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Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals

Lluís Mont[1]*, David Tamborero[1], Roberto Elosua[3], Irma Molina[1], Blanca Coll-Vinent[2], Marta Sitges[1], Bárbara Vidal[1], Andrea Scalise[1], Alejandro Tejeira[1], Antonio Berruezo[1], and Josep Brugada[1] on behalf of the GIRAFA (Grup Integrat de Recerca en Fibril-lació Auricular) Investigators

[1]*Thorax Institute, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), C/Villarroel 170, Barcelona, 08036 Catalonia, Spain;* [2]*Emergency Department, Hospital Clínic, University of Barcelona, Catalonia, Spain; and* [3]*Lipids Unit, Institut Municipal Investigacions Mèdiques (IMIM), Autonomous University of Barcelona, Catalonia, Spain*

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KEYWORDS
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Atrial volume

Aims The aetiology of atrial fibrillation (AF) remains unknown in some patients. The aim of the study was to identify new risk factors for developing lone AF (LAF).
Methods and results A series of 107 consecutive patients younger than 65, seen in the emergency room for an episode of LAF of <48 h duration were included in the study. A group of 107 healthy volunteers matched for age and sex were recruited as controls. All subjects answered a validated questionnaire concerning leisure and occupational activities performed throughout their lifetimes to estimate accumulated hours of physical effort, classified in four levels of intensity. Demographic and echocardiographic measurements were also recorded. There were 69% of males and mean age was 48 ± 11 years. AF was paroxysmal in 57% and persistent in the remaining 43%. Patients with AF performed more hours of both moderate and heavy intensity physical activity. They also were taller, and had a larger left atria, ventricle, and body surface area. At the multivariable analysis, only moderate and heavy physical activity, height, and anteroposterior atrial diameter were independently associated with LAF.
Conclusions Accumulated lifetime physical activity, height, and left atrial size are risk factors for LAF in healthy middle-aged individuals.

Atrial fibrillation (AF) is the most common arrhythmia and has a marked impact on morbidity and mortality.[1,2] Its incidence is increasing, but this rise is not due exclusively to population ageing or to the higher prevalence of newly described risk factors such as obesity.[3,4] Classically, AF has been associated with a number of cardiac and extracardiac diseases such as hypertension, structural heart disease, and hyperthyroidism. However, in some patients its aetiology remains unknown.[5] This condition has been termed lone AF (LAF). The prevalence of LAF ranges from around 2–10% in the AF population and may reach 30% in patients seeking medical attention.[5–7] Uncovering new risk factors may help broaden our understanding of AF epidemics and thus improve our ability to control them.

Previous studies have shown that the long-term practice of endurance sports increases the risk of developing AF.[8–13] However, the role of occupational physical activity has not been analysed. The purpose of the current study is to investigate whether people who perform long-term physical activity either at work or during their leisure time have an increased

* Corresponding author. Tel: +34 932275551; fax: +34 934513045.
E-mail address: lmont@clinic.ub.es

risk of developing AF, and also, to identify other potential risk factors for AF development in patients with LAF.

Methods

Design

The study was a prospective, age, and sex-matched case–control analysis conducted in a hospital setting. Written informed consent was obtained from all participants. The protocol was approved by the Ethics Committee of our Institution.

Identification of cases

Cases were consecutive paroxysmal or persistent LAF patients between 18 and 65 years recruited by one of the researchers (B.C.) in the emergency room at our Institution between January 2001 and June 2005 due to a AF of recent onset (in the past 48 h). Patients with permanent AF were excluded from the analysis, as were those unable to attend follow-up visits for any reason. LAF was defined as AF in the absence of any identifiable cause of the arrhythmia. In all cases, AF was the primary reason for the emergency room admission. Any concomitant disease was properly excluded. Exclusion criteria were presence of any cardiovascular disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic liver disease, infectious or inflammatory diseases and AF secondary to hypoxaemia, thyroid disease, drugs abuse, acute alcohol intoxication, and chronic alcohol abuse (defined as a consumption of $>$80 and $>$60 g/day in males and females, respectively). Atrial fibrillation was considered of 'vagal' origin when it occurred at least 80% of times during sleep and/or in post-prandial situations and 'adrenergic' when it occurred at least 80% of the time during high physical exertion and/or in situations of stress. The remaining patients were classified as suffering 'random' AF.

Selection of controls

Controls were age- and sex-matched with cases and were recruited from healthy relatives or visitors of patients seen at the cardiology department, not related to the LAF patients included in the study. Both cases and controls belonged to the same geographical area and social environment. Exclusion criteria were: age over 65, presence of structural heart disease [more than trivial valve regurgitation, any valve stenosis, known ischaemic heart disease, or left ventricular (LV) dysfunction of any aetiology], hyperthyroidism, alcohol abuse, hypertension requiring medical treatment, or pulmonary disease.

Physical activity assessment

A validated questionnaire concerning accumulated lifetime physical activity was administered by three trained physicians (I.M., A.S., and V.T.) to all individuals in both case and control groups.[14] The questionnaire included a detailed recording of occupational and exercise/sports activity. For each activity, the following variables were recorded: age of starting and age of ending, to calculate duration, and the number of months per year, number of days per week, and number of hours per day, to calculate frequency. Subjects were asked to classify the intensity of each physical activity in four levels: *sedentary*, activities requiring no physical effort with minimal walking; *light*, activities requiring minimal physical effort such as standing and slow walking with no increase in heart rate and no perspiration; *moderate*, activities that are not exhausting but that increase the heart rate slightly and may cause some light perspiration; and *heavy*, vigorous activities. For example, an individual working in agriculture or the building industry might present an average of 5 h of light intensity, 2 h of moderate intensity, and 1 h of heavy intensity activity for each working day. Sports such as cycling or swimming might involve either moderate or heavy intensity activity depending on the level of physical exercise. The accumulated lifetime hours of all occupational and exercise/sports activities for each level were calculated for each subject, taking into account their duration and frequency.

Echocardiography

All patients and control subjects underwent a comprehensive transthoracic echocardiography study. It was performed at outpatient clinic after discharge. Patients were in sinus rhythm for at least 2 weeks to exclude atrial stunning. Two-dimensional Doppler echocardiography was performed using a commercially available system and images were digitally stored for later off-line analysis. LV dimensions and ejection fraction (Simpson's biplanar method) were obtained from M-mode and 2D scans following the recommendations of the American Society of Echocardiography.[15]

Left ventricular diastolic function was assessed in terms of LV inflow diastolic velocities and lateral mitral annulus motion.[16,17] Early (E) and late (A) peak diastolic velocities of the LV inflow were determined by pulsed-wave Doppler with the sample volume placed at the tips of the mitral valve, and the E/A ratio was then calculated. Deceleration time (DT) of the E wave was also measured. Using colour M-mode Doppler, the propagation velocity of flow (V_p) into the LV was determined after changing the colour-coded scale so that the first aliasing wave front could be clearly seen and measured. The early and late peak diastolic velocities of the mitral annulus (Ea and Aa)[18,19] were determined using pulsed-wave Doppler tissue imaging, placing the sample volume at its lateral segment. Left atrial (LA) size was evaluated in the antero-posterior dimension (from the long parasternal view) and in the transversal (medio-lateral) and longitudinal (infero-superior) dimensions (from the apical four-chamber view). Maximum LA (end-systole) area and volume were also determined from the apical four-chamber view, by manually tracing the endocardial border in 2D scans.[20,21]

All cardiac dimensions were also indexed to the body surface area (BSA) of each patient or normal volunteer.[22]

Other variables

Subjects were classified as current cigarette smokers if they reported having smoked at least one cigarette/day during the previous year. Height and weight were measured with the individual dressed in an examining gown and barefoot. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Body surface area was calculated as $\sqrt{\text{height (m)} * \text{weight (kg)}/36}$.

Statistical analysis

Continuous data are expressed as mean $\pm$ SD or median (quartile 25, quartile 75) when the variables were not normally distributed. The χ^2 test was used to compare proportions between the groups. Student's t or Mann–Whitney U-tests were used to compare continuous variables. To assess the linear and non-linear relation between continuous variables and occurrence of LAF, a thin-plate Spline regression smoothing was performed. Physical activity was categorized into tertiles. Conditional logistic regression was used to determine the variables associated with LAF. The multivariable model was selected as the one that best fitted with the data (based on the likelihood ratio test), and that also showed the more precise estimation (narrower confidence intervals) of the magnitude of association with the variables of interest. A two-tailed nominal P-value of $<$0.05 was considered statistically significant. The analyses were performed using the SPSS 11.0 statistical package (SPSS, Chicago, IL, USA) and R version 2.4.0 (the R project for statistical computing).

Table 1 Demographic characteristics

	Patients ($n = 107$)	Controls ($n = 107$)	P-value
Age (years)	48.0 ± 11.6	47.6 ± 10.2	0.74
Male sex (%)	74 (69%)	74 (69%)	1.00
Smoking (%)	53 (50%)	53 (50%)	0.80
Paroxysmal/persistent AF(%)	61 (57%)/46 (43%)	–	–
Vagal AF (%)	75 (70%)		
First AF episode/recurrent AF (%)	46 (43%)/61 (57%)	–	–
Number of AF episodes	4.5 ± 6.9	–	–
AF duration (h)	15.4 ± 13.7		
Height (cm)	168 ± 8	165 ± 5	<0.001
BMI (kg/m^2)	25.1 ± 3.1	24.6 ± 0.9	0.104
BSA (m^2)	1.81 ± 0.18	1.73 ± 0.09	<0.001
Cumulated hours of physical activity occupational moderate[a]	0 (0–10 132)	0 (0–0)	<0.001
Occupational heavy[a]	0 (0–0)	0 (0–0)	0.317
Exercise/sports moderate[a]	1273 (0–4798)	0 (0–3741)	0.007
Exercise/sports heavy[a]	338 (0–3118)	0 (0–0)	<0.001
Occupational+exercise moderate[a]	6859 (637–13 163)	0 (0–5260)	<0.001
Occupational+exercise heavy[a]	338 (0–3118)	0 (0–0)	<0.001

AF, atrial fibrillation; BMI, body mass index; BSA, body surface area.
[a]Median (25th–75th quartile). Mann–Whitney U-test.

Results

Demographic characteristics of the 107 patients and 107 age- and sex-matched controls are shown in *Table 1*. Sixty-nine per cent of patients were male. Most AF episodes were paroxysmal and in most of the patients the origin was vagal, with a predominance of nocturnal episodes.

Anthropometric variables

Both height and BSA were associated with LAF. In contrast, BMI did not differ between patients and controls (*Table 1*).

Physical activity

Levels of lifetime physical activity in both patients and controls are also shown in *Table 1*. The cumulated hours of moderate and heavy intensity exercise/sports activity and moderate occupational physical activity were significantly higher in patients with LAF than in controls. Total hours of combined occupational an exercise/sports activities of moderate intensity were also significantly higher in LAF patients than in controls. Occupational and exercise/sports activities practiced by patients and controls are listed in *Table 2*.

Heart size

Several measurements of atrial and ventricular diameters and volumes were performed (*Table 3*). Left atrial diameters and volumes were larger in patients than in controls. Left ventricular diameters and LV mass were also higher among patients. Adjusting echo measurements according to BSA, the differences in LA diameters and volumes and LV mass were still significant, indicating that patients with LAF had larger atria and larger ventricular mass regardless of body size. There were no significant differences in LA size between patients with a first episode when compared with those with recurrent episodes.

Table 2 List of the most frequently occupational and exercise/sport activities distinguishing between moderate and heavy intensity practiced in patient and control groups

	Level of effort			
	Patient group (n)		Control group (n)	
	Moderate	Heavy	Moderate	Heavy
Occupational activities				
Service work	28	–	12	–
Industrial work	5	–	2	–
Agriculture	5	1	2	–
Building work	3	1	2	–
Security	3	–	2	–
Sports teaching	3	–	0	–
Exercise/sport activities				
Swimming	27	3	27	1
Running	8	18	6	11
Fitness centre	20	3	13	0
Soccer	1	20	1	8
Tennis	4	15	3	9
Cycling	3	8	11	3
Basketball	0	7	0	2
Others	9	7	8	3

Table 4 shows the results of diastolic function indexes. There were no differences in any of the measured parameters between patients and controls.

Multivariable regression analysis

Height showed a statistically significant non-linear relation with LAF occurrence whereas LA anteroposterior diameter

Table 3 Echocardiographic parameters both absolute and indexed to body surface area

	Patients ($n = 107$)	Controls ($n = 107$)	*P*-value
LA anteroposterior diameter (mm)	38.7 ± 5.3	35.8 ± 3.2	<0.001
LA longitudinal diameter (mm)	47.8 ± 6.8	40.9 ± 6.0	<0.001
LA transversal diameter (mm)	38.5 ± 5.6	31.6 ± 4.05	<0.001
LA area (cm^2)	18.3 ± 4.1	14.5 ± 2.4	<0.001
LA volume (mL)	46.5 ± 17.2	34.6 ± 10.0	<0.001
LV end diastolic diameter (mm)	50.4 ± 4.9	48.1 ± 4.1	<0.001
LV end systolic diameter (mm)	32.4 ± 4.7	30.4 ± 3.2	<0.001
LV mass (g)	187.7 ± 40.0	158.6 ± 32.1	<0.001
LV ejection fraction (%)	65.0 ± 4.5	63.1 ± 6.1	0.010
LA anteroposterior diameter/BSA (mm/m^2)	21.6 ± 3.6	20.6 ± 2.1	0.026
LA longitudinal diameter/ BSA (mm/m^2)	26.5 ± 3.7	23.6 ± 3.6	<0.001
LA transversal diameter/ BSA (mm/m^2)	21.4 ± 3.7	18.3 ± 2.6	<0.001
LA area/BSA (cm^2/m^2)	10.1 ± 2.2	8.4 ± 1.4	<0.001
LA volume/BSA (ml/m^2)	25.5 ± 8.4	20.0 ± 5.9	<0.001
LV end diastolic diameter (mm/m^2)	28.1 ± 3.1	27.8 ± 2.6	0.464
LV end systolic diameter (mm/m^2)	18.0 ± 3.2	17.5 ± 2.1	0.162
LV mass (g/m^2)	105.1 ± 21.9	89.6 ± 18.0	<0.001

LA, left atrial; LV, left ventricle; BSA, body surface area.

Table 4 Diastolic echocardiographic parameters

	Patients ($n = 107$)	Controls ($n = 107$)	*P*-value
E/*A*	1.20 ± 0.35	1.18 ± 0.27	0.666
E/Em	5.30 ± 2.05	5.36 ± 2.60	0.854
Propagation velocity of flow (cm/s)	56.14 ± 15.41	55.43 ± 13.93	0.763
Em/Am	1.17 ± 0.46	1.08 ± 0.48	0.275
Deceleration time of the E wave (ms)	209.9 ± 44.7	197.7 ± 40.1	0.053

E/*A*, ratio of early to late peak diastolic velocities of the left ventricular inflow.
Em/Am, ratio of early to late peak diastolic velocities of the mitral annulus.

was linearly associated with LAF (*Figure 1*). On the basis of this result, height was categorized into three groups (<165, 165–176.9, and ≥177 cm) in the conditional regression analysis.

Multivariable model showed that moderate and heavy physical activity, height, and LA anteroposterior diameter were independently associated with LAF (*Table 5*).

Table 6 shows the results of conditional regression analyses introducing moderate and heavy physical activity separately. Both variables retained independent predictive value for the occurrence of LAF. Owing to co-linearity the model including

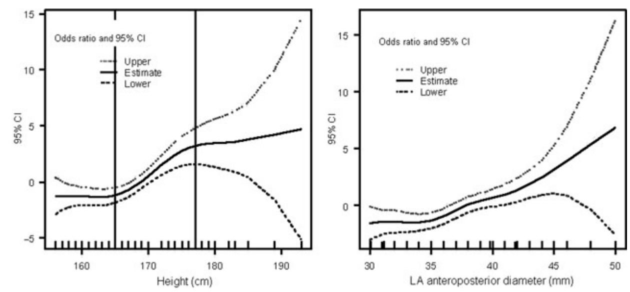

Figure 1 Thin-plate spline regression smoothing results assessing: (*A*) the non-linear relation between height and occurrence of lone atrial fibrillation and (*B*) the linear relation between left atrial diameter and occurrence of lone atrial fibrillation.

Table 5 Adjusted odds ratios and 95% confidence intervals of lone atrial fibrillation for cumulated moderate and heavy physical activity, height, and left atrial anteroposterior diameter

	Odds ratio (95% confidence interval)	*P*-value
Cumulated moderate and heavy physical activity		
0–2077 h	1	
2078–9318 h	5.60 (1.59–19.75)	0.0075
≥9319 h	15.11 (3.75–60.83)	0.0001
Height		
155–164.9 cm	1	
165–176.9 cm	13.54 (2.47–74.30)	0.0027
177–195 cm	23.23 (2.48–217.56)	0.0059
Left atrial anteroposterior diameter (mm)	1.40 (1.17–1.67)	0.0003

cumulated moderate, cumulated heavy physical activity as separate variables plus height and LA anteroposterior diameter did not converge; therefore, it is not depicted.

Discussion

The main finding of this study is the identification of previously unrecognized risk factors for LAF, in individuals with normal hearts and without precipitating conditions. Focal atrial tachycardias from pulmonary veins have recently been implicated the development of AF in normal hearts,[23] but little attention has been paid to other conditions that may create subtle changes in heart size and structure and may lead to LAF in patients without structural disease.

Role of physical activity

The most striking finding was the association of LAF and accumulated hours of physical activity. Previous studies have shown that long-term practice of endurance sport may indeed increase the risk of developing AF.[8–13] In the present study, we also observed an association with work-related physical activity. Furthermore, the association was present in both moderate and heavy physical activity in the second and third tertiles. The mechanism that may explain the association remains unknown, but it may be

Table 6 Adjusted odds ratios and 95% confidence intervals of lone atrial fibrillation for cumulated moderate and heavy physical activities adjusted for height and left atrial anteroposterior diameter

	Odds ratio (95% confidence interval)	*P*-value
Cumulated moderate physical activity		
0–138 h	1	
139–6625 h	6.47 (1.53–27.61)	0.0120
≥6626 h	22.89 (4.32–121.24)	0.0002
Height		
155–164.9 cm	1	
165–176.9 cm	9.51 (1.69–53.52)	0.0110
177–195 cm	16.52 (1.75–156.15)	0.0140
Left atrial anteroposterior diameter (mm)	1.35 (1.12–1.64)	0.0018
Cumulated heavy physical activity		
0 h	1	
1–563 h	1.77 (0.22–14.26)	0.5900
≥564 h	7.31 (2.33–22.96)	0.0006
Height		
155–164.9 cm	1	
165–176.9 cm	15.47 (2.23–107)	0.0056
177–195 cm	17.00 (1.51–192)	0.0220
Left atrial anteroposterior diameter (mm)	1.51 (1.25–1.83)	0.0002

related to a chronic volume and pressure overload caused by increased activity. In fact it is well known that the athlete's heart, although assumed to be a physiological adaptation, has increased atrial size and ventricular mass and altered diastolic function,[24,25] which, like hypertension, may in the long run create fibrosis and a substrate for AF. Recent data from Heidbüchel *et al*.[26] suggest that long-term cycling may cause arrhythmogenic changes in the right ventricle of susceptible individuals, further supporting the role of physical activity in the pathological remodelling not only of the atrium but also of the ventricle. Another recently proposed mechanism is the chronic inflammation related to endurance sport, although this remains purely speculative at present.[27]

Role of height and atrial size

Experimental studies and observations in animals suggest that the absolute size of the body, and to a lesser extent the atrium, may be of importance in the development of AF. For example, the prevalence of AF is much higher in horses[28] than in smaller animals, and it is also known that AF models are much easier to create in large mammals such as dogs and sheep than in small experimental animals such as rats or mice.[29] It was not until very recently that obesity (BMI) was shown to be a risk factor for AF.[30] More recently still, Hanna *et al*.[31] showed that the probability of AF was related to height and BSA in patients with heart failure. However, to our knowledge, this association has not been described in healthy patients. Height is strongly related to absolute atrial size,[32] but both variables in our series had an independent predictive value for AF, suggesting that in some patients at least atrial size depends on factors other than height, for example physical activity.

Finally, the third independent risk factor for the development of LAF was atrial size. It is known that patients with LAF and apparently normal hearts have larger atria than controls.[33] Atrial size is a major determinant of the occurrence of AF in patients with structural heart disease.[34] Therefore, it is not surprising that atrial size (absolute as well as indexed for BSA) is also a risk factor for AF in patients with apparently normal hearts. The important question is why these patients have larger atria than controls in the absence of heart disease. In the young healthy population, persistent volume and pressure overload due to long-term physical activity may play a role in this enlargement, similar to that observed in hypertensive patients. Subtle structural changes (fibrosis, changes in gap junctions) may create a substrate which, together with other triggers such as increased vagal tone or ectopy, may be the cause of AF. Some authors have suggested that episodes of AF, although paroxysmal, may promote remodelling, and that atrial enlargement in healthy individuals may be a consequence rather than the aetiologic factor. This hypothesis is highly unlikely in our population since LA dimensions in patients with a first episode did not differ from those with recurrent episodes.

The lack of association observed in our series between BMI and AF may be due to the low prevalence of obesity in this population of middle-aged healthy individuals.

The fact that physical activity is a risk factor for AF does not argue against exercise as a way of preventing coronary artery disease. It only offers a word of caution suggesting that the benefits obtained by physical activity, if excessively intense and over a great many hours, may be counteracted by the risk of AF.

Study limitations

Owing to the strict entry criteria in terms of age and lack of heart disease, the number of recruited patients is relatively small. The confidence interval of the hazard ratios is large. However, we do not think that this limitation affects the conclusions of the study, taking into account that the recognized risk factors have already been identified in other populations.

Another limitation is the definition of LAF. In our study, we established an arbitrary age limit of 65 years as inclusion criteria. Recently, the published guidelines for AF[35] suggest 60-years old as the upper limit to define LAF. In our series, ∼10% of the patients were between 60 and 65 years. However, if the analysis is performed without these patients and their controls, the results were the same.

Every effort has been made to avoid selection bias. However, since participation in the study is voluntary, we cannot rule out the possibility that the controls who agreed to participate were more sedentary than patients, for social or cultural reasons. However, since controls were recruited among relatives of patients of the cardiology department, we assumed that their geographical and social background was similar. The Hospital Clinic Universitari is a public hospital that attends to patients with State health insurance, which covers 100% of the population. Our sample can therefore be regarded as representative of the area of Barcelona.

Conclusions

Physical activity, height, and LA size are independent risk factors for the development of LAF in middle-aged, healthy individuals.

Acknowledgements

List of GIRAFA investigators

Coordinator: Lluis Mont.

Hospital Clínic, University of Barcelona (alphabetical order):

Manel Azqueta, Begoña Benito, Antonio Berruezo, Josep Brugada, Blanca Coll-Vinent, Victoria Delgado, Eric Gonzalez, Irma Molina, Santiago Nava, Carles Pare, Socorro Rivera, Ulises Rogel, Andrea Scalise, Marta Sitges, David Tamborero, Alejandro Tejeira, Jose Maria Tolosana, Barbara Vidal.

Institut Municipal Investigacions Mèdiques (IMIM), Autonomous University of Barcelona (alphabetical order):

Roberto Elosua, Lluis Molina, Joan Salvador Vila.

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