

Risk factors for atrial fibrillation: Not always severe heart disease, not always so ‘lonely’

Marcin Rosiak¹, Michał Dziuba², Michał Chudzik³, Iwona Cygankiewicz³,
Karol Bartczak⁴, Jarosław Drożdż¹, Jerzy Krzysztof Wranicz³

¹Cardiology Clinic, 1st Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Poland

²Department of Invasive Cardiology, 1st Chair of Cardiology and Cardiac Surgery,
Medical University of Lodz, Poland

³Department of Electrophysiology, 1st Chair of Cardiology and Cardiac Surgery,
Medical University of Lodz, Poland

⁴Department of Cardiac Surgery, 1st Chair of Cardiology and Cardiac Surgery,
Medical University of Lodz, Poland

Abstract

The precise mechanisms that cause atrial fibrillation (AF) are not completely understood. Clinicians should ask themselves whether AF is truly ‘lone’ or is the effect of an underlying, ‘masked’ disorder. Atrial fibrillation shares strong epidemiological associations with other cardiovascular diseases such as heart failure, coronary artery disease, valvular heart disease, diabetes mellitus and hypertension. In this review, we discuss the ‘new risk factors’ and the mechanisms by which they lead to AF. Based on the most recent studies, we present the current knowledge about the relationship between AF occurrence and the following disorders: metabolic syndrome and its components, sleep apnea and inflammation. Moreover, some aspects of the influence of lifestyle (alcohol consumption and physical activity) on AF events are described. (Cardiol J 2010; 17, 5: 437–442)

Key words: atrial fibrillation, risk factors, metabolic syndrome, obesity, diabetes, sleep apnea, inflammation, alcohol consumption, physical activity

Introduction

The precise mechanisms that cause atrial fibrillation (AF), which is the commonest arrhythmia encountered in clinical practice, are not completely understood.

Atrial fibrillation shares strong epidemiological associations with other cardiovascular diseases such as heart failure, coronary artery disease, valvular heart disease, diabetes mellitus and hypertension. Catecholamine excess, hemodynamic stress, atrial ischemia, atrial inflammation, metabolic stress and neurohumoral cascade activation could

promote AF. In some patients with AF, no underlying pathology is present and the etiology remains unknown. Then the arrhythmia is defined as ‘lone AF’. Atrial fibrillation is associated with increased morbidity and mortality, in part due to the risk of thromboembolic events [1], and in part due to its associated risk factors. The fully efficient therapeutic management of AF has not yet been discovered, mainly because of both a lack of understanding of several pathophysiological aspects of arrhythmia, and the complicated nature of as yet undiscovered causes of AF. Moreover, to date there has been no convincing proof that pure antiarrhythmic therapy

Address for correspondence: Marcin Rosiak, MD, PhD, Cardiology Clinic, 1st Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Poland, Sterlinga 1/3, 91–425 Łódź, Poland, tel/fax: +48 42 664 42 38, e-mail: rosiak.m@wp.pl

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(‘rhythm control’) is better than the rate control approach [2, 3]. The so-called ‘classical’ AF risk factors include advanced age, male sex, valvular disease, heart failure, hypertension and thyroid disease. In patients with one of the above mentioned disorders, arrhythmia is due to complicated changes in atria structure, and local inflammatory process finally leading to fibrosis. Lone AF is probably more related to electrophysiological phenomena (triggers) in structurally normal atria; but we still lack direct evidence to prove that theory. It could be the explanation why patients with real lone AF have a normal life expectancy and a low risk of stroke when compared to individuals without arrhythmia, and why paroxysmal lone AF does not often progress to persistent or permanent AF [4].

In the past, lone AF was considered to account for almost 30% of all AF cases [1, 2]. But the results of recent studies have demonstrated that lone AF is quite a rare disorder. Scientists from the Mayo Clinic, which served as a primary care institution for Olmsted County in the American state of Minnesota between 1950 and 1980, examined 3,623 patients with a first episode of AF. Follow-up began after the initial diagnosis of AF and continued until 2003 or death (median 26.8 years). This long-term data revealed that only 2% of the total population of patients with AF really present with lone AF — no concomitant heart disease, hypertension, hyperthyroidism, chronic obstructive pulmonary disease, or noncardiac disease that potentially could shorten life expectancy [4, 5]. Detection of the underlying disorder may result in implementation of effective treatment that could improve prognosis. That is why clinicians should ask themselves whether AF is truly ‘lone’ or is the effect of an underlying, ‘masked’ disorder.

In this review, we will discuss the ‘new risk factors’ and the mechanisms by which they lead to AF (Table 1).

Metabolic syndrome

The metabolic syndrome is characterized by a cluster of atherosclerotic risk factors, including obesity, hypertension, dyslipidemia and insulin resistance. It is estimated that it affects approximately 20–30% of the population in Western countries [6].

Obesity and overweight

The relationship between AF and obesity is well documented [7–9]. The risk of AF rises for about 8% per body mass index (BMI) unit increment [10, 11]. In The Niigata Preventive Medicine Study,

Table 1. Risk factors for atrial fibrillation.

Proposed risk factors	Controversial risk factors
Obesity	Dyslipidemia (low HDL)
Sleep apnea	Alcohol consumption
Strenuous physical activity	Diabetes
Inflammation	
Gene polymorphism	

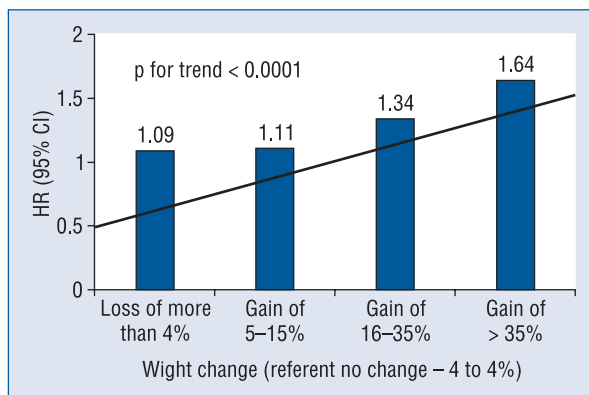


Figure 1. Hazard ratios of atrial fibrillation for weight change from age 20 to mid-life (adapted from Rosengren et al. [7]).

obesity was documented to be associated with an increased risk of AF occurrence (HR = 1.64; 95% CI 1.26–2.15) [12]. Similarly, in the Framingham cohort BMI unit increment per one was found to be an AF risk factor (HR = 1.19; 95% CI 1.08–1.30) [13]. Rosengren et al. [7] found that both body size enlargement between age 20 and midlife, defined as body surface area (BSA) gain and BMI gain, were strongly related to subsequent AF occurrence in men. Moreover, as documented by this study, individuals who put on 35% or more of their weight at age 20, were at the highest risk of AF development (HR = 1.31; 95% CI 1.02–1.68) (Fig. 1). The incidence of AF was also substantially increased in tall men. Those taller than 179 cm had almost double the risk of developing AF than men shorter than 172 cm (HR = 1.81; 95% CI 1.53–2.13). In contrary, in the Framingham Heart Study, height was not identified as a risk factor [13].

The manner in which obesity contributes to an increased risk of AF is unclear. Obesity may alter atrial anatomy, enlarge intraatrial pressure, and introduce oxidative stress and chronic inflammation — abdo-

minal fat depots are not any longer regarded as only an energy source, but as a cytokine-releasing organ as well. It has been established that in comparison to healthy individuals, patients suffering from metabolic syndrome have higher levels of both C-reactive protein (CRP) and tumor necrosis factor α [14, 15].

Hyperlipidemia

Atherogenic dyslipidemia may indirectly promote AF due to its atherogenic complications. Hypercholesterolemia could lead to temporal, and then permanent, changes in cell membranes of atrial myocytes by provoking injury of endothelium cells of atrial muscle microcirculation. These mechanisms may cause electric remodeling and its clinical manifestation — AF paroxysms. Yet there is no firm proof of direct interdependence. In a study by Watanabe et al. [12], low HDL-cholesterol level (< 40 mg/dL in men and < 50 mg/dL in women) was found to be a risk factor for AF (HR = 1.52; 95% CI = 1.09–2.14). No significant relationship was observed for other atherogenic lipid disturbances. Similarly, neither dyslipidemia nor any of its components were identified as AF risk factors in the Framingham population [13].

Diabetes and glucose intolerance

Epidemiological data shows that AF and diabetes often coexist. Due to its macrovascular complications, coronary artery disease and hypertension, diabetes promotes the appearance of AF. Yet it is not clear whether diabetes could, in a direct, electrophysiological way, lead to arrhythmia substrate generation. In the retrospective epidemiological study by Movahed et al. [16], covering a population of more than 800,000, diabetes was found to be an independent AF risk factor (HR = 2.13; 95% CI 2.10–2.16). On the other hand, this finding was not confirmed in the Framingham study [13], and therefore diabetes is not considered as an AF risk factor in the risk score based on the Framingham Heart Study. With such contradictory observations from two epidemiological studies that included populations of similar characteristics, it is difficult to conclude whether diabetes should be considered as an independent risk marker for developing AF.

Sleep apnea

The prevalence of obstructive sleep apnea in the general population is very high. It is estimated that as many as one in five people could present with

this disorder [17]. Sleep apnea generates periods of hypoxemia and hypercapnia, leads to sympathetic activation and blood pressure increase. Patients with sleep apnea are frequently diagnosed with co-existing autonomic imbalance [18], and diastolic heart dysfunction [19]. It is considered that these two mechanisms may potentially promote AF development. Gami et al. [20] compared AF patients to others in a cardiology practice who did not share a history of AF, and they found that sleep apnea was strongly associated with AF (HR = 2.18; 95% CI 1.34–3.54). A recent study of AF patients undergoing successful cardioversion at the Mayo Clinic demonstrated a remarkably high recurrence of AF in patients with untreated obstructive sleep apnea compared to patients with sleep apnea treated with positive airway pressure [21]. The results of studies targeting the effects of sleep apnea treatment on AF occurrence are ambiguous. Some of them documented that sleep apnea treatment reduces AF incidence [20], while others did not find such effects [21]. It is also not known whether sleep apnea can be considered as a true risk factor for AF or whether it is only a risk marker of other abnormalities predisposing to AF such as inflammation or diastolic heart dysfunction.

Inflammation

The classical factors which favor AF are in most cases identical to the risk factors of coronary artery disease. Since an inflammatory process has significant influence on the development of coronary artery disease, recently published studies have aimed to prove a hypothesis of the inflammatory process in the etiopathogenesis of AF as well.

One of the first studies on the potential relationship between inflammatory status under a form of an acute pericarditis and heart arrhythmias was published 30 years ago [22]. The study of Bruins et al. [23] was one of the first to propose the inflammatory hypothesis of AF, based on the observation that the highest concentration of CRP assessed on the second/third day after cardiac surgery was correlated with a high risk of AF occurrence.

In 2001, Chung et al. [24] for the first time demonstrated higher CRP values in ‘non-post-operative’ patients with atrial arrhythmias as compared to a control sinus rhythm group. C-reactive protein values in the AF group were double those in a control group. This pioneering study documented also the relationship between CRP levels and progression of arrhythmia. Higher CRP values were observed in patients with chronic, as compared to paroxysmal, AF.

C-reactive protein seems to be a useful marker of inflammation that not only differentiates patients with AF and sinus rhythm, but may be considered as a risk marker of AF occurrence in the future. In a retrospective Cardiovascular Health Study, which enrolled 5,491 patients with no previous history of arrhythmia, during nearly seven years of follow-up, AF was observed in 897 patients [25]. Baseline CRP was found to be an independent predictor of AF in univariate and multivariate analyses (HR for a 1-SD increase in CRP: 1.33; 95% CI 1.18–1.49, and 1.24; 95% CI 1.11–1.40, respectively) The results of the above mentioned study indicate that the inflammatory process may be considered as a cause rather than a result of AF. Nevertheless, this hypothesis should be treated with caution as it has not yet been confirmed by other studies.

Most studies have documented CRP as a useful predictor of AF recurrence after cardioversion, as well as post-surgery AF. In a study by Loricchio et al. [26], a high CRP level observed before cardioversion was found to be an independent multivariate risk marker of arrhythmia recurrence in patients with nonvalvular AF during a year of follow-up (HR=4.98; 95% CI 1.75–14.26). In a study by Lo et al. [27], CRP \geq 3.0 mg/L in patients undergoing coronary artery bypass surgery was related to a more than trebled risk of post-operative AF, both in patients operated on and off extracorporeal circulation (OR = 3.3; 95% CI 1.4–7.6).

A relationship between AF and inflammation may be supported by several clinical studies which documented that high levels of other inflammatory markers (like IL-6 or TNF) also differentiate patients with and without arrhythmia [28].

The histological examination of human heart biopsies has brought strong evidence of complicity in the inflammatory process and atrial tachyarrhythmia. The study of Frustaci et al. [29] documented more frequent prevalence of inflammatory infiltration, myocyte necrosis and fibrosis between atriomyocytes descended from the 12 patients with lone AF compared to patients undergoing surgery for Wolff-Parkinson-White syndrome without a history of AF. Similar conclusions were made in a study by Nakamura et al. [30] which observed an inflammatory process defined as an increased number of active T lymphocytes, macrophages and a higher expression of von Willebrand factor in biopsy of left atrial appendix of patients with nonvalvular AF, as compared to patients with noarrhythmia.

The theory of probable contribution of inflammation as a factor precipitating AF occurrence, as

well as arrhythmia maintenance, has resulted in clinical trials evaluating the antiarrhythmic efficacy of anti-inflammatory drugs. Despite conflicting clinical data, positive results of several retrospective analyses of ACE inhibitors and statins cannot exclude the role of inflammation in the development of AF [31, 32].

Summing up, the participation of inflammation on cardiac cell levels in the AF course is highly probable. However, an unanswered question still remains: is the inflammatory condition the cause of AF, or the result of repeated attacks and a marker that arrhythmia is becoming established?

Family occurrence of atrial fibrillation

People suffering from AF without perceptible structural cardiovascular disease may lean towards combining etiopathogenesis of that arrhythmia with a probable defect lying at the molecular bottom of heart cells. Fox et al. [33] proved in their multifactorial analysis that the risk of AF occurrence increases threefold (OR = 3.23, 95% CI 1.87–5.58) among the offspring of patients suffering from AF, particular those in whom the first attack appeared relatively early. On the other hand, research by Arnar et al. [34] shows that people, among whose relatives in the direct line is a person with AF diagnosed before the age of 60, are exposed to an almost fivefold greater risk of AF (RR = 4.67; 95% CI 3.57–6.08) compared to the rest of the population.

Atrial fibrillation, like diabetes or obesity, is a rather polygenic disease. Probably, most cases of arrhythmia demand activation of improper transcription pathways in many places simultaneously. So far, only single gene mutations have been isolated. The discovered defects of genes coding potassium channel protein (KCNE2, KCNH2, KCNJ2, KCNQ1), connexins 40, or atrial natriuretic propeptide cause homeostatic imbalance on the cell level and in consequence premature AF onset [35]. An exceptionally important meaning has been recently assigned to polymorphism locus 4q25. A probable gene for this region, PITX2, is believed to make a significant contribution to the embryogenesis of atrioventricular node and the development of cardiomyocytes on the border of the left atrium and the pulmonary vein — a place treated vulnerable to AF wave raising [35].

Molecular biology, as well as genetic engineering, is a field of science which is developing at a hectic pace. Discovering the new genes potentially involved in AF development will probably change

our point of view of the etiopathogenesis of arrhythmia, and open new possibilities of therapy.

Alcohol consumption

Moderate alcohol consumption is associated with a lower risk of cardiovascular disease than abstinence. Episodic heavy drinking may trigger AF paroxysms, first described by Ettinger et al. [36] in 1978 as the so-called ‘holiday heart syndrome’. Alcohol has a direct toxic effect on the myocardium, causes sympathetic activation, intra- and inter-atrial conduction disturbances, and may lead to electrolyte imbalance. Yet the relationship of the full range of alcohol consumption with the risk of AF in observational studies is far less consistent. In the Framingham Heart Study, alcohol consumption, regardless of the amount, was not a risk factor for AF in a ten year follow-up (HR = 1.05; 95% CI 0.96–1.16) [1]. Similar conclusions were drawn from the Cardiovascular Health Study [8, 37]. In that study, which lasted nine years and covered more than 6,500 participants aged 65 and over, the amount of alcohol intake was not related to AF development. Those who abstained from alcohol, those who consumed a moderate amount of alcohol (less than 1 drink per week), as well as heavier drinkers (14 or more drinks per week), had similar AF risks. Surprisingly, former drinkers, in comparison to both abstainers and current drinkers, had a higher risk of AF (HR = 1.25; 95% CI 1.02–1.54). According to the authors of this study, a higher risk of AF among former drinkers was possibly related to underlying health conditions that had led them to discontinue alcohol use (Fig. 2).

Physical activity

Moderate regular exercise plays a significant role in preventing cardiovascular disease. Nevertheless, recent data has shown a relationship between long-term endurance sport practice or rigorous occupational activity and a higher risk of AF in comparison with controls. Karjalainen et al. [38] were among the first, in 1998, to describe this. After ten years of follow-up, AF incidence among runners was 5.3%, compared with 0.9% among the control group. Middle-aged endurance sport practitioners (long distance runners or bikers) seem to be at higher AF risk [39]. The recently published GIRAFA study [40] was conducted among healthy men younger than 65 and showed that accumulat-

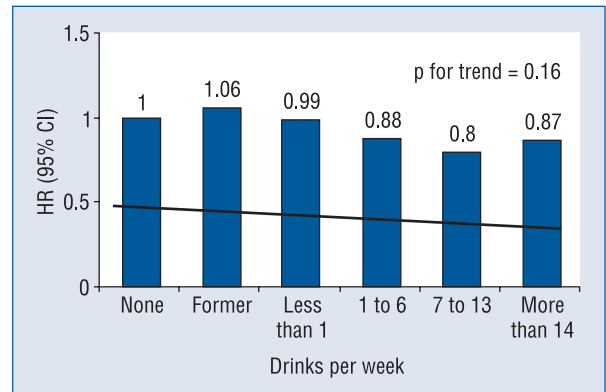


Figure 2. Hazard ratios (HR) of atrial fibrillation according to usual alcohol consumption (adapted from Mukamal et al. [37]).

ed lifetime physical activity, the sum of occupational and sport practice activity, is associated with increased AF occurrence. The mechanism that may explain the association remains unknown, but it may be 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, is related to an increased atrial size and altered diastolic function. Furthermore, alterations in the autonomic nervous system could also explain a higher AF risk, as an increased vagal tone induced by endurance physical activity may facilitate the appearance of arrhythmia.

Conclusions

We are still far from a complete understanding of the mechanisms causing AF. The role of so-called classical risk factors (arterial hypertension, valvular heart defects, heart failure, etc.) is not in doubt. Detecting those with ‘better health’ but still at risk of arrhythmia remains difficult. Moreover, it is not known if correcting so-called ‘novel’ risk factors reduces the AF risk. Gene polymorphism or active micro-inflammation affecting atriumyocytes are not ‘visible’ in the cardiologist’s surgery. Neither is the doctor’s intuition a help in these circumstances, because a tall, sporty, abstinent, 40 year old male is a person at risk as well.

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