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Heart 2010 96: 498-503 originally published online August 26, 2009
doi: 10.1136/hrt.2009.176321

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Accepted 28 July 2009
Published Online First 26 August 2009

ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Despite the common association of AF with cardiovascular disease, some patients can be classified as 'lone AF'. The latter is essentially a diagnosis of exclusion, and should be preceded by careful evaluation, including thorough collection of medical history, physical examination, blood pressure measurement, laboratory tests, ECG, echocardiography and, possibly, chest x-ray and exercise testing. Lone AF patients were initially thought to have a good prognosis with respect to thromboembolism and mortality, compared with the general AF population, but more recent data suggest otherwise. This review focuses on the clinical epidemiology and management aspects of lone AF, as well as various associated novel risk factors, such as familial, genetic and socioeconomic factors, alcohol, sports activity and biochemical markers.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. AF is the cause of one-third of all hospitalisations associated with cardiac rhythm disturbances and is estimated that 4.5 million people in the European Union have paroxysmal or persistent AF.[1] A great increase in the incidence, diagnosis and hospitalisation rate for AF has been observed in numerous studies.[2–4]

As a clinical problem, AF may be classified in different ways. An attempt to unify AF classifications was made in 2006 in the ACC/AHA/ESC guidelines for the management of patients with AF.[5] According to the guidelines, AF can be described as a first detected episode, then recurrent AF, and then further as paroxysmal, persistent and permanent AF. Based on the pathophysiology, a category of 'secondary AF' is distinguished to denote AF occurring in the setting of acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia or other acute pulmonary disease.

Despite the common association of AF with cardiovascular disease, some patients can be classified as 'lone AF'. The latter term was previously used to describe AF occurring in young individuals (under 60 years of age), without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.[2] However, does 'lone AF' really exist? This category essentially relies on the definition and also on how hard one really looks for the associated comorbidities.

Certainly, there has been relatively little acknowledgement of lone AF in clinical trials and sound data regarding its development, treatment and prognosis are sparse. These patients were initially thought to have a good prognosis with respect to thromboembolism and mortality, but more recent data suggest otherwise. In the Paris Prospective Study I,[6] lone AF was associated with higher mortality in middle-aged Frenchmen. Other studies underline the fact that patients with lone AF do not constitute a uniform group in terms of thromboembolic and cardiovascular risks, and may be further subdivided in lower-risk and higher-risk groups based on chronicity of AF[7] or left atrial diameter.[8] Moreover, in time, with ageing or development of cardiac abnormalities, some of those patients may no longer be regarded as 'lone AF'.[5]

The diagnosis of lone AF requires the exclusion of cardiopulmonary disease, other causes of AF and typical risk factors that may be associated with AF, such as hypertension, valvular abnormalities (typically of the mitral valve), cardiomyopathy, cardiac ischaemia, diabetes and thyroid disorders.[9] Therefore, the diagnosis of lone AF is essentially a diagnosis of exclusion, and should be preceded by careful evaluation, including thorough collection of patient's medical history, physical examination, blood pressure measurement, laboratory tests, ECG, echocardiography and, according to some experts, chest x-ray and exercise testing.[5]

This review focuses on the clinical epidemiology and management aspects of lone AF, as well as various associated novel risk factors, such as familial, genetic and socioeconomic factors, alcohol, sports activity and biochemical markers.

SEARCH STRATEGY

We searched using electronic databases (Medline, Embase, DARE). Additionally, abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. Animal studies were not considered. Where necessary, relevant authors of these studies were contacted to obtain further data. The main data search terms were 'arrhythmias', 'atrial fibrillation', 'lone atrial fibrillation', 'management' and 'treatment'.

INCIDENCE AND CLINICAL COURSE OF LONE AF

The overall prevalence of AF is 0.4%–1% in the general population.[10 11] Among that group, lone AF occurs in 1.6–11.4% of all cases of AF.[2 3 12] However, some authors report the proportion of lone AF among all cases of AF to be over 30%.[13] However this high prevalence of lone AF might be easily explained with the limitations of ALFA study (Etude en Activité Libérale de la Fibrillation Auriculaire), as it was designed to define the clinical characteristics and outcomes of patients with AF but not the incidence of AF in a French patient population. The second limitation is that this study

underestimates the relative frequency of asymptomatic AF and ambulatory 24-hour ECG recording was not systematically part of the investigation.[13] Examples of epidemiological studies of lone AF are summarised in table 1.

The clinical course of lone AF also suggests that many of these patients have a paroxysmal form of the arrhythmia, with an estimated risk of progression to permanent AF of 29% over 30 years, as shown in table 2, and a relatively low risk of mortality, heart failure and thromboembolic complications.[14] Another study confirmed the prevalence of a paroxysmal form of lone AF (94% of patients) with lower progression rate (7.8%), but this was evaluated on the basis of a shorter follow-up period.[15]

Of note, the prognosis of patients with paroxysmal lone AF appears to be good, given this may primarily be an electrical problem (related to pulmonary vein foci), whereas patients with chronic lone AF are at increased risk of embolic complications and higher mortality rates. Indeed, chronic lone AF is not a benign disorder and needs more attention than paroxysmal lone AF.[7]

Interestingly, patients originally diagnosed with lone AF may follow divergent courses based on their left atrial volume. In one study, patients initially diagnosed with lone AF and normal sized atria had a benign clinical course throughout long-term follow-up, while those with increased left atrial volume at diagnosis or later during the follow-up experienced more adverse events, such as cerebral infarction, myocardial infarction and congestive heart failure.[8] Thus, lone AF patients probably need careful follow-up with repeated evaluation of risk factors and comorbidities, as those underlying conditions may change in the course of time, changing the prognosis of these patients and the therapeutic approach. In particular, increasing age and the development of hypertension may increase the risk of cerebrovascular events.[14] Also, approximately 44% of patients with an initial diagnosis of lone AF may represent occult cases of arterial hypertension. In these patients, hypertension may affect AF recurrence and treatment outcomes.[16]

There may also be multiple factors of a medical, genetic or habitual nature that are crucial for the development of AF (including lone AF), though many are not included in a list of typical risk factors and comorbidities. Thus, so-called 'idiopathic' AF (ie, without any cause) may not be the same condition as lone AF given that the latter may have some associated non-cardiovascular pathologies or presumed risk factors.[5] One recent review of this field even proposed an unofficial term of 'not-so-lone AF' to emphasise the potential influence of these factors.[17]

RISK FACTORS FOR LONE AF

Epidemiological data show a male predominance in patients with lone AF, since men comprise 78% of this patient population.[14] In a recent study, this sex difference was further investigated, showing that proportion of males was greater among sporadic lone AF and possible familial probands (defined as one first-degree or second-degree relative with lone AF) compared with confirmed familial probands (ie, two or more relatives with lone AF). Sporadic lone AF was also more common in men than women.[18]

A familial incidence of lone AF has also been investigated. Lone AF patients have a first-degree family member with AF more frequently compared with those with other forms of AF.[19] Of note, relatives of probands with lone AF are at substantially increased risk of developing this arrhythmia compared with the general population.[20] As far as we are aware, the familial distribution of lone AF has not been linked with any specific genetic mechanisms, although particular genetic mutations that contribute to lone AF incidence have been described, including mutations in genes for potassium and sodium channels, connexins, components of the renin-angiotensin-aldosterone system and the MinK gene.[21–35]

Obesity is associated with an increased incidence of AF as a whole, with a 3–8% increased risk of incidence of AF with each unit increase in body mass index (BMI).[36 37] However, in lone AF, the data indicating a relation to BMI are lacking, although a hypothesis proposed suggests that lone AF patients are statistically taller and leaner than other patients with AF.[38]

Socioeconomic factors seem to play some part in lone AF. A Type A behaviour pattern and acute life stress may affect the development and spontaneous conversion of AF. For example, patients with acute stress show the highest probability of spontaneous conversion to sinus rhythm (as soon as the source of stress is resolved), followed by patients with Type A behaviour.[39] In another study, acute stress induced changes in lifestyle, including an increase in coffee consumption, leading to a higher risk of AF, although patients who developed AF after an acute stress also showed the highest probability of spontaneous conversion.[40] High coffee consumption and obesity were associated with an increased risk of persistent AF.[40]

Alcohol consumption has also been associated with lone AF. Over 30 years ago, paroxysmal AF coincidence with occasional intake of high amounts of alcohol and was labelled as the so-called 'holiday heart syndrome'.[41] In the Framingham study, long-term alcohol consumption showed a weak correlation with AF, unless high consumption was taken into account (>36 g/day).[42] In another study, high alcohol intake in men was found to increase the risk of AF.[43]

Sports activity has been correlated with lone AF incidence. In one study, endurance sport practice (eg, marathon running) was associated with a higher risk of incident lone AF in multivariate regression models.[44] In marathon runners, left atrial

Table 1 Epidemiological studies of lone AF

	Year of publication	Number of LAF patients	LAF as a percentage of the whole AF population	Sex	Age (range/ mean, years)	Duration of follow-up (range/mean, years)
Brand *et al*[3]	1985	43	11.5%	74% M/26% F	–/70	–/10.9
Onundarson *et al*[85]	1987	8	32%	–	–	–/14.2
Kopecky *et al*[2]	1987	97	2.7%	80% M/20% F	15–60/44	–/14.8
Davidson *et al*[86]	1989	32	4.6%	59% M/41% F	30–55/46.8	2–16/4.9
Scardi *et al*[7]	1999	145	1.93%	81% M/19% F	–/43.4	1–35/10.4
Osranek *et al*[8] (Olmsted population)	2005	46	–	83% M/17% F	–/45.8	–/27
Jahangir *et al*[14] (Olmsted population)	2007	76	–	78% M/22% F	–/44.2	2.5–42.2/25.2

AF, atrial fibrillation; F, female; LAF, lone atrial fibrillation; M, male.

Table 2 Mortality and morbidity associated with lone AF

	Number of LAF patients	Sex	Age (range/ mean, years)	Paroxysmal and persistent/ chronic AF (%)	Recurrence rate (% of paroxysmal LAF patients)	Progression to chronic LAF (% of paroxysmal LAF patients)	Risk of thromboembolic events (number per 100 person-years)	Cardiovascular death (number per 100 person-years)
Brand *et al*[3]	43	74% M	–/70	0/100	–	–	2.4	–
Onundarson *et al*[85]	8	–	–	0/100	–	–	0	0
Kopecky *et al*[2]	97	80% M	15–60/44	78/22	58%	16%	0.55	0.97
Davidson *et al*[86]	32	59% M	30–55/46.8	94/6	56%	–	0.64	0
Scardi *et al*[7]	145	81% M	–/43.4	86.2/15.8	–	23%	1.26	0.23
Osranek *et al*[8] (Olmsted population)	46	83% M	–/45.8	100/0	–	–	0.54	0.69
Jahangir *et al*[14] (Olmsted population)	76	78% M	–/44.2	93/7	–	29%	0.9	0.63

AF, atrial fibrillation; F, female; LAF, lone atrial fibrillation; M, male.

inferosuperior diameter and left atrial volume were both significantly associated with a higher risk of incident lone AF. In another analysis,[45] only moderate and heavy physical activity (measured as accumulated lifetime activity), the height and anteroposterior left atrial diameter were independently associated with lone AF. The proportion of patients with lone AF who report current sport practice (31%) is higher than that observed in controls (14%).[46] Indeed, current sport practice seems to be associated with a higher prevalence of lone AF and the practice of more than 1500 lifetime hours of sport appears to be the threshold for the observed association.[46] In a Spanish study, the proportion of sports enthusiasts among patients with lone AF was much higher than that reported in the general population of Catalonia (63% vs 15%).[47]

Another factor that has been related to lone AF is sleep apnoea syndrome (SAS). SAS seems to form a background for a higher incidence of AF, owing to its influence on autonomic imbalance and various haemodynamic factors.[48] AF may also increase the risk of SAS,[49] but no such relation has been established in patients with lone AF. In summary, SAS seems to be common in lone AF, but SAS is more common in patients with AF than in gender-matched, age-matched and cardiovascular morbidity-matched community control subjects (figure 1).[50]

Finally, drug-induced lone AF should also be considered, given that there are some specific groups of medicines that may induce atrial fibrillation, including the following: cardiovascular drugs (eg, dopamine, adenosine, acetylcholine), respiratory system drugs (especially sympathicomimetic inhalants, xanthenes, corticosteroids), cytostatics (eg, cisplatin, 5-fluorouracil, and etoposide), central nervous system drugs ((anti)cholinergics, dopamine agonists, antidepressants/antipsychotics, anti-migraine drugs, anaesthetics), genitourinary system (drugs for erectile dysfunction) and drugs for premature labour (eg, hexoprenaline, terbutaline, magnesium sulfate).[51]

NATRIURETIC PEPTIDES

The relation between biochemical markers and lone AF has been investigated in several studies. One group of biomarkers of potential importance for lone AF in terms of diagnosis, prediction of recurrence and treatment monitoring are the natriuretic peptides, of which brain natriuretic peptide (BNP) has been most thoroughly researched.

Plasma BNP concentrations in lone AF patients is significantly higher than in age-matched and sex-matched healthy subjects. Age, left atrial diameter and a history of AF were independent predictors of elevated BNP.[52] Another study has confirmed that individuals with lone AF have higher BNP levels than those with sinus rhythm; in this study, the left atrial volume index, the pulmonary artery systolic pressure and the early mitral inflow velocity (E)/mitral annular velocity (E') were found to be independently correlated with BNP level in lone AF patients.[53] That BNP levels correlate with LA volume index and E/E' in patients with lone AF raises the possibility that the BNP level reflects early left ventricular dysfunction and LA enlargement in the lone AF population.

Apart from BNP, atrial natriuretic peptide (ANP) is another sensitive biomarker of cardiac contractile dysfunction. Both peptides are elevated in patients with AF and underlying structural heart disease. Similarly, in lone AF, median NT-proBNP levels have been reported to be significantly elevated, while pro-ANP levels showed no significant difference between patients with lone AF and controls.[54] Indeed, the elevated proBNP but normal proANP in these patients is a discordant natriuretic peptide pattern, which is present even in lone AF patients when in sinus rhythm, and may represent an underlying subclinical predisposition to lone AF.[54]

Restoration of sinus rhythm in patients with lone AF seems to be an interesting model for any biomarker study, as it allows investigators to track patients' reactions to conversion to sinus rhythm. For example, the probability of a successful cardioversion was inversely correlated with NT-proBNP values, and patients who maintained sinus rhythm after cardioversion show a significant NT-proBNP decrease.[55] Patients who experienced a relapse of AF had NT-proBNP levels that are significantly higher before cardioversion in comparison to patients without relapse and levels remained unchanged during follow-up.[55] In another study, plasma BNP levels were high in all lone AF patients, and dramatically decreased 24 hours after external electrical cardioversion.[56] However, the question remains as to whether the increased BNP levels are a result of the incident lone AF itself, or are a sign of asymptomatic cardiac alteration not detectable by echocardiography, and only uncovered by biochemical study.

APELIN

Another biomarker potentially linked to lone AF is apelin. The latter is an endogenous peptide hormone that appears to have a physiological role in counter-regulation of the angiotensin and vasopressin systems.[57] Circulating apelin levels are elevated early in the natural history of heart failure, but ultimately are depressed in overt chronic heart failure (CHF).[57] In subjects with lone AF, mean apelin levels were significantly lower when compared with control subjects in sinus rhythm.[58] That finding implies that patients with lone AF have a subtle perturbation of the cardiac humoral axis and that abnormal apelin level is similar as seen in CHF.

INFLAMMATION

An interesting theory linking lone AF with an underlying inflammatory process has also been proposed. In one study,

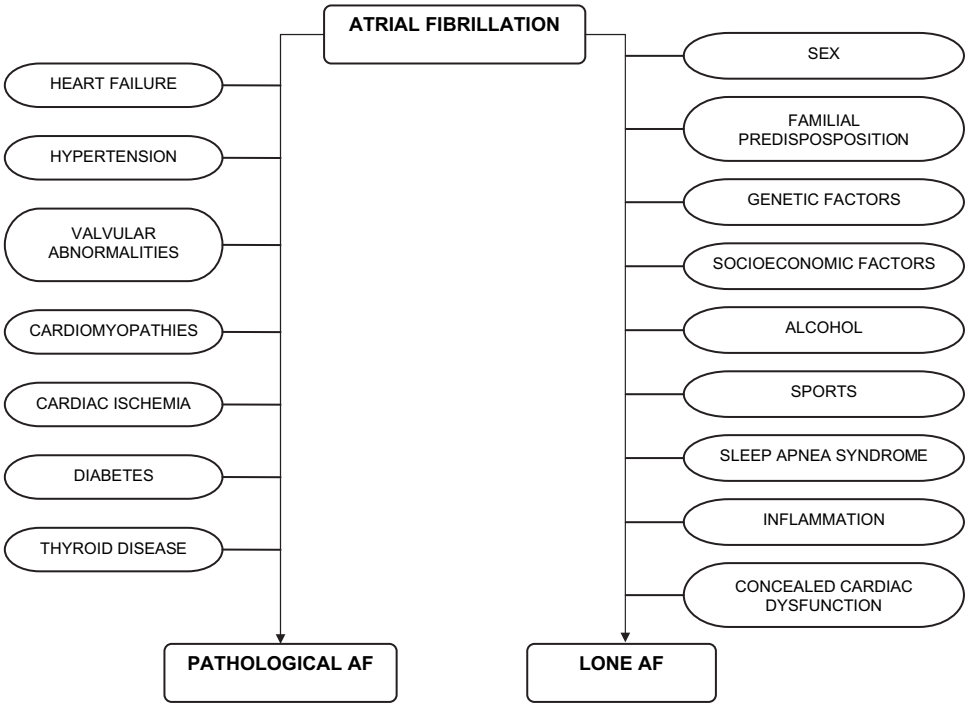

Figure 1 Pathophysiological pathways of lone atrial fibrillation.

endomyocardial biopsies of the right atrial septum and of the two ventricles were performed in patients with paroxysmal lone AF refractory to conventional antiarrhythmic treatment, and compared with biopsies from the right atrial septum of patients with Wolff-Parkinson-White syndrome.[59] All lone AF atrial biopsy specimens showed severe hypertrophy with vacuolar degeneration of the atrial myocytes and ultrastructural evidence of fibrillolysis, lymphomononuclear infiltrates with necrosis of the adjacent myocytes, and in some patients, non-specific patchy fibrosis. Ventricular biopsies also showed abnormalities in the form of inflammatory infiltrates, but only in 25% of patients. Abnormal atrial histology was compatible with a diagnosis of myocarditis in 66% of patients (active in 25%) and of non-inflammatory localised cardiomyopathy in 17% and was represented by patchy fibrosis in 17%. Interestingly, those pathological changes in 75% of patients were found only in atrial septal biopsies but not in biventricular biopsies.

An inflammatory cause of AF was also proposed on the basis of abnormal alterations of C reactive protein (CRP) and interleukin-6 levels in subjects with AF.[60–62] Indeed, higher CRP levels increases the risk of AF incidence in healthy subjects.[61] High-sensitivity CRP (hs-CRP) is higher in lone AF patients compared with controls [63] although other studies have suggested otherwise.[60] hs-CRP also seems to predict recurrent AF, in lone AF patients who are not taking antiarrhythmic drugs.[63]

MANAGEMENT

For all patients with AF there are two general treatment strategies: rhythm or rate control, and recent clinical trials comparing both management strategies have suggested that effective anticoagulation and heart rate control are not inferior to rhythm control.[5]

For younger individuals, and especially those with paroxysmal lone AF, rhythm control may perhaps be a better initial approach, especially where the patient is symptomatic. However, antiarrhythmic medications are often required to maintain sinus rhythm, although left atrial (LA) ablation is gaining popularity.[5] Patients with lone AF of relatively short duration are less prone to early recurrence of AF than those with heart disease and longer AF duration, and therefore may not need prophylactic administration of antiarrhythmic drugs. In patients with symptomatic lone AF, a β-blocker may be tried first (preferably, cardioselective β-blockers such as metoprolol, bisoprolol), but other agents such as flecainide, propafenone and sotalol are particularly effective.[5 18 64–66] Amiodarone and dofetilide are recommended as alternative therapy. In patients with adrenergically mediated AF, β-blockers represent first-line treatment, followed by sotalol and amiodarone. In patients with adrenergically mediated lone AF, amiodarone should be chosen later in the sequence of drug therapy because of its potential toxicity with long-term use.[5]

Regardless of the rate versus rhythm control strategy, the need for anticoagulation is based on stroke risk factors and not on whether sinus rhythm is maintained. In patients with lone AF, the risk of thromboembolism is low without treatment. Indeed, the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established.[64] Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients with lone AF without any risk factors for thromboembolism. The precise recommendation for anticoagulation in lone AF according to the ACC/AHA/ESC guidelines is 'Aspirin (81–325 mg/day) or no therapy (class I)'.[5] In the Japan AF Stroke trial, aspirin administered at 150–200 mg daily for prevention of stroke in patients with non-valvular AF, did not seem to be either effective or safe.[67] Treatment with aspirin caused a marginally higher risk of major bleeding and therapy was unlikely to be superior to no antithrombotic therapy.[67] Protection against thromboembolism is not recommended even during pregnancy for patients with lone AF and/or low thromboembolic risk.[5]

In patients with lone AF, non-antiarrhythmic agents were also found to have a beneficial influence in terms of arrhythmia recurrence. Available evidence supports the efficacy of statins in maintaining sinus rhythm in patients with persistent lone AF. Statins decrease the risk of recurrences after successful direct-current cardioversion.[68 69] The mechanisms by which these drugs prevent AF recurrence are not fully understood but include direct antiarrhythmic effects involving alterations in transmembrane

ion channels.[70] There are also some data showing that the addition of ACE inhibitors to an antiarrhythmic therapy (class Ic agents) decreases the rate of AF recurrences and facilitates the maintenance of sinus rhythm after cardioversion.[71] The combination of irbesartan and amiodarone also decreased the rate of AF recurrences in lone AF patients, with a dose-dependent effect.[72]

Another option for treatment of lone AF is catheter ablation, the value of which is well established and which has found its place in the guidelines.[5] Nevertheless, there have been other ablation and surgical techniques proposed for patients with lone AF, including the Cox maze III surgery,[73 74] beating-heart pulmonary vein isolation with a microwave device through a standard sternotomic approach[75] and, finally, a relatively new, minimally invasive surgical approach with the use of small right inframammary incisions[76] or video-assisted, thoracoscopic approach.[77–80]

CONCLUSIONS

Patients with lone AF form a group that is distinct from AF with underlying cardiovascular disease. The therapeutic approach is different for lone AF patients, particularly in terms of anticoagulation, and therefore a diagnosis of lone AF should be kept separate from the diagnosis of other types of AF. Although lone AF by definition has no underlying cause related to cardiovascular disease, it may be associated with other medical, habitual and social factors. Clearly, there is a need for further research and lone AF patients need careful follow-up. Emerging risk factors should be taken into consideration in the evaluation, diagnosis and treatment of lone AF.[81–87]

Competing interests The authors state no conflict of interest and have received no payment in preparation of this manuscript. No pharmaceutical company supported or was involved with the preparation of this article. All authors have no conflicts to disclose.

Provenance and peer review Not commissioned; externally peer reviewed.

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