INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages. [1]

AF is associated with increased rates of death, stroke and other thromboembolic events, heart failure, hospitalizations, degraded quality of life, reduced exercise capacity, and left ventricular (LV) dysfunction. [1]

Various classification systems have been proposed for AF. One is based on the ECG presentation. Another is based on epicardial or endocavitary recordings or non contact mapping of atrial electrical activity. Several clinical classification schemes have also been proposed, but none fully accounts for all aspects of AF. [2]

Clinically, it is reasonable to distinguish five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF. When a patient has had 2 or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal, when sustained beyond seven days, AF is classified as persistent. [2]

Termination with pharmacological therapy or direct-current cardioversion does not change the designation. First-detected AF may be either paroxysmal or persistent AF. The category of persistent AF also includes cases of long-standing AF (eg, greater than 1 year) usually leading to permanent AF, in which cardioversion has failed or has not been attempted. [2]

Atrial fibrillation (AF) may be caused by many cardiac and non-cardiac conditions, including hypertension, valvular heart disease (in particular, of the mitral valve), ischemic cardiomyopathy, diabetes mellitus, and thyroid disease. The vast majority of patients with AF suffers from one or more of these conditions and around 60 years old.[3]

However, a subset of patients with AF is <60 years and routine evaluation, including physical examination, laboratory tests including thyroid function and echocardiography, does not reveal any abnormalities. Those patients are considered to suffer from 'lone AF'.[3]

The term "lone AF" has been variously defined but generally applies to young individuals (under 60 y of age), without clinical or echocardiographic evidence of cardio-pulmonary disease, including hypertension. These patients have a favorable prognosis with respect to thrombo-embolism and mortality. Over time, patients may move out of the lone AF category due to aging or development of

cardiac abnormalities such as enlargement of the left atrium. Then, the risks of thromboembolism and mortality rise accordingly. [3]

By convention, the term “non-valvular AF” is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.[2]

In 1997, the role of inflammation in the genesis of AF has gained attention. The incidence of AF after cardiac surgery points to inflammation as a contributing factor in causing AF. Bruins et al.[4] first described a relationship between circulating markers of inflammation and the occurrence of AF after cardiac bypass surgery. They demonstrated that, after surgery, a biphasic complement activation occurs, which corresponds with the time course of post-operative AF. Furthermore, inflammation may also be associated with thrombosis and hence with AF related complications. [4]

Also in lone AF, inflammation may play a role. Atria of patients with lone AF frequently demonstrate a histopathological signs of inflammation. Researchers [5] investigated atrial biopsies of patients with lone AF and found signs of myocarditis in 66% of these individuals.[5]

Whether AF is a cause or consequence of inflammation will remain a matter of debate.

Inflammation generates multiple responses at a distance from the site at which it is presented. Many of these changes are accompanied by the so-called acute-phase reactive proteins (which accompany both chronic and acute inflammatory responses). CRP is a non-disease-specific acute-phase reactant that has traditionally been used to detect acute lesions, infections, and inflammation, as well as to assess the activity of inflammatory diseases. It is mainly produced in the liver under the control of cytokines, particularly interleukin-6, which is a polypeptide used as a cellular signal produced by activated cells, generally macrophages, at the disease site. CRP, so-called due to its ability to precipitate C polysaccharide from Streptococcus pneumoniae, was the first acute phase protein to be described and is a good systemic marker of inflammation and tissue damage. [6]

CRP levels can be altered by various patient characteristics or treatments. Drugs such as niacin, and antiplatelet drugs, as well as weight loss and exercise, have proved to be effective in reducing CRP levels. [7]

AIM OF THE WORK

The Aim of this case-control study that is to evaluate the correlation between presence of lone atrial fibrillation and inflammation Measured by serum CRP level.

REVIEW OF LITERATURE

Introduction:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages. [(1)]

This arrhythmia is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality. Hospitalization of patients with AF is also very common. This arrhythmia is a major cardiovascular challenge in modern society and its medical, social and economic aspects are all set to worsen over the coming decades. Fortunately a number of valuable treatments have been devised in recent years that may offer some solution to this problem.[(2)]

Mechanisms and causes of AF:

Two concepts of the underlying mechanism of AF have received considerable attention, factors that trigger the onset and factors that perpetuate this arrhythmia.

In general, patients with frequent, self-terminating episodes of AF are likely to have a predominance of factors that trigger AF, whereas patients with AF that does not

terminate spontaneously are more likely to have a predominance of perpetuating factors. Although such a gross generalization has clinical usefulness, there is often considerable overlap of these mechanisms. The typical patient with paroxysmal AF has identifiable ectopic foci initiating the arrhythmia, but these triggers cannot be recorded in all patients. Conversely, occasional patients with persistent or permanent AF may be cured of their arrhythmia by ablation of a single triggering focus, suggesting that perpetual firing of the focus may be the mechanism sustaining this arrhythmia in some cases.[8]

In recent years, advanced mapping technologies, along with studies in animal models, have suggested the potential for complex pathophysiological mechanisms responsible for AF, including the following:

1- Continuous aging or degeneration of atrial tissue and the cardiac conduction system.

2- Progression of structural disease, such as valvular heart disease and cardiomyopathy.

3- Myocardial ischemia, local hypoxia, electrolyte derangement and metabolic disorders (e.g., atherosclerotic heart disease, chronic lung disease, hypokalemia, and hyperthyroidism).

4- Inflammation related to pericarditis or myocarditis, with or without cardiac surgery.

5- Genetic predisposition.

6- Spontaneous or drug-induced autonomic dysfunction.[8]

The electrophysiological (EP) mechanisms responsible for AF may include a rapid focal tachyarrhythmia in the pulmonary veins (PVs) and or other atrial regions with fibrillatory conduction, multiple reentrant wavelet conduction initiated by premature atrial complexes (PACs) and or atrial tachyarrhythmias, and or formation of stable or unstable reentrant circuits of very short cycle lengths (CLs) that generate fibrillator conduction. Additionally, AF can in itself lead to functional and structural changes in the atrial myocardium that favor its maintenance. These remodeling processes are probably precipitated by high rate activity and intracellular calcium overload, followed by activation or enhancement of multiple subcellular mechanism. [8]

Atrial Fibrillation Begets Atrial Fibrillation:

Atrial fibrillation often progresses from its paroxysmal form to a more persistent and permanent form. The evolution of this disease over time can be partially explained by atrial remodeling, which may occur sooner rather than later depending on whether atrial fibrillation is allowed to continue, with progression of the structural heart disease. Three kinds of atrial remodeling have been proposed: electrical, structural, and contractile. the instrumented goat model documented that ‘atrial

fibrillation begets atrial fibrillation'[9]. In this model, there was evidence of electrical remodeling with shortening of the atrial refractory period compared to control within 24 h of atrial fibrillation. In addition, there was a loss of rate adaptation of atrial refractoriness manifested by short atrial effective refractory periods (AERPs) even at slower heart rates. The decrease in atrial refractory periods resulted in an increase in the rate of atrial fibrillation, which therefore became more complex. Perpetuation of atrial fibrillation resulted in even shorter atrial fibrillatory intervals. [10]

Classification of AF:

Atrial fibrillation (AF) has been described in various ways, such as paroxysmal or chronic, lone, idiopathic, non-valvular, valvular, or self-terminating. Each of these classifications has implications for the response to therapy, and the lack of a consistent nomenclature has led to difficulties in comparing one study with another.[8]

At the initial detection of AF, it may be difficult to be certain of the subsequent pattern of duration and frequency of recurrences. Thus, a designation of first detected episode of AF is made on the initial diagnosis. When the patient has experienced two or more episodes, AF is classified as recurrent. After the termination of an episode of AF, the rhythm can be classified as paroxysmal or persistent. [8]

Paroxysmal AF is characterized by self-terminating episodes that generally last less than seven days. Persistent AF generally lasts longer than seven days and often requires electrical or pharmacological cardioversion. Permanent AF refers to AF that has failed cardioversion or has been sustained for more than one year, or when further attempts to terminate the arrhythmia are failed. Although useful, this arbitrary classification does not account for all presentations of AF and is not clearly related to any specific pathophysiology or mechanism of arrhythmogenesis. Additionally, the pattern of AF may change in response to treatment. Paroxysmal AF often progresses to longer, non–self-terminating episodes. Moreover, AF initially responsive to pharmacological or electrical cardioversion tends to become resistant and cannot then be converted to normal sinus rhythm (NSR). Additionally, AF that has been persistent may become paroxysmal with antiarrhythmic drug therapy, and AF that had been permanent may be cured or made paroxysmal by surgical or catheter-based ablation. Furthermore, The severity of symptoms associated with AF, anticoagulation status, and patient preference affect the decision of whether and when cardioversion is attempted, which would then affect the duration of sustained AF, leading to a diagnosis of persistent or permanent AF. [8]

Lone AF what do we know?

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. 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.[3]

Certainly, there has been relatively little acknowledgement of lone AF in clinical trials and sound data regarding its development, treatment and prognosis are sparse. In the Paris Prospective Study I [11] lone AF was associated with higher mortality in middle-aged Frenchmen. Other study[12] 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 or left atrial diameter. Moreover, in time with ageing or development of cardiac abnormalities, some of those patients may no longer be regarded as 'lone AF'.[12]

The diagnosis of lone AF requires the exclusion of 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. 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.[13]

Prevelance and clinical course of lone AF:

The overall prevalence of AF is 0.4% - 1% in the general population.[14] Lone AF occurs in 1.6- 11.4% of all cases of AF.[15] However, some authors report the proportion of lone AF among all cases of AF to be over 30%.[16]Examples of epidemiological studies of lone AF as summarized in table (1).

Table (1): Epidemiological studies of lone AF [16]

	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.

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.[17] Another study,[18] 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. 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.[18]

Interestingly, patients originally diagnosed with lone AF may follow divergent courses based on their left atrial volume. In one study,[19] 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 congestive heart failure. 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 a development of hypertension may increase the risk of cerebrovascular events. 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.[19]

Table (2): Mortality and morbidity associated with lone AF.[17]

	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.

Risk factors for lone AF:

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 (i.e., 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. One recent review of this field even proposed an unofficial term of ‘not-so lone AF’ to emphasize the potential influence of these factors.[8]

Epidemiological data show a male predominance in patients with lone AF, since men comprise 78% of this patients population.[20]In a recent study.[21] The sex difference was further investigated, showing that sporadic lone AF was also more common in men than women.

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.[22] Of note, relatives of patients with lone AF are at substantial increased risk of developing this arrhythmia compared with the general population.[23] The familial distribution of lone AF has not been linked with any specific genetic mechanisms, a 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.[24]They have demonstrated that the gap-junction protein connexin40 (Cx40) is expressed mainly in the atrium and conduction system. Lack of Cx40 has been reported to result in increased atrial vulnerability