet inhibitors, BP lowering and cholesterol lowering medication. Presence of the following co-morbidities were registered; diabetes, myocardial infarction, heart failure, hypertension, ischemic stroke, TIA, COPD, vascular disease, and sleep apnea.

Figure 1. Flowchart showing the inclusion of participants in the study



Statistics

Data analysis was performed with SPSS statistical software (IBM SPSS statistics, Inc., version 29.0.0.0 (241)). Continuous variables are reported as mean with standard deviation (SD) and categorical variables as number and percentage. The distribution of AF burden and episodes, as well as the differences pre- and post, were visually inspected and were not normally distributed. When analysing the difference between mean AF burden, and episodes, respectively, before and after CPET, a non-parametric Wilcoxon's signed rank test was therefore used, and two-sided p-values are reported.

Results

A total of 48 patients (26 men and 22 women) had ILR recordings during the follow-up period and were included in this study. The mean age was 63.1 years (SD 10.6), and the median time since first diagnose of AF was 3 years. Out of these 48 patients, 36 (75%) had paroxysmal and 12 (25%) had persistent AF. A total of 22.9% had previously undergone an ablation procedure, with 6.3% (n=3) undergoing more than one. A total of 39.6% (n=19) had previously undergone cardioversion, with 16.7% (n=8) undergoing more than 3 cardioversions (Table 2). Besides hypertension, which was present in 50% of participants, there was a relatively low co-morbidity burden with diabetes in 2%, myocardial infarction in 6%, heart failure in 4%, ischemic stroke in 2%, TIA in 6%, COPD in 4%, vascular disease in 2%, and sleep apnea in 4% (Table 2). The majority of patients were on anticoagulation medication (63%) or blood pressure medication (53.4%), while 28% were on betablockers and 10.9% on any antiarrhythmic medication.

Table 1. Clinical characteristics and exercise test data

	Men (n=26)	Women (n=22)
	Mean (SD)	Mean (SD)
AF burden pre CPET (%)	2.6 (6.1)	3.8 (10.0)
Age (years)	61.6 (10.3)	64.6 (64.6)
Height (cm)	183 (6.0)	168 (5.7)
Weight (kg)	95.9 (17.3)	80.7 (16.5)
Waist (cm)	106 (14.6)	93.6 (12.9)
Fat mass (kg)	30.6 (10.3)	32.7 (13.1)
Muscle mass (kg)	38.7 (5.1)	26.5 (3.1)
Fat percent	29.7 (6.4)	39.1 (8.5)
Total cholesterol (mmol/L)	4.8 (1.1)	5.0 (1.2)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.7 (0.4)
LDL cholesterol (mmol/L)	3.2 (1.1)	3.1 (1.2)
Triglycerides (mmol/L)	1.2 (0.6)	1.1 (0.4)
Hs-CRP (mg/L)	2.3 (3.6)	2.2 (2.1)
Resting heart rate (beats/min)	56 (4.6)	68 (8.1)
Creatinine (micromol/L)	75.4 (10.5)	73.4 (15.8)
eGFR (mL/min/1,73m^2)	87.6 (5.5)	75.7 (16.2)
Glucose (mmol/L)	5.4 (0.5)	5.3 (0.6)
Systolic BP (mmHg)	136 (20.8)	129 (16.5)

Diastolic BP (mmHg)	86.4 (9.9)	78.1 (5.2)
CPET data		
Km/h at peak	6.8 (1.5)	5.9 (1.6)
% Incline at peak	10.8 (3.0)	10.3 (2.7)
Borg scale at peak	18 (0.9)	18 (1.2)
VO_{2peak} (ml/kg/min)	30.6 (6.9)	26.9 (6.4)
VO_{2peak} (L/min)	2.9 (0.6)	2.1 (0.4)
VCO_{2peak} (L/min)	3.1 (0.8)	2.3 (0.6)
Ventilation at peak	107 (24.3)	72.3 (13.9)
Breathing frequency at peak	23.9 (4.5)	25.6 (5.6)
HR_{max} (beats/min)	161 (21.9)	155 (18.0)
RER_{max}	1.15 (0.08)	1.11 (0.07)
1-min HRR (beats/min)	185 (14.0)	168 (14.0)

SD, standard deviation, CPET, cardiopulmonary exercise test, RER, respiratory exchange ratio, HRR, heart rate recovery, Hs-CRP, high-sensitive C-reactive protein, BP, blood pressure, HDL, high density lipoprotein, LDL, low density lipoprotein, eGFR, estimated glomerular filtration rate, VO_{2peak}, peak oxygen uptake

Cardiopulmonary exercise test data

The mean VO_{2peak} was 30.6 ml/kg/min (SD 6.9) for men, and 26.9 (SD 6.4) for women. The mean absolute VO_{2peak} was 2.9 L/min and 2.1 L/min for men and women, respectively. At peak effort men and women obtained a respiratory exchange ratio (RER) of 1.15 and 1.11, respectively, while rating a mean perceived exertion of 18 (`very hard`) on the Borg scale. The mean maximal heart rate was 161 (SD 21.9) and 155 (SD 18.0) for men and women, respectively.

Table 2. Disease and medication characteristics of the participants (n=48)

	n	%
Male	26	54.0
Paroxysmal AF	36	75.0
Persistent AF	12	25.0
Previous ablation	11	22.9
≥1 ablation	3	6.3
Previous cardioversion	19	39.6
≥3 cardioversions	8	16.7
Years since AF diagnose (median)	3	
Co-morbidities		
Diabetes	1	2.1
Myocardial infarction	3	6.3
Heart failure	2	4.2
Hypertension	24	50.0
Ischemic stroke	1	2.1
TIA	3	6.3
COPD	2	4.2
Vascular disease	1	2.1
Sleep apnea	2	4.2
Medications		
Betablockers	13	28.3
Antiarrhythmics	5	10.9
Anticoagulation	29	63.0
Platelet inhibitors	4	8.9
Blood pressure lowering	25	54.3
Cholesterol lowering	18	39.1

AF, atrial fibrillation, TIA, transient ischemic attack, COPD, chronic obstructive pulmonary disease.

AF burden and episodes

AF burden

During the 14-days of data collection, 22 participants recorded at least one AF episode while 26 did not experience any AF. When comparing the mean of the 7-day period before CPET (3.1%) to day 1 after CPET (5.0%), the difference was 1.9 (p=0.31). When excluding those

without any AF, mean daily AF burden before (6.8%) compared to day 1 after CPET (10.8), was 4.0 (p=0.31).

The overall mean daily AF burden during the week before CPET was 3.1% (SD 8.1), and 4.5% (SD 15.0) during the week after CPET (Table 3 and Figure 1). Hence, the overall difference in mean AF burden pre vs. post CPET was 1.4 (p=0.43). When excluding those without any AF during this 14-days period, mean daily AF burden before CPET was 6.8% (SD 10.9) and 9.8% (SD 21.2) in the 7 days after (Table 4). The difference between pre-post in mean AF burden excluding participants without any AF was 3.0 (p=0.43). Overall, 14 participants had decreased AF burden after CPET, while 7 had an increased AF burden, compared to the week before. One participant, however, had no AF the week before CPET, but went into 100% AF after day 1 post CPET and stayed in AF throughout the week (54.1% on day 1).

Table 3. AF burden (percentage time-in-AF) and number of episodes pre-post CPET

	Pre CPET (n=48)	Post CPET (n=48)
	Mean (SD)	Mean (SD)
Mean daily AF burden	3.1 (8.1)	4.5 (15.0)
AF burden day 1	2.6 (9.5)	5.0 (16.1)
AF burden day 2	4.3 (14.4)	4.2 (17.0)
AF burden day 3	3.0 (9.9)	3.1 (15.5)
AF burden day 4	2.5 (9.5)	4.7 (16.8)
AF burden day 5	4.0 (12.9)	3.7 (15.6)
AF burden day 6	2.9 (12.3)	4.4 (17.4)
AF burden day 7	2.4 (8.8)	6.5 (20.7)
Mean daily AF episodes	1.0 (3.1)	1.1 (3.1)
AF episodes day 1	0.9 (2.7)	1.0 (2.8)
AF episodes day 2	0.6 (2.0)	1.2 (4.4)
AF episodes day 3	1.5 (6.1)	1.4 (4.6)
AF episodes day 4	0.7 (2.3)	1.3 (4.3)
AF episodes day 5	0.8 (3.1)	0.9 (2.8)
AF episodes day 6	1.3 (4.2)	1.0 (3.0)
AF episodes day 7	1.3 (4.0)	0.8 (2.4)

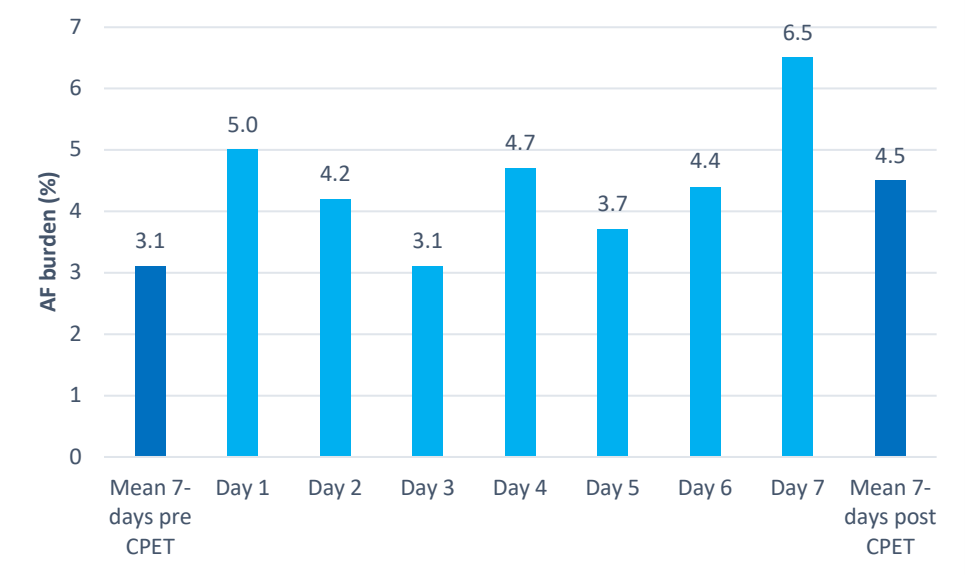
Day 1.-7, days before or after CPET, respectively. SD, standard deviation, CPET, Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day, AF episodes = number of episodes.

Table 4. AF burden (percentage time-in-AF) and number of episodes pre-post CPET excluding those without any AF during follow-up

	Pre CPET (n=22)	Post CPET (n=22)
	Mean (SD)	Mean (SD)
Mean daily AF burden	**6.8 (10.9)**	**9.8 (21.2)**
AF burden day 1	5.8 (13.5)	10.8 (22.8)
AF burden day 2	9.4 (20.4)	9.1 (24.5)
AF burden day 3	6.5 (14.0)	6.7 (22.6)
AF burden day 4	5.5 (13.6)	10.2 (23.9)
AF burden day 5	8.8 (18.2)	8.2 (22.4)
AF burden day 6	6.4 (17.8)	9.6 (25.0)
AF burden day 7	5.3 (12.5)	14.2 (29.1)
Mean daily AF episodes	**2.3 (4.4)**	**2.4 (4.4)**
AF episodes day 1	2.0 (3.7)	2.3 (3.9)
AF episodes day 2	1.3 (2.9)	2.5 (6.4)
AF episodes day 3	3.3 (8.8)	3.1 (6.4)
AF episodes day 4	1.6 (3.3)	2.8 (6.1)
AF episodes day 5	1.9 (4.5)	2.0 (3.9)
AF episodes day 6	2.9 (5.9)	2.1 (4.1)
AF episodes day 7	2.8 (5.6)	1.7 (3.4)

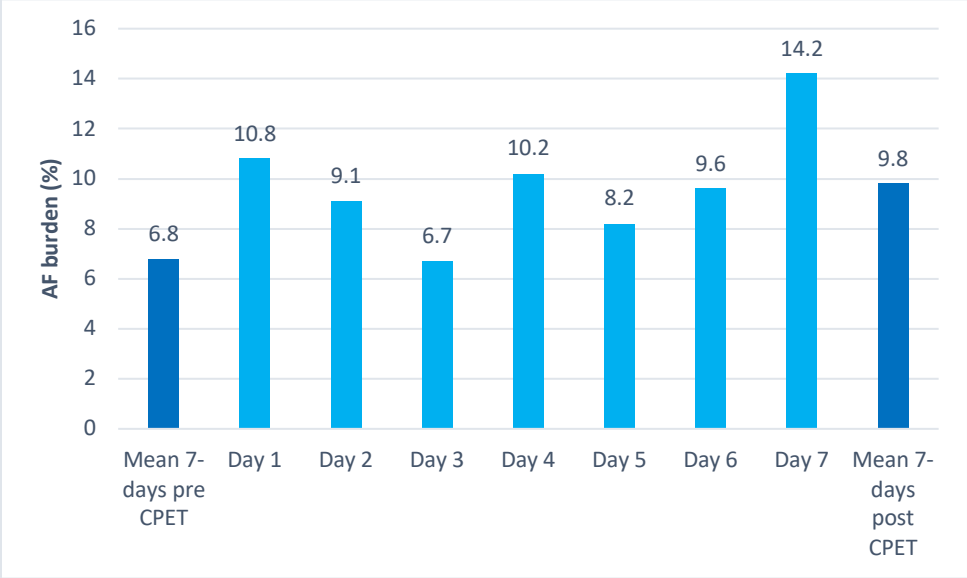
SD = standard deviation, CPET = Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day, AF episodes = number of episodes.

Figure 2. Mean daily AF burden pre and post CPET



Day 1.-7, days after CPET, mean of before and after CPET, Numbers are presented as % out of 100, CPET = Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day.

Figure 3. Mean daily AF burden pre and post CPET - excluding participants without AF

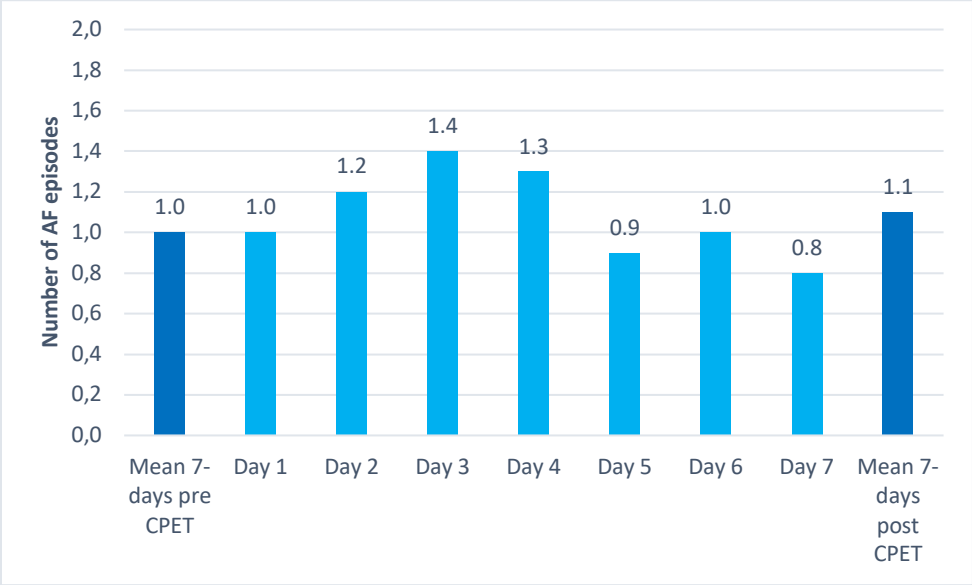


Excluding participants with 0 AF (n=26), total n=22, day 1.-7, days after CPET, mean of before and after CPET, Numbers are presented as % out of 100, CPET = Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day.

Episodes

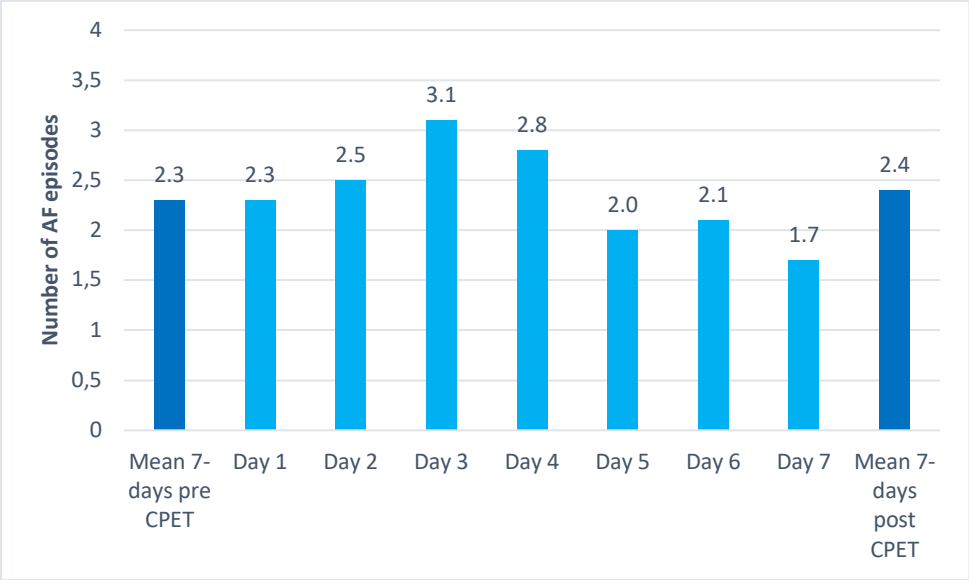
The mean episode frequency at day 1 after CPET was similar to the daily mean of the week before (p=0.43. There was no difference between the daily mean of the week before and day 1 after CPET also when excluding those without ant AF (p=0.43. The mean number of daily AF episodes before CPET was 1.0 (SD 3.1), and 1.1 (SD 3.1) the week after CPET (Table 3 and Figure 1). The difference in mean number of episodes for the whole periods (0.1) was neither significant (p=0.97). When excluding those without any AF, the mean number was 2.3 (SD 4.4) the week before and 2.4 (SD 4.4) the week after CPET (Table 4). The difference of 0.1 episodes per day was not significant (p=0.97). Among those with any registered AF during the two periods, 10 had fewer and 9 had more AF episodes, after CPET, while 3 had the same number of AF episodes.

Figure 4. Mean daily episodes pre and post CPET



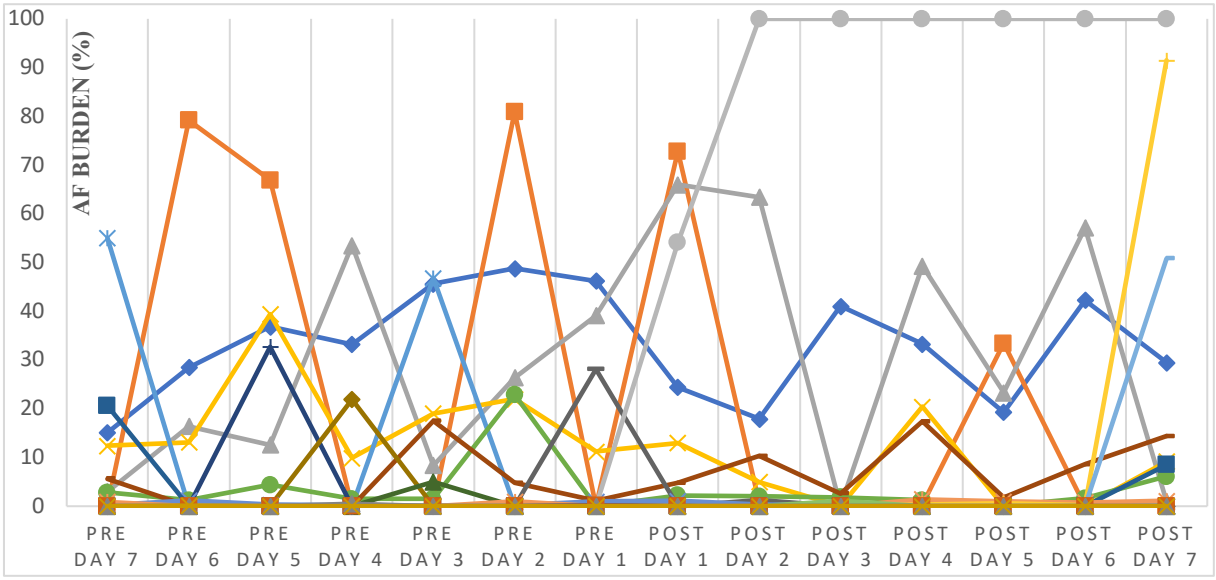
Day 1.-7, days after CPET, mean of before and after CPET, CPET = Cardiopulmonary Exercise Test, AF episodes = number of episodes.

Figure 5. Mean daily episodes pre and post CPET - excluding participants without AF



Excluding participants with 0 AF (n=26), total n=22, day 1.-7, days after CPET, mean of before and after CPET, CPET = Cardiopulmonary Exercise Test, AF episodes = number of episodes.

Figure 6 – Individual data on daily AF burden (%) pre- and post for the patients with any AF



Excluding participants without AF (n=26), total n=22, individual datapoints for each participant, ranging from day 1-7 pre and day 1-7 post CPET, CPET = Cardiopulmonary Exercise Test, AF burden = total % spent in AF in a day.

Discussion

We found no significant immediate effects of vigorous exercise on AF burden in this study. There was no significant decline in the mean AF burden the day after a maximal exercise test compared to the preceding week. Rather, the AF burden was 1.9%-points higher the day after testing although not significant. Neither, when comparing the mean of the whole weeks pre and post CPET, the difference was significant. Similar findings were observed when excluding participants without any AF during the whole 14-day period. These results indicate that one short bout of highly vigorous intensity exercise does not alter AF burden. However, out of the total 22 participants who had any AF during follow-up, only 7 had an increase in AF burden, while 14 decreased their AF burden after CPET. Hence, we can neither conclude that vigorous exercise was a common trigger of increased AF. Also, we observed a large heterogeneity in AF burden after exercise, and one participant had almost 100% AF after CPET. Since such long-standing episodes of AF highly impact the total mean AF burden, we also analyzed the difference in number of AF episodes. However, the difference between the week before CPET and the day or week after was neither significant regarding number of episodes. It is noteworthy that there was a higher mean episode frequency after CPET, although the number of patients who either experienced lower or higher episode frequency was similar.

Immediate effects of PA

The long-term effects of regular exercise on AF risk and recurrence are well-known. Regular PA may also provide a protective effect on AF onset (Bonnesen et al.,2021) and lower odds of progression from paroxysmal to sustained AF (Buckley et al., 2021), while specific aerobic exercise over time may reduce AF burden (Malmo et al., 2016). Few other studies have however examined the relationship between vigorous exercise and the immediate effects on AF in a controlled setting, which make the study novel. In this study we found no immediate impact of exercise on AF burden. There could be several possible explanations for these findings. It could be limitations of the study design, such as a small sample size. Our hypothesis could be wrong, but findings from a few other studies indicate an immediate positive exercise effect on AF burden. There could be individual differences which makes exercise effect impact people differently, such as sex, heart size, other heart diseases, genetics, and medication.

Damages to the heart muscle could be one such factor and cardiac troponin (cTn), a biomarker for heart damage, could be used to see if troponin release after CPET is correlated to an increase in AF and possibly explain some of the individual differences (Eijsvogels et al., 2016). However, future studies with a larger sample size that enable subgroup analysis are needed to unveil differences in exercise response on AF.

Exercise as a trigger for AF

Little is known regarding potential triggers of AF episodes for patients with paroxysmal or persistent AF. The pulmonary vein seems to be a trigger site for AF (Santangeli et al., 2016) and play an important role in the circulation system with its delivering of oxygen-rich blood to the heart and many factors could impact this triggering. Such factors include alcohol, psychic stress, caffeine, sleep, lack of sleep, tiredness, and infection (Groh et al., 2019, Hansson et al., 2004). Importantly, many patients report physical exertion and exercise as common triggers. Thus, our findings are not in line with the self-reported findings from Groh et al and Hansson et al.

Our data indicated that vigorous exercise does not immediately increase AF burden or number of AF episodes. If exercise really act as a common trigger, there could be differences as to which type or dose of exercise increase AF burden. The increase in sympathetic activity could

play an acute triggering role, and therefore explaining the reason as to why many patients reported that exercise had a triggering effect.

The findings from Groh and Hansson were collected using a questionnaire. Answers to questionnaires are subjective, compared to the objective measurement of an ILR which we used. The differences in findings could be down to overreported perceived AF. The objective measurement indicates that exercise does not commonly trigger AF. In addition, the data from Bonnesen et al showed that a reduction from average level of PA increased the risk of AF (Bonnesen et al., 2021). Furthermore, both Groh and Hansson do not specify exercise. It is not possible to know if the exercise stimuli are the same in those studies compared to our use of a CPET which is a relatively short-term exercise bout, but with a near maximal intensity. Therefore, future studies should provide knowledge regarding how different training doses (specifically intensity and duration) may potentially trigger AF.

There are similarities between exercise symptoms and AF symptoms, making the possibility of miss-reporting of AF. Symptoms of AF include the feeling of a fast or pounding heartbeat, dizziness, fatigue, light-headedness, shortness of breath and feeling of weakness. All of which are symptoms that can be experienced through exercise. Both exercise and AF increases heart rate. If an AF episode happens during exercise, the heart rate could become very high and make patients more symptomatic than with AF during rest. This may be one reason why many patients are anxious about vigorous exercise.

The similarities between exercise and AF symptoms, the possible differences in exercise stimuli between studies, and the potential overreporting of subjective AF are all possible reasons as to why exercise has been reported as a common trigger for AF.

AF burden

As we have seen from our analysis, vigorous exercise does not seem to impact AF burden. Although not entirely the same study design, a previous study indicated that a reduced AF burden can occur as early as in the first week of exercise (Malmo et al., 2016). In that study, the type of exercise was high intensity aerobic interval training 3 times a week. In our study the only exercise stimuli was one bout of exercise to maximal exhaustion. The difference between these two studies is that the former results were observed after one week of three interval sessions in addition to a maximal exercise test. In the Malmo study, the participants

exercised using 4x4 interval training at 85-95% HRmax. Our CPET typically last between 10-15 minutes + warm up. Importantly, there are differences in design. Interval training is done to 85-95% HRmax, while CPET is done to voluntary exhaustion (which is confirmed by Borg scale at peak and RERmax). It is possible that the differences in results (between the two studies) stem from the differences in intensity and/or number of minutes in 85-95% HRmax. Perhaps, one single bout of vigorous exercise is not enough to achieve this reduction in AF burden as Malmo et al reported. The difference from 1 to 4 training sessions may be sufficient to play a role.

Furthermore, we know that a reduction in PA, compared to the average PA level of the individual, increases the odds of AF onset the next day (Bonnesen et al., 2021). This association was even stronger in groups with low activity overall, indicating that regular PA is protective for AF. Our data indicated that vigorous exercise did not impact AF burden. While other studies have shown a positive exercise effect. There is need for further research into what contributes to the reported differences in the possible reduction of AF burden from exercise. However, the difference in findings could be due to influence by outliers (one participant went into 100% AF day 2 post CPET).

AF episodes

Reporting of AF onset during an exercise test initiated in sinus rhythm is considered rare (Keteyian et al., 2019). Our participants were all in sinus rhythm at the start of testing. Although our study did not focus on acute onset, we recorded the daily number of episodes. We found that highly vigorous exercise did not trigger significantly more episodes. Hence, the data from this pilot support the notion that exercise does not trigger AF episodes.
An important aspect of AF is rhythm control and reversion to sinus rhythm spontaneously. There are some observations that possibly indicate a role of vigorous exercise in reverting AF (Gates et al., 2019). Further investigation is needed to prove whether exercise can be used to revert AF to sinus rhythm and understand the mechanisms involved.

Strengths and limitations

The main strengths of the study are the sample of well-characterized patients with a confirmed AF diagnosis, and the use of an ILR to detect AF. The ability to continuously monitor and record every AF episode and its duration is an objective measuring of AF burden, compared to the previously used self-report or long- and short-term ECG monitoring. Furthermore, the use of CPET as the exercise stimuli made us able to control the intensity of the exercise (i.e., vigorous exercise), which was proven by the measuring of RER_{max} and Borg scale. In addition, all participants followed a standardized exercise test protocol.

The algorithms used to detect AF episodes and duration in the ILR are reported to have high sensitivity but may be prone to false positive AF detection (Ip et al., 2020). Hence, there is a limitation that each AF episode was not validated. Therefore, the data could be over- or underestimated in some participants, with more likelihood of overestimations. ECG-monitoring is an alternative objective AF measurement and may be more accurate. However, long-term ECG is troublesome for the patient to use for more than 2-3 days, and one must manually review the ECG data afterwards, making it time-consuming. Moreover, this study is a pilot with relatively few participants (n=48), which makes it prone to outliers and no former power calculations were performed before the start of the study. This means that the findings in this study can only be used as indications with further research needed.

Even though inclusion criteria stated that participants needed to be inactive, we could not be sure that they stayed inactive in the 7-day period both pre and post CPET. After CPET some participants was randomly selected to be part of the exercise group (in the main NEXAF study). These participants were directly instructed not to exercise before the first session after 7 days. The control group did not get this information, meaning less control regarding exercise activity in the 7-days after CPET. Further, the participants had to be in sinus rhythm during testing and was instructed to inform study personnel if they experienced symptoms of AF close to testing day. Evidence of AF from the ILR lead to moving of test day, which could have impacted total AF burden pre CPET, possibly underestimated, because patients with a high AF burden would be more likely to have AF at test day.

CPET gives a relative short exercise-stimuli where participants are exercising with vigorous intensity. Therefore, we can't translate our findings to the effect of longer exercise-duration or exercise with other intensities (moderate and low).

or short-term ECG monitoring.

Interpretation and implications

Our findings do not indicate that vigorous exercise causes more AF, or that it is a common trigger of AF episodes. Our participants did not experience any adverse events after exercise. Hence, this pilot study indicate that vigorous exercise is safe for AF patients and could be recommended to obtain other well-known benefits of vigorous exercise.

Future research

This study highlights the need for further research on the immediate effects of exercise on AF burden. Our results indicate that vigorous exercise does not profoundly impact AF burden, although our data is limited. Therefore, further research is required in order to fully investigate the relationship between exercise and AF in the short and long term. There is a need for a larger study with a larger population, as a larger study may allow identification of subgroups or individuals that may have short-term beneficial or adverse effects of exercise. Such subgroups could be different AF phenotypes (i.e., paroxysmal, and persistent AF, previous ablation, cardioversion etc.), co-morbidities, cardiac structural and functional properties, or medications. In addition, the impact of exercise on reversion to sinus rhythm could be studied in larger datasets also including patients in AF rhythm during exercise. Further, we need research to investigate and understand the mechanisms involved in exercise with AF.

Conclusion

One single bout of vigorous exercise did not seem to reduce AF burden or number of AF episodes the following day or week. Due to the observed heterogeneity in AF response to exercise, further research is needed. However, exercise did neither increase AF burden, and while awaiting further data, both moderate and vigorous exercise could be recommended to AF patients, in line with the general PA recommendations.

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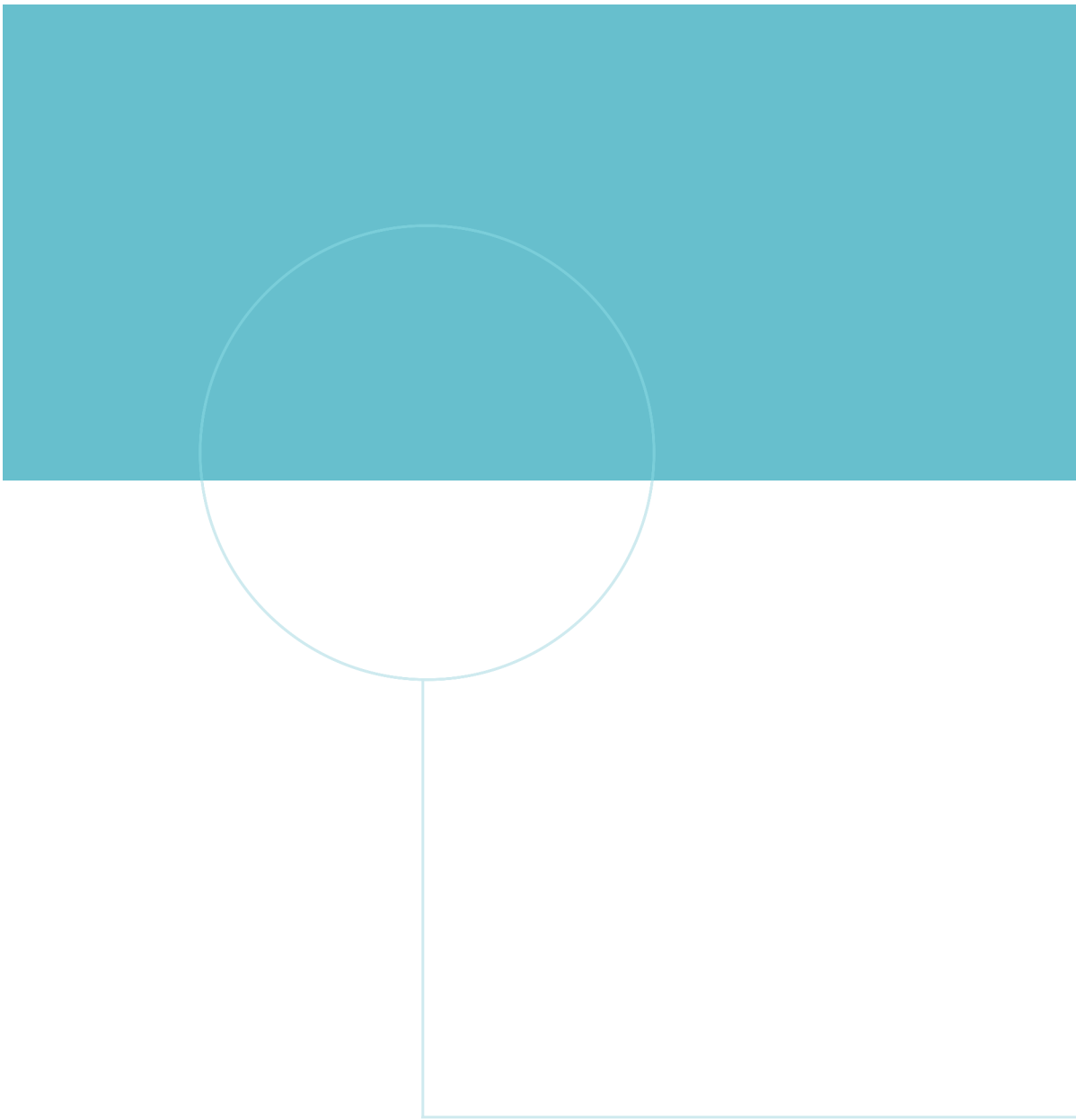

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