ORIGINAL ARTICLE

Natural History of and Risk Factors for Idiopathic Atrial Fibrillation Recurrence (FAP Registry)

Francesc Planas,[a] César Romero-Menor,[b] Gabriel Vázquez-Oliva,[c] Teresa Poblet,[d] and Francesc Navarro-López,[e] on behalf of the investigators of the FAP Study conducted in district hospitals and outpatient clinics of Catalonia, Spain

[a]Servicio de Cardiología, Hospital Municipal de Badalona (FP), Badalona, Barcelona, Spain.
[b]Servicio de Cardiología, Hospital de Sant Boi, Sant Boi de Llobregat, Barcelona, Spain.
[c]Servicio de Cardiología, Hospital Comarcal de la Selva-Blanes, Barcelona, Spain.
[d]Servicio de Cardiología, Hospital de l'Esperit Sant (TP), Santa Coloma de Gramenet, Barcelona, Spain.
[e]Servicio de Cardiología, Hospital Clínic (IMCV/IDIBAPS), Universidad de Barcelona, Barcelona, Spain.

Introduction and objectives. The natural history of idiopathic atrial fibrillation is not well understood. The aim of this study was to investigate the frequency of and risk factors for disease recurrence.

Methods. The study involved 115 patients with a first episode of paroxysmal atrial fibrillation of unknown origin who were included the FAP registry, which contains data from 11 district hospitals in Catalonia, Spain. All patients underwent comprehensive clinical, laboratory, electrocardiographic and echocardiographic investigations at baseline and were followed up periodically every 6 months to identify the occurrence of new symptomatic episodes and their complications.

Results. During a mean follow-up period of 912 (445) days, 32 (27.8%) patients experienced recurrence of atrial fibrillation. Those who experienced recurrence had a significantly higher left ventricular ejection fraction (*P*=.023) and smaller end-systolic volume (*P*<.001), and they were more likely to consume alcohol regularly (*P*=.013). Cox regression analysis confirmed that these variables had independent prognostic value. In contrast, the occurrence of syncope during the initial episode was associated with a lower likelihood of recurrence (*P*=.017).

Conclusions. The risk of recurrence of idiopathic atrial fibrillation was high, and was enhanced by moderate alcohol consumption and increased left ventricular activity, probably of sympathetic origin. This trend was less marked in paroxysmal atrial fibrillation of vagal origin.

Key words: *Atrial fibrillation. Follow-up studies. Risk factors. Alcohol. Autonomic nervous system. Echocardiography.*

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Historia natural y factores de riesgo de recurrencia de la fibrilación auricular primaria (Registro FAP)

Introducción y objetivos. La historia natural de la fibrilación auricular (FA) primaria o idiopática tiene aspectos poco conocidos. El objeto del estudio fue describir la frecuencia y los factores determinantes de las recurrencias.

Métodos. Se estudió a 115 pacientes atendidos en su primera crisis de FA paroxística sin causa conocida incluidos en el «registro FAP», en el que participan 11 centros comarcales de Cataluña. Se les practicó un estudio clínico, analítico, electrocardiográfico y ecocardiográfico exhaustivo y fueron seguidos periódicamente cada 6 meses para detectar la aparición de nuevas crisis sintomáticas y sus complicaciones.

Resultados. Durante el seguimiento de 912 ± 445 días de promedio, 32 (27,8%) pacientes presentaron una recidiva de la fibrilación auricular. Los pacientes con recurrencias tenían una fracción de eyección más elevada (p = 0,023), un menor volumen telesistólico (p < 0,001) y eran con mayor frecuencia consumidores habituales de alcohol (p = 0,013). El análisis de regresión de Cox confirmó el valor predictivo independiente de estas variables. En cambio, la presencia de lipotimias en el episodio agudo se asoció con una menor tendencia a recidivar (p = 0,017).

Conclusiones. La fibrilación auricular idiopática mostró una notable tendencia a las recidivas, favorecida por el consumo moderado de alcohol y el aumento de la actividad ventricular, probablemente de origen simpático. La tendencia fue menor en la fibrilación paroxística de origen vagal.

Palabras clave: *Fibrilación auricular. Estudios de seguimiento. Factores de riesgo. Alcohol. Sistema nervioso autónomo. Ecocardiografía.*

INTRODUCTION

Idiopathic or primary atrial fibrillation (AF) is defined by the absence of identifiable structural or functional heart disease or any other known etiological factor.[1,2] Its prevalence ranges between 2% and 31%,[1,3,4] and it

*The centers and investigators involved in the FAP Study are listed at the end of the article.
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Correspondence: Dr. F. Navarro-López
Servicio de Cardiología. Hospital Clínic.
Villarroel, 179. 08036 Barcelona. España.
E-mail: fnavarro@ub.edu

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ABBREVIATIONS

AF: atrial fibrillation.
EF: ejection fraction.
LVEF: left ventricular ejection fraction.
LVEDV: left ventricular end-diastolic volume.
LVESV: left ventricular end-systolic volume.

represents 20% to 22% of all the cases of AF detected in our patient population.[5,6] In the initial phases, it usually presents as a transient episode that remits in less than seven days (paroxysmal AF) or subsides readily with medication in less than 48 hours (persistent AF, of short duration).[1-4,7] It is considered to be a more benign clinical form of AF secondary to heart disease or other causal factors, although it exhibits a certain tendency to recur and is not totally free of complications. However, given the variability among the populations studied and the criteria that must be met for its diagnosis, the available data concerning its course do not always coincide.[3,8-11] Most of the large series published in recent years grouped together patients of widely differing etiologies that only had in common the presence of AF, in which the rates of recurrences and complications depend to a great extent on the underlying disease.[12-15]

For the purpose of analyzing specifically the natural history of idiopathic AF and the factors responsible for recurrences, we performed a long-term follow-up study of a group of patients included in the "FAP Registry", a prospective, multicenter, observational study dealing with primary atrial fibrillation in which 11 health care centers in Catalonia, Spain, participated.[6]

METHODS

Study Design

The study population included 115 consecutive patients examined in the emergency services or cardiology units of seven district hospitals and four outpatient clinics after detection of a first episode of idiopathic AF. These patients underwent a comprehensive initial study and were followed periodically according to the protocol and the data collection forms of the FAP Registry, described elsewhere, which include 80 variables.[6] Briefly, patient selection required electrocardiographic confirmation of AF, restoration of sinus rhythm within seven days and diagnosis of idiopathic AF by exclusion in the initial study (or during follow-up) of any identifiable heart disease or known etiological factor, namely: sinus node disease (heart rate under 50 beats/minute); coronary heart disease (history of angina, infarction or electrocardiographic signs indicative of ischemia or necrosis); cardiomyopathy; heart failure; muscular dystrophy; hypertension (documented in the medical record or detection of an arterial pressure ≥140/≥90 mm Hg on two or more occasions) or antihypertensive therapy; bronchial asthma, chronic lung disease or bronchodilator therapy; active or inactive hyperthyroidism (thyrotropin [TSH], thyroxine [T_4]); recent trauma or surgery; hard-to-control insulin-dependent diabetes mellitus; electrolyte imbalance; renal failure (creatinine >2mg/dL); prior or recent history of substantial alcohol consumption (>40 g alcohol/day in men and >20 g/day in women, amount estimated on the basis of the question on the number of glasses consumed per week) and/or drug abuse; antiarrhythmic or vasoactive drugs; pacemaker dependence; development of AF during hospital stay; left ventricular hypertrophy (thickness >11 mm); depressed left ventricular ejection fraction (LVEF) (<50%) or left ventricular end-diastolic diameter >56 mm.

Data concerning the medical history, physical examination, electrocardiogram, serum biochemistry and blood test were collected, and adverse events and complications, such as the development of chronic AF and of thromboembolic events, were evaluated in the initial study and during the systematic periodical visits (every six months). An echocardiogram was carried out annually. Patients were considered to be a regular drinkers if they consumed wine, beer or spirits on a daily basis in amounts lower than those considered to be the cut-off point for exclusion from the study; otherwise, they were considered to be occasional drinkers or nondrinkers. The onset of an episode of symptomatic AF (documented by electrocardiogram) 48 hours after spontaneous, electrical or pharmacological cardioversion was considered to be a recurrence.

Statistical Analysis

The data are expressed as the mean plus or minus the standard deviation or as percentages. The differences between the groups of patients with and without recurrences were analyzed using Student's *t* test or the χ^2 test. For the analysis of bivariate correlations, the Pearson correlation coefficient was employed.

The cumulated risk of AF recurrence was estimated by means of Kaplan-Meier curves, and the differences between groups were assessed by the log-rank test. To identify those factors having independent predictive value with respect to recurrences, Cox regression analysis was employed. *P* values less than .05 were considered to indicate statistical significance. The analysis was performed with an SPSS statistical software package (version 12).

RESULTS

Characteristics of the Study Population

The 115 patients examined for a first AF episode were part of a group of 181 consecutive individuals diagnosed with primary or idiopathic AF in a baseline study, 64 of whom were excluded for having a previous history of

AF and two because they had been treated with bronchodilators or anorectic agents during follow-up. The periodic follow-up examinations supported the initial diagnosis of idiopathic AF. There were 64 men (64.3%) and 41 women (35.7%), whose ages ranged between 23 and 82 years (52.3[14.1] years). In all the episodes, sinus rhythm was restored within 48 hours (although the inclusion criteria permitted a period of up to seven days), in 20 cases, with no treatment whatsoever (paroxysmal AF).[2] The remaining patients received intravenous amiodarone (5-10 mg/kg body weight; n=65), flecainide or propafenone (n=13) or digoxin or beta blockers (n=17; persistent AF of more than 48 hours' duration). Treatment was initiated early to reduce the heart rate or accelerate the restoration of sinus rhythm (class IIa indication of the ACC/AHA/ESC guidelines, 2001).[1] Thus, the restoration was probably spontaneous in many cases. Electrical cardioversion was applied in one case.

Recurrence Risk

During the follow-up period (mean duration: 912[445] days), recurrence was diagnosed in 32 patients, 12 of whom experienced two. The cumulative percentage of patients with recurrences was 27.5%(5%) in the first year, 35.5%[6%] after two years and 41%(7%) after three years (Fig. 1). The frequency of episodes of primary AF was 0.84(0.7)/year and the mean interval between episodes was 699(436) days, ranging from one week to 5.5 years. The cumulative frequency curve did not differ significantly (*P*=.833) from that of the 64 patients excluded from the study for having had a previous recurrence (retrospective analysis).

Risk Factors for Recurrence: Univariate Analysis

Baseline Clinical Characteristics (Table 1)

No significant differences were detected between the patients with or without recurrences, with the exception of the higher incidence of regular alcohol consumption among those who had recurrence (*P*=.014).

Clinical and Electrocardiographic Characteristics of Primary Atrial Fibrillation Episodes

The circumstances surrounding the onset, the symptoms of acute episodes and the electrocardiographic findings were similar in the two groups (Table 2), except for the incidence of palpitations in acute episodes (*P*=.012) and the observation that none of the 16 patients with syncope in the initial episode experienced recurrences (*P*=.017).

Echocardiographic Findings

As shown in Table 3, the left ventricular end-systolic volume (LVESV) (*P*<.001) and left ventricular end-diastolic volume (LVEDV) (*P*=.017) were lower, and LVEF was higher (*P*=.023) among patients who experienced recurrences. In contrast, there was no difference in left atrial size. We were unable to demonstrate any association between LVEF or LVESV and the remainder of the variables studied, such as age, sex, body

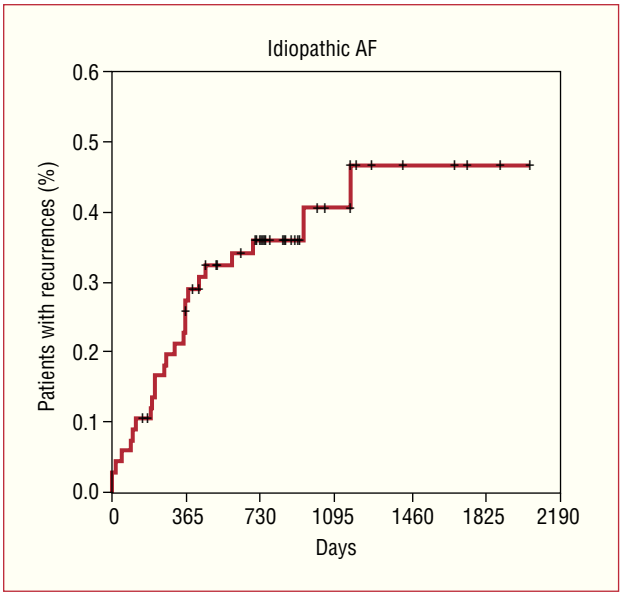

Figure 1. Cumulative frequency curve corresponding to patients with recurrence of atrial fibrillation (AF).

TABLE 1. **Demographic Characteristics and Risk Factors**

	With Recurrence (n=32)	Without Recurrence (n=83)	*P*
Demographic characteristics			
Age, mean (SD), y	54.50 (13.6)	52.13 (14.3)	.426
Men	21 (65.6)	53 (63.9)	.859
Weight, mean (SD), kg	74.9 (10.1)	74.5 (12.3)	.907
Height, mean (SD), cm	168.3 (8)	172 (10)	.226
Risk factors			
SAP, mean (SD), mm Hg	132.8 (14.6)	132.5 (20.5)	.935
DAP, mean (SD), mm Hg	79.5 (9.8)	79.5 (12.3)	.994
Mild hypertension*, n (%)	1 (3.1)	7 (8.4)	.552
Smoking, n (%)	9 (28)	28 (33.7)	.723
Diabetes, n (%)	3 (9.4)	12 (14.5)	.677
Alcohol consumption, n (%)	16 (50)	20 (24)	.014
Laboratory findings			
Hemoglobin, mean (SD), g/L	14.5 (1.2)	14.8 (1.6)	.502
Hematocrit, mean (SD), %	43.5 (2.8)	44.3 (4.8)	.456
Blood glucose, mean (SD), mg/dL	105.5 (35.6)	119.1 (51.8)	.226
Potassium, mean (SD), mEq/L	4.3 (0.4)	4.2 (0.4)	.705
TSH, mean (SD), µU/mL	1.9 (1.2)	2.3 (1.6)	.288
T4, mean (SD), µg/dL	1.25 (0.2)	1.19 (0.2)	.424

DAP: diastolic arterial pressure; K: potassium; SAP: systolic arterial pressure; SD: standard deviation T4: free T4 (thyroxine); TSH: thyrotropin (thyroid-stimulating hormone).
*Mild hypertension: no drug therapy and normal electrocardiogram.

TABLE 2. **Characteristics of the Atrial Fibrillation Episodes**

	With Recurrence (n=32)	Without Recurrence (n=83)	*P*
Circumstances surrounding onset			
While resting, n (%)	8(25.0)	28(33.7)	.495
While sleeping, n (%)	0	(8.4)	.207
Postprandial, n (%)	1(3.1)	2(2.4)	.662
While urinating, n (%)	3(9.4)	3(3.6)	.437
Symptomatology			
Palpitations, n (%)	31(96)	60(72.6)	.012
Dyspnea, n (%)	10(31.3)	19(22.9)	.493
Chest pain, n (%)	8(25)	19 (22.9)	.994
Syncope or presyncope, n (%)	0(0)	16(19.3)	.017
Electrocardiogram			
Heart rate, mean (SD), QRS/min	134(31)	136(25)	.805
Maximum RR, mean (SD)	682.6(242)	714(238)	.595
Minimum RR, mean (SD)	330.6(148)	358.3(91)	.291
Difference in RR, mean (SD), %	48(18)	47(14)	.995
Episode duration, mean (SD), h	9.5(14)	8.8(13.8)	.834
Spontaneous reversion, n (%)	9(28.1)	11(13.2)	.107

RR: relative risk; SD: standard deviation.

TABLE 3. **Echocardiographic Findings**

	With Recurrence (n=32)	Without Recurrence (n=83)	*P*
Circumstances surrounding onset			
While resting, n (%)	8(25.0)	28(33.7)	.495
LV wall thickness, n (%)	8.94(1.3)	9.31(1.2)	.143
Septal thickness, n (%)	9.22(1.6)	9.50(1.2)	.318
LVEDD, mean (SD), mm	47.6(4.8)	49.7(4.7)	.036
LVESD, mean (SD), mm	28.1(4.7)	31.7(5.5)	.003
Left AD, mean (SD), mm	36.1(5.1)	36.2(5.2)	.972
LVEDV, mean (SD), mL	119.5(24)	105.6(6.0)	.170
LVESV, mean (SD), mL	28.0(11.0)	42.7(17.7)	<.001
LVEF, mean (SD), %	66.1(9.2)	60.4(9.9)	.007
LVEF ≥65, n (%)	24(75)	34(41)	.002

AD: atrial diameter; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; SD: standard deviation.

weight, height, arterial blood pressure, heart rate, atrial size or alcohol consumption. Only the LVEDV was significantly lower in women than in men (122[22] mL vs 105[27] mL; *P*<.001). The follow-up echocardiographic recordings revealed no significant changes in the variables studied. The mean time to onset of recurrences, estimated according to the Kaplan-Meier method (Fig. 2), was significantly shorter in patients with a LVEF ≥65% (803[134] days) than in those with a lower LVEF (1616[152] days; *P*=.02). The same was observed in the patients with a LVESV <40 mL (915[166] days) when compared with those with higher LVESV (1642[180] days; *P*=.006).

Multivariate Analysis: Independent Risk Factors

Cox regression analysis, in which all the variables with a *P* value <10 in the univariate analysis (ventricular dimensions, palpitations, syncope, alcohol consumption), together with age, sex, arterial blood pressure, and atrial diameter, factors that, theoretically, could be related to recurrence, identified the LVESV (or the left ventricular end-systolic diameter), regular alcohol consumption, and the absence of syncopal episodes in the first AF episode as the only independent predictive factors for recurrence (Table 4).

Complications

There were no embolic episodes or deaths during follow-up; nor were there significant changes in the laboratory or echocardiographic studies. During the study period, eight patients (6.9%) developed chronic AF, in the absence of any detectable related factors.

DISCUSSION

Risk of Recurrence

Our findings support the widely accepted view that the prognosis for primary AF, with no apparent cause, is relatively benign, although recurrences may occur with certain frequency and interfere with the life of the affected individual. The elevated incidence observed in our series (affecting 27.5% of the study population during the first year) is somewhat higher than that reported in the medical literature, and can be considered representative of a suburban population with free access to medical care provided by the social security system, which facilitates the detection of episodes. However, the published studies are far from being comparable. In the prospective ALFA study,[9] for example, the rate of recurrence within 6 to 12 months among 167 patients with paroxysmal AF was 31.3%, higher than that observed in our study, but 53.9% of the subjects presented underlying heart disease.

Factors Associated With Recurrences

The study has identified the following three independent risk factors that may play a role in the pathogenesis of primary AF and its recurrence.

More Active Ventricular Function

In the echocardiographic study, during sinus rhythm, the patients with recurrences presented increased left ventricular activity in comparison with the rest of the patients, as shown by the indexes of systolic function: increased LVEF and reduced LVESV. Given that no

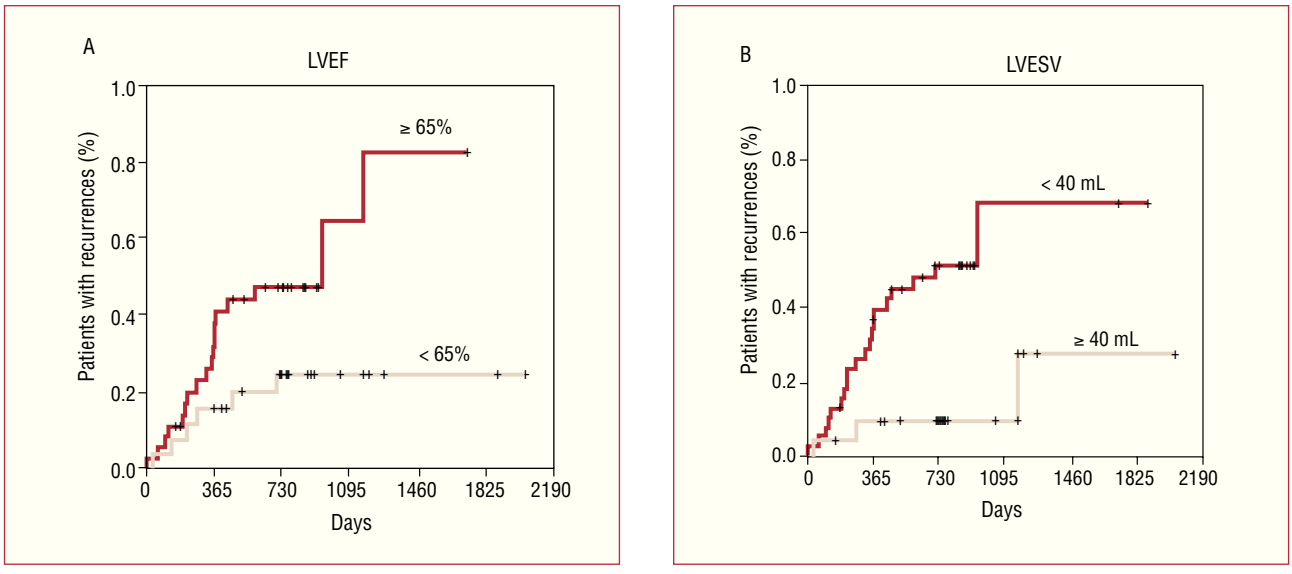

Figure 2. Cumulative frequency of recurrences according to the LVEF and the LVESV. The mean time to onset of recurrences, estimated using the Kaplan-Meier method, was significantly shorter (A) in patients with LVEF ≥65% (*P*=.02) and (B) in patients with LVESV <40 ml (*P*=.006).
LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume.

relationship was observed between the LVEF or LVESV and the variables that can influence them, the increased contractility may be attributed to a predominance of sympathetic tone. This circumstance is indicated by some authors who have studied the role of the autonomic nervous system in triggering AF by analyzing the changes in heart rate at the beginning and end of the episode, as recorded by Holter monitoring, although their conclusions do not always coincide.[16-20] Bettoni et al[16] concluded that the onset of AF was associated with an increase in adrenergic tone, followed by an abrupt increase in vagal tone. Lombardi et al[17] also detected an increase in sympathetic tone in the majority of their cases, and in vagal tone in the remainder. In contrast, in another series, Akyurek et al[18] stressed the importance of the decrease in heart rate variability, with depressed vagal tone.

The greater frequency of palpitations in these patients may also be indicative of an increased sympathetic activity, although differences in heart rate are not observed. However, the possibility that the perception of palpitations and, thus, the frequency of recurrences detected by electrocardiography, might be influenced, in part, by the sensitivity of each patient can not be ruled out. Should this be the case, the patients who do not perceive palpitations may experience recurrences of which they are not conscious.

In our series, the relationship usually observed between the tendency to recur and left atrial size, reported in patients with AF of different etiologies,[3,4,13] was not detected. In a study involving 50 patients with recurrent AF treated with flecainide, Haissaguerre et al[21] were also unable to confirm the existence of a relationship between left atrial size and either left ventricular dimensions or shortening fraction.

Moderate Alcohol Consumption

Although anecdotal evidence implicates excessive alcohol consumption in some cases of AF ("holiday heart syndrome"), the relationship between chronic alcohol consumption and risk for AF is still a matter of controversy, since the results of the published studies do not always agree.[22] The Copenhagen City Heart Study, an epidemiological study carried out in the general population, confirmed that the risk of AF increases in heavy drinkers (more than 35 drinks a week, nearly 50 g ethanol/day). The results of our clinical registry, from which individuals with a history of elevated acute or

TABLE 4. **Independent Predictive Factors for Recurrences: Cox Regression Analysis**

Dependent Variable	Predictive Variables	β±SE	P	RR	95% CI
Recurrence	LVESV	–0.028±0.011	.011	0.97	(0.95-0.99)
	Alcohol	0.851±0.323	.008	2.34	(1.24-4.41)
	Presyncope	–1.321±0.605	.029	3.74	(1.14-12.25)

CI: confidence interval; LVESV: left ventricular end-systolic volume; RR: relative risk; SE: standard error
Variables included in the analysis: LVESV, palpitations, syncope, regular alcohol consumption (variables that presented differences in the univariate analysis, with *P*<.10), and age, sex, arterial blood pressure and left atrial size (which have been reported to be possible determining factors for atrial fibrillation).

chronic consumption were excluded, indicate that light to moderate drinking, within limits that are not usually considered excessive, can be an important risk factor of AF recurrence and should be taken very much into account in the prophylactic strategy. However, we should have certain reservations since the establishment of a dose-effect relationship was not the purpose of this study. Aside from the fact that the total cumulative dose was not determined, the assessment of alcohol consumption and the definition of the seriousness of the ingestion are subject to errors, owing, in part, to the wide variability in the daily intake. Nevertheless, the results clearly indicate that moderate alcohol consumption is an independent risk factor for ventricular function.

Acute alcohol ingestion has been shown to lead to an exaggerated sympathetic activation,[23] and this mechanism could be invoked to explain, at least in part, a decreased LVESV and an increased LVEF. However, if the effect of alcohol were toxic, we should expect a deterioration of these indexes and an increased LVEDV.[24]

Absence of Syncopal Episodes (Atrial Fibrillation of Vagal Origin)

Most of the syncopal events that present at the onset of an episode of AF are consistent with a vasovagal mechanism,[25,26] a circumstance that identifies a group of patients with vagal primary AF in whom the likelihood of recurrence is low, possibly due to the fact that the vagal hyperactivity is a transient episodic event.

Complications

The absence of thromboembolic complications during the follow-up period in our series supports the widely accepted view that the prognosis of primary AF is relatively benign given that, by definition, the major cerebrovascular risk factors (hypertension, heart failure) are not present. This contrasts with the experience reported in studies in which all types of AF were included.[3,4,7] Despite the fact that 60% of our patients were over 50 years old, the results are similar to those of the Trieste Area Study[11] involving 96 young patients (under 50 years of age) with lone paroxysmal AF who underwent follow-up for 10(8) years, in whom there was only one case of ischemic stroke, two cases of transient ischemic attack and no deaths. On the other hand, in a 23-year follow-up of chronic idiopathic AF, Jouven et al[27] found a relative risk for cardiovascular death of 4.22.

The proportion of patients who developed chronic AF (6.9%) was somewhat smaller than that reported in the ALFA study[9] (8% of the patients with paroxysmal AF).

Limitations of the Study

Periodical follow-up examinations minimize the possibility that cases of apparently primary AF might be associated with the early stages of cardiomyopathy or AF of some other origin; even so, in the absence of specific studies, the risk that the participation of other factors, such as arterial blood pressure or sleep apnea, whose relationship to AF has been clearly documented in recent years,[28] may not be inadequately assessed can not be completely ruled out.

Moreover, there exists the risk that some only mildly symptomatic episodes of paroxysmal AF, for which the patient does not seek medical attention, go undetected, and that the real incidence of recurrence may be higher than that recorded. On the other hand, the requirement that electrocardiography be performed to confirm the recurrence rules out the possibility of false positives.

CONCLUSIONS

Idiopathic or primary AF, with no apparent underlying cause, has a benign course, although it exhibits a marked tendency to recur. This trend is favored by the increased ventricular activity, probably of sympathetic origin, and by regular consumption of moderate amounts of alcohol. In contrast, AF of vagal origin, identified by its association with presyncopal symptoms, shows little likelihood of recurrence.

These observations should be duly confirmed since they indicate the possibility that patients with recurrent, apparently idiopathic AF with a LVESV of less than 40 mL or an ejection fraction greater than or equal to 65% might benefit from total abstention from alcohol consumption or the prescription of beta blockers.

Centers and Investigators Involved in the FAP Study

Hospital Municipal de Badalona: F. Planas, L. San Vicente; Hospital Esperit Sant, Santa Coloma de Gramenet: T. Poblet; Hospital Sant Boi de Llobregat: C. Romero-Menor; Hospital Comarcal de Blanes: G. Vázquez-Oliva; Hospital Comarcal de Calella: M. Vilaseca; Hospital Comarcal Alt Penedés: A. Descalzi; Hospital de Palamós: F. Antúnez: Instituto Universitario Dexeus: M.J. Salvador; CAP Sant Andreu: X. Armengol, Policlínica Rehastet: L. Banchs; Consulta Rocafort: M. Campillo.

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