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

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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 in 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 = 0.023) and smaller end-systolic volume (P < 0.001), and they were more likely to consume alcohol regularly (P = 0.013). 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 = 0.017).

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.

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. Its prevalence ranges between 2% and 31%, and it...
METHODS

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 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 [T₄]); 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 χ² 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).
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). 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). 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

Table 1. Demographic Characteristics and Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>With Recurrence (n=32)</th>
<th>Without Recurrence (n=83)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54.50 (13.6)</td>
<td>52.13 (14.3)</td>
<td>.426</td>
</tr>
<tr>
<td>Men</td>
<td>21 (65.6)</td>
<td>53 (63.9)</td>
<td>.859</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>74.8 (10.1)</td>
<td>74.5 (12.3)</td>
<td>.907</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>168.3 (8)</td>
<td>172 (10)</td>
<td>.226</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mean (SD), mm Hg</td>
<td>132.8 (14.6)</td>
<td>132.5 (20.5)</td>
<td>.935</td>
</tr>
<tr>
<td>DAP, mean (SD), mm Hg</td>
<td>79.5 (8.8)</td>
<td>79.5 (12.8)</td>
<td>.994</td>
</tr>
<tr>
<td>Mfr hypertension*, n (%)</td>
<td>1 (3.1)</td>
<td>1 (3.6)</td>
<td>.552</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>9 (28)</td>
<td>28 (33.7)</td>
<td>.723</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3 (9.4)</td>
<td>12 (14.5)</td>
<td>.677</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>16 (50)</td>
<td>20 (24)</td>
<td>.014</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>14.5 (1.2)</td>
<td>14.8 (1.6)</td>
<td>.502</td>
</tr>
<tr>
<td>Hematocrit, mean (SD), %</td>
<td>43.5 (2.8)</td>
<td>44.3 (4.6)</td>
<td>.456</td>
</tr>
<tr>
<td>Blood glucose, mean (SD), mg/dL</td>
<td>105.5 (35.6)</td>
<td>119.1 (51.8)</td>
<td>.226</td>
</tr>
<tr>
<td>Potassium, mean (SD), mEq/L</td>
<td>4.3 (0.4)</td>
<td>4.2 (0.4)</td>
<td>.705</td>
</tr>
<tr>
<td>TSH, mean (SD), µU/mL</td>
<td>1.9 (1.2)</td>
<td>2.1 (1.6)</td>
<td>.288</td>
</tr>
<tr>
<td>T4, mean (SD), µg/dL</td>
<td>1.25 (0.2)</td>
<td>1.19 (0.2)</td>
<td>.424</td>
</tr>
</tbody>
</table>

DAP: diastolic arterial pressure; K: potassium; SAP: systolic arterial pressure; SD: standard deviation; T4: free T4 (thyroxine); TSH: thyrotropin (thyroid-stimulating hormone).

*Mfr hypertension: no drug therapy and normal electrocardiogram.
significantly shorter in patients with a LVEF according to the Kaplan-Meier method (Fig. 2), was studied. The mean time to onset of recurrences, estimated recordings revealed no significant changes in the variables vs 105±27 mL; significantly lower in women than in men (122±22 mL size or alcohol consumption. Only the LVEDV was weight, height, arterial blood pressure, heart rate, atrial dimensions, palpitations, syncope, alcohol consumption), a

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
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. Bettoni et al16 concluded that the onset of AF was associated with an increase in adrenergic tone, followed by an abrupt increase in vagal tone. Lombardi et al17 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 al18 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 al21 were also unable to confirm the existence of a relationship between left atrial size and either left ventricular dimensions or shortening fraction.

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

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Predictive Variables</th>
<th>β±SE</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>LVESV</td>
<td>–0.028±0.011</td>
<td>.011</td>
<td>0.97</td>
<td>(0.95-0.99)</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td>0.85±0.323</td>
<td>.008</td>
<td>2.34</td>
<td>(1.24-4.41)</td>
</tr>
<tr>
<td></td>
<td>Presyncope</td>
<td>–1.321±0.605</td>
<td>.029</td>
<td>3.74</td>
<td>(1.14-12.25)</td>
</tr>
</tbody>
</table>

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, 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 was toxic, we should expect a deterioration of these indexes and an increased LVEDV.

**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, 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

**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,29 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. Vilasosc; Hospital Comarcal Alt Penedés: A. Descalzi; Hospital de Palamós: F. Antúnez; Instituto Universitario Dexeus: M.J. Salvador; CAP Sant Andreu: X. Armengol; Policlínica Rehaster: L. Bancho; Consulta Rocafort: M. Campillo.

Promoter: The Paroxysmal Atrial Fibrillation (Fibrilación Auricular Paroxística, FAP) Research Group; Research support: M. Cardona, Anagram ESIC.

**REFERENCES**


