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Emerging risk factors and the dose–response relationship between physical activity and lone atrial fibrillation: a prospective case–control study

Naiara Calvo[1,2], Pablo Ramos[1,2], Silvia Montserrat[1,2], Eduard Guasch[1,2], Blanca Coll-Vinent[1,2], Mònica Domenech[2,3], Felipe Bisbal[1,2], Sara Hevia[2], Silvia Vidorreta[2], Roger Borras[2], Carles Falces[1,2], Cristina Embid[1,2,4], Josep Maria Montserrat[1,2,4], Antonio Berruezo[1,2], Antonio Coca[1,2,3], Marta Sitges[1,2], Josep Brugada[1,2], and Lluís Mont[1,2]*

[1]Unitat de Fibril.lació Auricular, Hospital Clínic, Universitat de Barcelona, Barcelona, Catalonia, Spain; [2]Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Catalonia, Spain; [3]Unitat d'Hipertensió i Risc Vascular, Hospital Clínic, Catalonia, Spain; and [4]Unitat del Son. Servei Pneumologia, Hospital Clínic, CIBERES Barcelona, Catalonia, Spain

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Aims The role of high-intensity exercise and other emerging risk factors in lone atrial fibrillation (Ln-AF) epidemiology is still under debate. The aim of this study was to analyse the contribution of each of the emerging risk factors and the impact of physical activity dose in patients with Ln-AF.

Methods and results Patients with Ln-AF and age- and sex-matched healthy controls were included in a 2:1 prospective case–control study. We obtained clinical and anthropometric data transthoracic echocardiography, lifetime physical activity questionnaire, 24-h ambulatory blood pressure monitoring, Berlin questionnaire score, and, in patients at high risk for obstructive sleep apnoea (OSA) syndrome, a polysomnography. A total of 115 cases and 57 controls were enrolled. Conditional logistic regression analysis associated height [odds ratio (OR) 1.06 [1.01–1.11]], waist circumference (OR 1.06 [1.02–1.11]), OSA (OR 5.04 [1.44–17.45]), and 2000 or more hours of cumulative high-intensity endurance training to a higher AF risk. Our data indicated a U-shaped association between the extent of high-intensity training and AF risk. The risk of AF increased with an accumulated lifetime endurance sport activity ≥2000 h compared with sedentary individuals (OR 3.88 [1.55–9.73]). Nevertheless, a history of <2000 h of high-intensity training protected against AF when compared with sedentary individuals (OR 0.38 [0.12–0.98]).

Conclusion A history of ≥2000 h of vigorous endurance training, tall stature, abdominal obesity, and OSA are frequently encountered as risk factors in patients with Ln-AF. Fewer than 2000 total hours of high-intensity endurance training associates with reduced Ln-AF risk.

Keywords Lone atrial fibrillation • Endurance training • Exercise • Abdominal obesity • OSA • Risk factors

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, substantially increasing the risk of stroke, hospitalization, and mortality. Well-defined risk factors for AF include advanced age, hypertension, structural heart disease, diabetes mellitus, and thyroid disease. However, AF may develop in patients without these traditional aetiologic factors, known as lone AF (Ln-AF).[1]

In recent years, emerging Ln-AF risk factors such as high-intensity endurance sport,[2] obesity,[3] and obstructive sleep apnoea[4] (OSA) syndrome have been identified. However, the role of physical activity in the risk of developing AF remains under debate. Moreover, in

* Corresponding author. Tel: +34 93 227 5551; fax: +34 93 451 4148. *E-mail address*: lmont@clinic.ub.es

What's new?

- Emerging risk factors long-term high-intensity endurance training, obstructive sleep apnoea, obesity, and tall stature are found in over 75% of patients with lone AF.
- The relationship between physical activity and Ln-AF incidence follows a U-shaped curve, with individuals having exercised for limited periods of time being at the lowest risk.
- The lifetime-accumulated hours of vigorous training is the most powerful predictor of exercise-induced AF.

the absence of traditional aetiologic factors for AF, a complete work-up is frequently not performed and little is known about the impact of these emerging risk factors.[5]

The aims of our study were to explore the contribution of physical activity to Ln-AF, focusing on the dose–response relationship; to analyse whether a complete work-up in patients with Ln-AF may uncover previously undiagnosed risk factors; and to study the prevalence of these risk factors and their contribution to AF risk.

Methods

We designed a prospective, observational, cross-sectional study. Patients with Ln-AF and age- (±3 years) and sex-matched healthy controls were recruited. Written informed consent was obtained from all participants. The protocol was approved by the Ethics Committee of our institution.

An extended description of Methods is provided in the Supplementary material online.

Patient population

The study population (cases) consisted of consecutive patients with Ln-AF at their first visit at our centre. Lone atrial fibrillation was defined as AF in the absence of any cardiopulmonary identifiable cause of the arrhythmia, hypertension, or diabetes. Control subjects were recruited among healthy hospital visitors, excluding relatives of AF patients. All individuals underwent a comprehensive clinical history and echocardiography to rule out exclusion criteria. Exclusion criteria were >60 years of age, any cardiovascular disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease and liver, thyroid, infectious or inflammatory diseases, as well as AF secondary to illicit-drug or alcohol abuse.

Anthropometric indexes

Weight, height, waist and hip circumference, and body mass index (BMI) were assessed in all participants. Abdominal obesity was defined according to international guidelines: >102 cm (men) or >88 cm (women).

Blood sample analytics

Cytokines mediating systemic inflammation [interleukin 1 (IL-1), interleukin 6 (IL-6), and C-reactive protein (CRP)], neurohormones [atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and aldosterone], and proteins involved in extracellular matrix turnover [matrix metalloproteinase 2 (MMP-2), matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase 1 (TIMP-1)] were measured in blood samples.

Echocardiographic parameters

All participants underwent a comprehensive transthoracic echocardiography study. Left ventricular (LV) dimensions, ejection fraction, diastolic function, and left atrial (LA) antero-posterior diameter were measured.

Regular sport practice

A modified version of the validated Minnesota Leisure-Time Physical Activity Questionnaire was administered by a research nurse. This questionnaire estimates lifetime-accumulated physical activity and identifies those individuals at an increased risk of exercise-induced AF.[2] For each activity, the following variables were recorded: age of starting and ending, months of practice per year, days practised per week and hours per day (see Supplementary material online, S1). Participants were asked to classify the intensity of each physical activity into four categories: sedentary (intensity 1), activities requiring no physical effort with minimal walking; light (intensity 2), activities requiring minimal physical effort such as slow walking, with no increase in heart rate and no perspiration; moderate (intensity 3), activities that are not exhausting but slightly increase heart rate and may cause some light perspiration; and high intensity (intensity 4), vigorous activities resulting in intense sweating and deep-breathing.

Berlin questionnaire

The Berlin questionnaire identifies patients at high risk for OSA. It comprises three items: snoring, wake-time sleepiness or tiredness, and the presence of either obesity or hypertension (see Supplementary material online, S2). When available, the patient's bed-partner was asked to confirm the accuracy of responses on snoring. Scores from the first and second categories were positive if responses indicated frequent symptoms; the third category was positive if BMI > 30 kg/m^2 (hypertensive patients were excluded *per protocol*). Patients were considered at high risk for OSA if scored positive in two or three categories.[6]

Polysomnography

Participants with a high-risk Berlin questionnaire score underwent overnight laboratory-based video polysomnography. The apnoea–hypopnea index (AHI) was calculated as the average number of apnoea's and hypopneas per hour; OSA was diagnosed when AHI was ≥5.[6]

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using a Spacelabs 90207/90217 monitor (Richmond, WA, USA). According to current guidelines, average BP > 130/80 mmHg on 24-h ABPM was considered as masked hypertension.

Statistical analysis

Continuous data are expressed as mean ± SD. Categorical variables are expressed as number (percentage). Blood-test parameters did not follow normal distribution; their square-root-transformation was used. We used receiver-operating characteristic (ROC) and positive likelihood ratio to evaluate the optimal cut-off point for accumulated high-intensity training and stature.

Conditional logistic regression and backward-stepwise selection algorithms were used to determine the variables associated with Ln-AF. Variables to be included in the multivariate model were selected using a *P*-value of <0.10 in univariate analysis. Local likelihood regression was used to establish the association between Ln-AF and total hours of high-intensity training.

A two-tailed *P*-value of <0.05 was considered statistically significant. The analyses were performed using R v3.0.1 (the R project for Statistical Computing; Vienna, Austria).

Sample size was estimated on the basis of previous observations.[2] We estimated 114 AF patients and 57 healthy individuals in a 2:1 design would provide an 80% power to detect a significant ($P < 0.05$) estimate of an AF-risk odds ratio (OR $\neq$ 1) between the two study groups if prevalence of intense physical activity was 50% in the Ln-AF group and 33% in the control group.

Results

A total of 115 cases and 57 controls were included (2:1 match, except for 1 control that was matched to 3 cases). Most participants (87%) were male, aged 46 ± 10 years (*Table 1*). Atrial fibrillation characteristics are summarized in Supplementary material online, *Table S1*. Atrial fibrillation was paroxysmal in 60% of cases and had vagal triggers in 46%. In 14% of cases, AF was present at the inclusion visit.

Anthropometric indices

Anthropometric data are shown in *Table 1*. Patients with Ln-AF were taller (177 vs. 174 cm, OR 1.06 [1.01–1.11]). There were no differences in BMI between groups, but waist circumference was significantly larger in cases than in controls (95 vs. 91 cm, OR 1.06 [1.02–1.11]). The proportion of participants with abdominal obesity was higher in cases than in controls (27 vs. 14%, OR 3.03 [1.09–8.39]).

Blood sample analyses

Enhanced systemic inflammation was observed in patients with Ln-AF, evidenced by increased CRP and IL-1 (*Table 2*). ANP and BNP were also increased in Ln-AF patients, but no changes were found in collagen-turnover parameters. Sensitivity analyses excluding patients with ongoing AF at the inclusion visit did not affect these results (see Supplementary material online, *Table S2*).

Berlin questionnaire and obstructive sleep apnoea diagnosis

High-risk Berlin questionnaire scores were more common in cases than controls (35 vs. 10%, OR 5.03[1.88–13.43]). Definite OSA was diagnosed in 22% of cases and 5% of controls (OR 5.01 [1.44–17.45]) (*Table 1*).

Echocardiographic parameters

Echocardiographic parameters are shown in *Table 3* and Supplementary material online, *Table S3*. Both crude- and indexed-LA diameter were larger in patients with Ln-AF; there were no differences between cases and controls in LV-wall thickness or diastolic function. Left ventricular ejection fraction was marginally lower in patients with Ln-AF (59 vs. 63%, OR 0.92 [0.86–0.98]).

Table 1 Baseline clinical characteristics

Variable	Lone AF patients (*n* = 115)	Control group (*n* = 57)	OR (95% CI)	*P*-value
Age (years)	46 ± 10	46 ± 10		
Male (%)	100 (87%)	50 (86%)		
Height (cm)	177 ± 8	174 ± 8	1.06 (1.01–1.11)	0.03
Weight (kg)	83 ± 13	78 ± 12	1.04 (1.01–1.07)	0.02
BMI (kg/m^2)	26 ± 3	26 ± 3	1.07 (0.97–1.19)	0.18
Waist circumference (cm)	95 ± 11	91 ± 10	1.06 (1.02–1.10)	<0.01
Hip circumference (cm)	100 ± 9	101 ± 8	1.00 (0.96–1.03)	0.83
High-risk score for OSA	39 (34%)	6 (10%)	5.03 (1.88–13.43)	<0.001
Definite OSA	23 (22%)	3 (5%)	5.01 (1.44–17.45)	0.01

BMI, body mass index; OSA, obstructive sleep apnoea.

Table 2 Analytic measurements

Variable	Lone AF patients (*n* = 115)	Control group (*n* = 57)	OR (95% CI)	*P*-value
IL-1 (ng/mL)	0.12 (0.29)	0 (0.08)	2.69 (1.05–6.98)	0.045
IL-6 (pg/mL)	1.2 (1.5)	0.8 (0.7)	1.73 (0.92–3.22)	0.086
CRP (mg/dL)	0.08 (0.24)	0.05 (0.09)	4.77 (1.11–20.59)	0.036
Aldosterone (ng/dL)	6.4 (5.7)	6.65 (4.4)	1.14 (0.74–1.74)	0.55
ANP (fmol/mL)	51 (50)	29 (20)	1.42 (1.15–1.75)	0.001
BNP (pg/mL)	22.5 (53.4)	8.7 (13.3)	1.45 (1.19–1.77)	<0.001
MMP-2 (ng/mL)	290.6 (65.5)	283.5 (66.3)	1.0 (0.8–1.26)	0.97
MMP-9 (ng/mL)	103.6 (104.1)	88.8 (69.1)	1.07 (0.96–1.19)	0.21
TIMP-1 (ng/mL)	76.5 (23.4)	78.5 (14.4)	0.85 (0.63–1.17)	0.32

Sport activity

The lifetime-accumulated hours of exercise, the average number of hours of vigorous exercise per year, and the age at beginning of vigorous training were significantly associated with AF in the univariate analysis (*Table 4*). Only lifetime total hours of exercise remained significant in the multivariate analysis. The lifetime-accumulated hours of high-intensity endurance training was significantly higher in cases than in controls (4686 vs. 985 h, OR 1.02 [1.01–1.03] per 100-h increase). A ROC analysis showed that an accumulation of 2000 h was the best cut-off predicting AF presence. This cut-off point served to split participants into three clinically meaningful groups: (i) sedentary (no high-intensity exercise); (ii) <2000 h of lifetime-accumulated, high-intensity endurance training, comprising individuals who had performed limited vigorous activity; and (iii) ≥2000 h of lifetime-accumulated, high-intensity endurance training, comprising heavy-performer individuals (*Table 5*). In comparison to sedentary individuals, AF risk increased with ≥2000 h lifetime-accumulated high-intensity training (OR 3.88 [1.55–9.73]). Conversely, a history of <2000 h of high-intensity training significantly protected against AF (OR 0.38 [0.12–0.98]). When considered as a continuous variable, the relationship of lifetime-accumulated high-intensity training to AF risk followed a U-shaped dose–response curve (*Figure 1*).

Regression analyses suggested significant cardiac remodelling with increasing lifetime-exercise hours (see Supplementary material online, *Table S4*). Competitive athletes at the regional or national

Table 3 Echocardiographic assessment of lone AF patients and controls

Variable	Lone AF patients (n = 115)	Control group (n = 57)	OR (95% CI)	*P*-value
LA-AP diameter (mm)	39 ± 6	36 ± 4	1.15 (1.06–1.24)	<0.001
LVEDD (mm)	51 ± 6	51 ± 4	1.02 (0.95–1.09)	0.57
LVESD (mm)	33 ± 6	32 ± 4	1.06 (0.98–1.13)	0.11
IVW (mm)	10 ± 2	10 ± 1	0.96 (0.74–1.26)	0.79
PW (mm)	10 ± 2	10 ± 1	0.88 (0.67–1.16)	0.37
LVEF (%)	59 ± 8	63 ± 5	0.92 (0.86–0.98)	<0.01
Diastolic pattern: impaired relaxation (%)	7	6	1.47 (0.37–5.89)	0.72

LA-AP, left atrial antero-posterior diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVW, interventricular wall; PW, posterior wall; LVEF, left ventricular ejection fraction.

Table 4 Exercise-related parameters associated with AF

	Univariate analysis			Multivariate analysis
	OR (95% CI)	*P*-value	Stand. β	OR (95% CI)
Age at beginning vigorous exercise (per year)	0.96 (0.93–0.99)	0.01	−0.504	
Lifetime-accumulated vigorous exercise (per 100 h)	1.02 (1.0069–1.032)	0.003	1.22	1.041 (1.013–1.07)
Hours of vigorous exercise per year (per 10 h)	1.023 (1.005–1.042)	0.015	0.588	

Table 5 Risk of AF associated with the presence of emerging risk factors

Variables	Univariate			Multivariate		
	OR	CI (95%)	*P*-value	OR	CI (95%)	*P*-value
Abdominal obesity	3.03	1.09–8.39	0.03			
Height (>179 cm)	3.31	1.52–7.19	<0.01	2.11	0.93–4.83	0.06
Obstructive sleep apnoea	5.01	1.44–17.45	0.01	4.27	1.16–15.65	0.02
Sport activity						
Sedentary	1			1		
High-intensity exercise <2000 h	0.38	0.12–0.98	0.04	0.48	0.16–1.47	0.19
High-intensity exercise ≥2000 h	3.88	1.55–9.73	<0.001	2.83	1.18–6.79	0.02

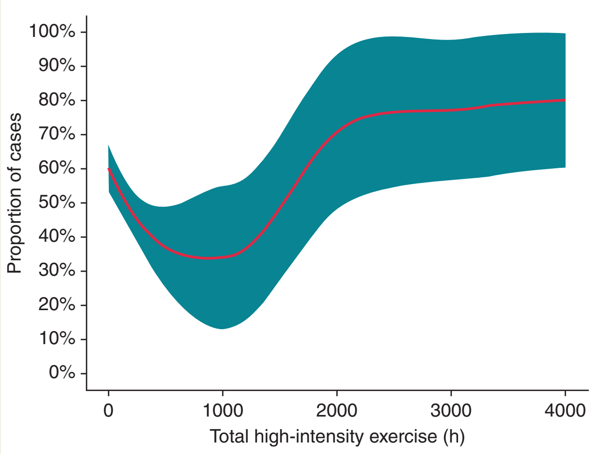

Figure 1 Percentage (95% CI) of participants with lone AF (cases) according to accumulated high-intensity physical exercise (local likelihood regression). Of note, proportion is dependent on cases/control matching in a specific study sample; in our study (2:1 matching), a percentage of 66% would indicate lack of association between exercise and AF.

Table 6 Risk of AF in specific exercise subgroups

	Unadjusted data	Adjusted for lifetime-accumulated exercise
Competitive sport	2.74 (0.88–8.47)	0.88 (0.23–3.43)
Exercise type		
Team sports	1	1
Endurance sports	3.4 (1.37–8.4)	5.68 (1.72–18.7)
Other	3.03 (0.9–9.7)	4.59 (0.5–41.1)

level were at a higher risk of AF (OR 2.74 [0.88–8.47]), but this effect was largely blunted after adjusting for total exercise hours (*Table 6*). Patients with Ln-AF who had been engaged in intensive training were predominantly participating in cycling, marathon running, and diverse team sports (see Supplementary material online, *Table S5*). After adjusting for cumulated hours of exercise, endurance sports carried a higher AF risk in comparison to team sports (OR 5.68 [1.72–18.7]) (*Table 6*).

Blood pressure

The ABPM revealed that 38% of controls and 34% of cases suffered masked hypertension (OR 0.78 [0.35–1.72]) (see Supplementary material online, *Table S6*). This proportion was maintained after excluding AF patients treated with beta-blockers or calcium-antagonists or regular exercisers (not shown). Masked hypertension had no impact on LA size among controls. Nevertheless, LA was enlarged in Ln-AF patients with masked hypertension in comparison with those without masked hypertension (see Supplementary material online, *Figure S1*).

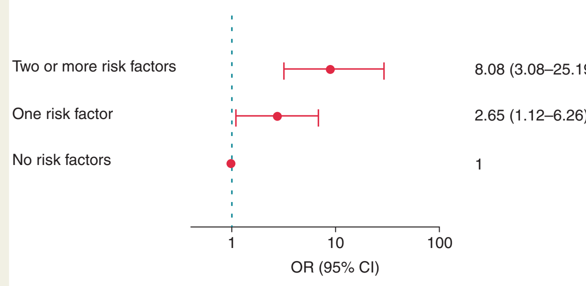

Figure 2 Risk of AF in patients according to the presence of risk factors shown in *Table 5* (OR and 95% CI).

Overall and cumulative risk

Multivariate analysis showed that prolonged high-intensity endurance training, OSA, and tall stature were independently associated with Ln-AF (*Table 5*). Overall, at least one emerging risk factor was found in 76% of patients with Ln-AF (81 of 107 patients): 43% of patients had performed ≥2000 h of vigorous exercise, 44% were taller than 179 cm, abdominal obesity was present in 27% of them and OSA in 21% of patients. Atrial fibrillation risk was higher in individuals with more than one of these factors (*Figure 2*).

Discussion

To the best of our knowledge, this is the first study exhaustively analysing the prevalence and contribution of non-traditional emerging risk factors to AF incidence in a population of unselected patients with Ln-AF (*Table 5*). We show that after a comprehensive exploration, a non-traditional aetiologic factor can be identified in most patients with Ln-AF. Furthermore, we describe for the first time a U-shaped association between the duration of high-intensity training and the risk of developing Ln-AF.

Lone atrial fibrillation

The notion of 'Lone AF' was first coined to identify young patients with AF and no evidence of causative heart disease, hypertension, or diabetes. We focussed our work in the identification of recently described 'emerging' aetiologic factors in the absence of these well-known aetiologic factors. Nevertheless, it should be acknowledged that the 'lone AF' concept has been frequently mixed up with 'idiopathic AF', thus leading to inconsistent definitions and misleading discussions.[1] We show that at least one emerging risk factor can be identified in most Ln-AF patients, hence disputing the notion of 'idiopathic AF' in our cohort.

Sport activity

We establish a U-shaped dose–response between lifetime-accumulated high-intensity endurance training and risk of Ln-AF. Individuals having exercised vigorously for a limited number of hours were at the lowest risk of AF (*Figure 1*). Moreover, we find that the lifetime-accumulated hours of vigorous activity is the most powerful predictor for exercise-induced AF, suggesting that the total accumulated insult to the atria correlates to the arrhythmic substrate.

Physical inactivity is a well-known major cardiovascular risk factor; in contrast, regular exercise prevents cardiovascular events. Our study extends previous findings on the health benefits of exercise to patients with Ln-AF: sedentary individuals are at increased risk of AF when compared with those engaged in regular, time-limited, training. Conversely, as in the previous studies,[2,7–10] we found that AF risk increases with long-term, vigorous, endurance sport practice (≥2000 h in our cohort).

The upper limit of 'safe' endurance training has been elusive. Elosua *et al.*[2] demonstrated that an accumulated sport practice of >1500 h was associated with an increased risk of AF. Data from Drca *et al.*[9] suggested that >5 h/week of vigorous intensity exercise at 30 years of age increased AF incidence beyond the sixth decade of life. In our study, a 2000-h threshold better discriminated individuals at risk for exercise-induced AF. However, the training/AF-risk dose–response curve is likely continuous and shows a high inter-individual variability. Undertaking epidemiological studies to identify a threshold for screening purposes in this setting might be spurious, and clinical decisions should be individualized.

In this work we show that, in comparison to individuals involved in collective sports, those undergoing intense endurance training are at a higher risk of AF. To our knowledge, only one study has found a higher than expected AF incidence in team sports practitioners,[11] in contrast to a large body of evidence for endurance athletes.[7–9] A more sustained haemodynamic overload in endurance athletes likely contributes; however, our study was not designed to address these differences.

The mechanisms involved in exercise-induced AF are increasingly being identified.[12] In our study, abdominal obesity is more frequent in sedentary than highly active patients (34 vs. 16%, $P = 0.01$); we therefore speculate that regular training protects against AF by reducing abdominal obesity burden.

Our data suggest that regular vigorous exercise should be assessed in patients with an Ln-AF diagnosis. Although experimental[12] and clinical[8] reports suggest that deconditioning might reverse exercise-induced AF substrate and prevent recurrences, further studies are warranted to establish a therapeutic role for training discontinuation in exercise-induced AF.

Obesity

Several studies have pointed to obesity as an independent risk factor for AF. Nevertheless, the definition of obesity is inconsistent across studies. Body mass index has been extensively used to identify individuals at risk of AF.[3] Other groups have implicated the metabolic syndrome in the development of AF.[13] In the REGARDS study, AF prevalence was higher in patients with a larger waist circumference.[13] Zhang *et al.*[14] reported that BMI and waist circumference predicted AF incidence and suggested the superiority of waist circumference over BMI. The present study extends these observations to patients with Ln-AF, and demonstrates that waist circumference is superior to BMI as an Ln-AF predictor. Therefore, we propose systematic assessment of waist circumference in the evaluation of patients with Ln-AF.

Masked hypertension

In the general population, hypertension is the most important risk factor for AF. For the first time, we have assessed the prevalence of masked hypertension by mean of ABPM in patients with Ln-AF. Our data show that one in three Ln-AF patients has abnormally high blood pressure values. Similarly, a small study by Katritsis *et al.*[15] revealed that 44% of patients with Ln-AF were diagnosed with hypertension after a 3-year follow-up, but a control group was not provided. In our study, masked hypertension was equally frequent in cases and controls, thus suggesting it has no significant role in Ln-AF pathology. Nevertheless, masked hypertension was associated with more dilated atria in patients with Ln-AF. It is likely that masked hypertension contributes to AF-induced LA dilation, thereby accelerating AF self-perpetuation mechanisms. The LA of Ln-AF patients might be more sensitive to haemodynamic stretch. Further studies are needed to address this issue.

Obstructive sleep apnoea syndrome

In patients with AF, OSA prevalence ranges from 32 to 49%.[4,16] Our data reveal that OSA is present in 22% of Ln-AF patients, conferring a five-fold increase in AF risk. Patients with structural heart disease and hypertension were excluded from our Ln-AF cohort, accounting for a lower prevalence of OSA in this series in comparison with previous reports.

Obstructive sleep apnoea increases AF risk through autonomic imbalance and chronic structural remodelling,[17] and thereby increases AF recurrence after electric cardioversion[4] and AF-ablation procedures.[16,18] Most studies have proved continuous positive airway pressure (CPAP) to be beneficial in preventing AF-relapses, although conflicting results have also been published.[4]

A rationale for OSA screening stems from its high prevalence in Ln-AF patients and the potential benefits of CPAP therapy in terms of AF prevention. We show that Berlin questionnaire score efficiently identifies a subpopulation of Ln-AF patients at high risk of OSA who should undergo polysomnography for a definitive OSA diagnosis. Overall, >65% of patients with a high-risk Berlin questionnaire score were diagnosed with OSA. This efficient and easy-to-administer tool should be included systematically in initial evaluation of Ln-AF patients.

Height

Reports studying an association between stature and AF incidence are scarce. This association was first suggested by Hanna *et al.*[19] in an epidemiological study including >25 000 patients with heart failure. They showed a progressive increase in AF risk from lower to higher stature-quartile. Later studies extended this relationship to patients with Ln-AF,[10] and Rosenberg *et al.*[20] revealed that taller individuals were at higher risk of incident and prevalent AF in the general population. The present study confirmed an association between stature and Ln-AF, independently of other emerging AF risk factors. Mechanisms mediating this association are largely unknown. Stature keeps its prognostic significance even after adjusting for LA diameter.[10] A recent study suggested that single nucleotide polymorphism rs1046934 mediates the association between stature and AF risk.[21] Further studies are needed to elucidate whether stature is a risk factor or a risk marker.

Left atrial enlargement

Left atrial abnormalities, including dilatation, are frequent in Ln-AF patients.[2] Initially, AF risk factors contribute to atrial dilation; recurrent AF events promote AF self-perpetuation, partially through LA dilation.[22] Similar to previous studies, our results demonstrate LA dilatation in patients with Ln-AF. However, its role is uncertain, and both primary and AF self-perpetuation mechanisms might account for atrial dilatation in our Ln-AF cohort.

Inflammation

We found an enhanced systemic pro-inflammatory status in patients with Ln-AF. The persistence of this association in patients with sinus rhythm, along with well-known pro-inflammatory effects of factors such as OSA and abdominal obesity, suggests that inflammation mediates Ln-AF substrate in our patients. However, further studies are needed to confirm this hypothesis.

Limitations

Some limitations of our study should be acknowledged. First, we estimated lifetime-accumulated physical activity through a retrospective questionnaire, which is subject to inaccuracies. We adapted our questionnaire from the widely used Minnesota Leisure-Time Questionnaire, and validated it in a previous work. Parameters such as maximum VO_2 might serve to precisely quantify actual fitness, but fail to estimate physical activity performed during the whole life. Secondly, our study was conducted with a rather small sample size, but was powered enough to address our aims and obtaining significant positive correlations. Thirdly, although our population had a low cardiovascular risk (no symptoms, no ECG or echocardiographic regional abnormalities, low predicted risk), we cannot completely exclude coronary disease in all individuals.

Conclusion

Limited high-intensity training protects against Ln-AF. Conversely, long-lasting high-intensity endurance training, height, abdominal obesity, and OSA are frequent risk factors for Ln-AF. A diagnosis of Ln-AF should lead to exhaustive efforts to rule out underlying emerging risk factors.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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