Atrial fibrillation (AF) is a prevalent arrhythmia in patients with cardiovascular disease. The classical risk factors for developing AF include hypertension, valvular disease, (ischaemic) cardiomyopathy, diabetes mellitus, and thyroid disease. In some patients with AF, no underlying (cardiovascular) pathology is present and the aetiology remains unknown. This condition is known as lone AF. However, in recent years, other factors playing a role in the genesis of AF have gained attention, including obesity, sleep apnoea, alcohol abuse and other intoxications, excessive sports practice, latent hypertension, genetic factors, and inflammation. In this review, we address these ‘new risk factors’ (i.e. as opposed to the classical risk factors) and the mechanisms by which they lead to AF.

Introduction

Atrial fibrillation (AF) may be caused by many cardiac and non-cardiac conditions, including hypertension, valvular disease (in particular, of the mitral valve), (ischaemic) cardiomyopathy, diabetes mellitus, and thyroid disease. The vast majority of patients with AF suffers from one or more of these conditions and is >60 years of age. However, a subset of patients with AF is <60 years and routine evaluation, including physical examination, laboratory tests including thyroid function, echocardiography, and exercise stress testing, does not reveal any abnormalities. These patients are considered to suffer from ‘lone’ AF, i.e. AF without an underlying (cardiovascular) disorder.

There is increasing evidence that, from a pathophysiological point of view, the underlying mechanism of lone AF is different than that of AF in the setting of underlying disease. The latter is ‘substrate related’, i.e. due to diseased and dilated atria with stretch and fibrosis. In contrast, lone AF is probably more related to electrophysiological phenomena (triggers) in structurally normal atria. This explains why patients with real lone AF have a normal life expectancy when compared with individuals without arrhythmia (Figure 1), a low risk for stroke, and why paroxysmal lone AF does not often progress to persistent or permanent AF. In contrast, AF in the setting of underlying cardiac pathology usually progresses from paroxysmal to persistent and permanent AF together with the progression of the underlying cardiac substrate and is associated with an increased incidence of stroke.

Although having a benign course, regular follow-up of patients with lone AF is warranted. In time, risk factors such as hypertension, heart failure, diabetes, and peripheral vascular disease may develop, changing prognosis. Obviously, the patient also ages. The incidence of stroke is strongly related with the presence or development of these risk factors and age in patients with lone AF. In addition, prognosis in patients with lone AF has been shown to be strongly related to the presence or development of left atrial dilatation, which might suggest the formation of an atrial structural substrate.

Furthermore, clinicians should ask themselves when AF is truly lone. Underlying hypertension is often not recognized anymore after institution of rate-control therapy by β-blockers or calcium channel blocking agents. Long-term data from the Mayo Clinic revealed that only 2% of the total population of patients with AF really have lone AF. Apart from the (cardiovascular) conditions traditionally known to be related to AF, other factors may also be involved in the pathogenesis of arrhythmia, i.e. being risk factors for AF. In what follows, we discuss some of these risk factors and the underlying mechanisms by which these conditions may contribute to the development of, apparently lone, AF. These underlying factors also may alter the prognosis. Adequate treatment or reduction of these risk...
Obesity

Obesity is an ever increasing problem in the western world and is associated with an increased incidence of AF. There is a 3–8% higher risk of new onset AF with each unit increase in body mass index (BMI), and this association is independent of other cardiovascular risk factors such as lipid levels, blood pressure, and diabetes. When compared with persons with a normal BMI (18.5–25 kg/m²) and adjusted for other risk factors such as age, smoking, alcohol consumption, and blood pressure, the hazard ratio (HR) for AF is 1.75 for overweight men and 1.39 for overweight women (BMI 25–30 kg/m²). These hazards rise to 2.35 and 1.99, respectively, for obese persons (BMI >30 kg/m²).

The mechanisms by which obesity may lead to AF are unknown. It is hypothesized that an increased left atrial size is an important factor because the dimensions of the atria are strongly correlated to the BMI, possibly due to diastolic dysfunction because of thickening of the myocardium, elevated plasma volume, and increased neurohormonal activation. Wang et al. found that after adjustment for left atrial diameter, BMI was no longer associated with AF risk. Other factors which may be related to the development of AF in obese individuals include autonomic dysfunction and sleep apnoea. It is intriguing to speculate that weight reduction may lower the risk of AF.

Sleep apnoea

Obstructive sleep apnoea (OSA) is characterized by periodic reduction or even cessation of breathing during sleep due to narrowing of the upper airways. This induces intermittent hypoxaemia and hypercapnia, sympathetic activation, and changes in blood pressure. Furthermore, the elevated intrathoracic pressure caused by inspiration against an obstructed airway causes an increased transmural pressure gradient which in turn may lead to atrial stretch. In addition, the intermittent hypoxaemia may lead to pulmonary vasoconstriction, resulting in elevated pulmonary artery pressures. Finally, OSA is associated with autonomic imbalance and diastolic dysfunction. Together, these factors may lead to an enhanced vulnerability to AF.

Conversely, a paroxysm of AF may lead to central sleep apnoea, probably due to an acute decrease in the left ventricular function, resulting in an increase in pulmonary wedge pressure and consequent stimulation of pulmonary vagal receptors.

Patients with AF have a high prevalence of OSA, and conversely, the prevalence of AF is increased in patients with OSA, also in the absence of an underlying cardiac disease. Gami et al. found the presence of OSA to be a strong predictor of incident AF (HR, 2.18, 95% confidence interval 1.34–3.54). In addition, measures of OSA severity such as the degree of nocturnal oxygen desaturation were also strong predictors of incident AF (Figure 2). However, the treatment of OSA with continuous positive airway pressure (CPAP) did not affect the incidence of AF in this retrospective analysis. In contrast, a prospective analysis by Kanagala et al. demonstrated that patients with OSA have a higher recurrence rate of AF after a successful cardioversion than patients without OSA. In contrast to the data of Gami et al., treatment with CPAP did reduce the recurrence rate in these OSA patients.

Alcohol and other substances

A paroxysm of AF after binge drinking (holiday heart syndrome) was first described by Ettinger in 1978. There are several proposed mechanisms by which alcohol consumption relates to the development of AF. First, alcohol has a direct toxic effect on cardiac myocytes. Secondly, during both drinking and withdrawal of alcohol, a hyperadrenergic state is achieved, and alcohol causes an impaired vagal tone. Furthermore, alcohol causes an increase in intra-atrial conduction time, which is also reflected by a prolongation of the P-wave. In contrast, moderate alcohol intake is associated with a lower risk of coronary disease and may thus reduce the risk of developing AF.

It has been demonstrated that patients admitted with lone AF have been drinking more in the previous week than controls. Evidence exists, however, that also chronic consumption of alcohol is associated with an increased risk of AF. This association is independent of other cardiovascular risk factors such as lipid levels, blood pressure, and diabetes. When compared with persons with a normal BMI (18.5–25 kg/m²) and adjusted for other risk factors such as age, smoking, alcohol consumption, and blood pressure, the hazard ratio (HR) for AF is 1.75 for overweight men and 1.39 for overweight women (BMI 25–30 kg/m²). These hazards rise to 2.35 and 1.99, respectively, for obese persons (BMI >30 kg/m²).
increased risk of developing AF. In the Framingham study, there was a weak relationship between long-term moderate alcohol consumption and AF. However, when the amount of alcohol consumed was more than 36 g/day (approximately more than three drinks/day), the risk of developing AF was increased by 34%. In a large prospective Danish study in almost 48,000 people, there was a modest and significant increase in the risk of AF by increasing alcohol consumption in men but not in women. Comparable results were found in a similar population. In a prospective population-based cohort study among inhabitants of Copenhagen, alcohol intake of more than 35 drinks a week was associated with a higher risk of AF in men. Few women consumed this amount of alcohol and therefore, in women, this relationship could not be assessed.

Contrasting results were found in the Cardiovascular Health Study. In this prospective cohort study of risk factors for coronary heart disease and stroke in over 5000 men and women ≥65 years old, after 3 years follow-up, alcohol intake was inversely correlated with the risk of AF, although the mean amount of alcohol consumed was low (two to three drinks/week). After 9 years follow-up, current moderate alcohol intake was neither associated with a higher nor lower risk of AF in this study. Also after AF had developed, alcohol intake was not related to mortality in this elderly population.

Another stimulant which, generally, is thought to be associated with AF is caffeine. However, this relationship has never been demonstrated. In an animal study, intravenous administration of caffeine in dogs surprisingly resulted in a reduction of the propensity for AF. Furthermore, in a large population study, no relation was found between the level of caffeine intake and incident AF.

Smoking promotes cardiovascular disease and hence AF. However, there is evidence that nicotine also has direct effects on the atria which may form a substrate for AF. In isolated rat hearts, administration of nicotine induces changes in atrial conduction and refractoriness. These changes were related to the age of the rats. Younger rat hearts were more susceptible to AF than older rat hearts after nicotine administration. Recently, Goette et al. investigated the amount of atrial fibrosis and expression patterns of collagens in right atrial appendages of patients admitted for coronary bypass surgery. These patients had no history of AF. In smokers, the only factor related to the amount of fibrosis was the number of pack-years. In both smokers and non-smokers, the amount of fibrosis was related to the development of post-operative AF. Furthermore, exposition of atrial tissue of non-smokers to nicotine resulted in an up to 10-fold mRNA expression of collagen III, comparable with the expression found in smokers.

Sports and exercise

Although regular exercise is well known to reduce cardiovascular morbidity, excessive (endurance) sport practice is associated with a higher prevalence of AF. Athletes may present with any arrhythmia, but AF is a most usual cause when an athlete suffers from palpitations. Arrhythmia may occur both at rest (vagal conditions) and during exercise.

Mont et al. determined the proportion of individuals engaging in frequent and long-term sports activity in patients with lone AF. In a group of 1160 consecutive patients, 70 individuals had lone AF and were <65 years. Of these 70 patients, 32 had engaged in long-term sport practice, defined as at least 3 h a week for at least 2 years. Surprisingly, these were all men. In 57% of the sportsmen with AF, the paroxysms started in vagal situations (in rest, after exercise, or eating), compared with only 18% in the non-sport male patients with lone AF. Of all men with lone AF in this study, 63% had been participating in sports; this percentage is significantly higher than that of males in the general population who practice sports at a similar intensity (15%). In a case–control study, the same group reported the current sport activity to be associated with a three times higher prevalence of lone AF and a five times higher prevalence of vagal lone AF when compared with controls.

Of note, these associations were observed when the cumulative time of lifetime sports practice exceeded 1500 h. Recently, these authors additionally demonstrated a relation between lone AF and cumulative work-related physical activity.

Karjalainen et al. evaluated the presence of AF in 228 veteran male orienteers (cross-country runners) and compared this with the prevalence of AF in a matched control group (n = 212). The mean age was 47.5 years in the orienteer group and 49.6 years in the controls. Lone AF was diagnosed in 12 orienteers (5.3%) vs. 2 control subjects (0.9%), whereas there was no difference in the prevalence of AF in the presence of risk factors. Heidbuchel et al. assessed the influence of sports activity on the risk of AF after the ablation of atrial flutter. Of 137 patients undergoing ablation of the right atria because of atrial flutter, 31 (23%) participated in endurance sports on a regular basis. A history of competitive sports practice was associated with an elevated risk of developing AF [multivariate HR 1.81 (1.10–2.98, P = 0.02)] after the ablation. In addition, continuation of endurance sports (19 patients) after the ablation showed a trend towards an increased risk of AF [multivariate HR 1.68 (0.92–3.06), P = 0.08].

There are several mechanisms by which sports may induce AF. First, sporting results in enlargement of the cardiac chambers and an increase in the left ventricular mass and left atrial diameter as an adaptation mechanism. One could speculate whether these adaptations are associated with the development of fibrosis or electrophysiological remodelling in the atria. Pelliccia et al. determined the left atrial dimension in 1777 competitive athletes and found a dimension of ≥40 mm in 20% of these individuals. Nevertheless, the prevalence of AF was only 0.3% in this group. Another factor favouring AF in sportsmen is the increased vagal tone, resulting in bradycardia and shortening of the atrial refractory period. Furthermore, during exercise, hypovolaemia may develop because of fluid loss, resulting in altered pressures leading to an increased vulnerability to AF. Finally, changes in electrolytes due to sweating can cause changes in atrial electrophysiology.

A possible link between sports and AF is the use or abuse of anabolic steroids. There is anecdotal evidence of sportsmen developing AF after the use of these drugs. The mechanism by which anabolic steroids cause AF is largely unknown but changes in the autonomic function and the baro-reflex have been demonstrated in animal models.
Increased pulse pressure

Besides overt (systolic) hypertension, other aberrations in blood pressure may predispose to AF. Mitchell et al. evaluated the relationship between pulse pressure (i.e. the difference between systolic and diastolic pressure) and the incidence of AF in 5331 individuals in the Framingham Heart Study. During 20 years follow-up, AF developed in 698 persons after a median period of 12 years. After correction for other risk factors, pulse pressure was associated with an increased risk of incident AF (adjusted HR 1.26 per 20-mm Hg increment). Although systolic pressure was associated with incident AF, this association was stronger when the diastolic pressure was added in the statistic model. A given systolic pressure was associated with a higher incidence of AF when the diastolic pressure was lower. Surprisingly, mean arterial pressure was not related to AF incidence in this study.52

Genetic atrial fibrillation

Some individuals with lone AF have a family history of AF, suggesting a genetic cause in these patients. Apart from genes that have been demonstrated to modulate the incidence of AF in patients with underlying heart disease,53 also genes leading to lone AF have been detected. The first family with AF was described in 1943.54 Not until more than 50 years later, in 1997, the first genetic locus on chromosome 10q22-24 for a form of monogenic AF was identified.55 After that, others discovered other loci of familial AF.56-58 Mutations in specific genes have subsequently been found. These genes are mostly encoding for potassium channels (KCNQ1,59 KCNE2,60 KCNJ2,61 and KCNA562) but also mutations in the sodium channel gene SCN5A,63 the connexin40 gene GJA5,64 and the K(ATP) gene ABCC965 have been demonstrated to cause monogenic forms of AF. These mutations have been shown to result in changes in the atrial electrophysiology, either by changing the shape of the action potential or by causing alterations in atrial conduction, leading to an electrophysiological substrate for arrhythmia. Although these genetic forms of lone AF are probably very rare, a careful family history should be taken when a patient presents with (lone) AF.

Inflammation

In recent years, 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. 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.66 Furthermore, inflammation may also be associated with thrombosis and hence with AF-related complications.57,68

Also in lone AF, inflammation may play a role. Atria of patients with lone AF frequently demonstrate histopathological signs of inflammation. Frustaci et al.69 investigated atrial biopsies of patients with lone AF and found signs of myocarditis in 66% of these individuals. Many studies have found a relationship between circulating markers of inflammation, including C-reactive protein, high-sensitivity C-reactive protein, and interleukins (IL5). on one hand and the clinical course of AF on the other. C-reactive protein is a well known marker of the inflammatory status and is produced in the liver as a response to IL-6, IL-1, and tumour necrosis factor-α. An elevated level of circulating C-reactive protein is associated with an enhanced risk of developing AF in healthy individuals.70,71 Patients with AF have higher C-reactive protein levels than individuals in sinus rhythm and also persistent AF patients have higher C-reactive protein levels than paroxysmal AF patients.72 Also, the duration of AF is correlated to the level of circulating C-reactive protein. The chance of successful chemical73 or electrical74 conversion and subsequent maintenance of sinus rhythm is inversely correlated to C-reactive protein levels.

Whether AF is a cause or consequence of inflammation remains a matter of debate. Kallergis et al.75 recently evaluated the high-sensitivity C-reactive protein levels in 52 patients with persistent AF undergoing cardioversion. High levels of high-sensitivity C-reactive protein before cardioversion were associated with an increased recurrence of AF after cardioversion but also high-sensitivity C-reactive protein levels decreased in patients with maintenance of sinus rhythm, suggesting inflammation is a consequence, rather than a cause, of AF. Likewise, Marcus et al.76 recently demonstrated a fall of C-reactive protein and IL-6 after the ablation of atrial flutter.

Drug therapy targeting inflammation in the treatment of AF is promising. Angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, aldosterone receptor blockers, statins, and peroxisome proliferator-activated receptor-γ activator pioglitazone possess anti-inflammatory properties which, apart from their effect on underlying cardiovascular disease, may have beneficial effects on AF burden.77-80 A comprehensive description of studies investigating these effects is beyond the scope of this review. However, large prospective trials addressing the effect of these drugs on the clinical course of AF in correlation with inflammatory markers are currently lacking.

Conclusion

In most patients, AF develops from a substrate that is the common final pathway of different underlying cardiovascular disorders. The process of atrial remodelling leading to this substrate already commences a long time before the first episode of AF occurs. Therefore, treating the underlying disease is the first step in trying to prevent AF and reduce AF burden once the first paroxysms appear in these patients.

In a significant subset of patients, no underlying cardiovascular disease is present and these individuals are considered to suffer from lone AF. However, there may be other conditions present in such patients that predispose to AF. Many of these factors are life style-related, such as drinking, excessive sports practice, or obesity, possibly resulting in sleep apnoea. Previously, socio-economic factors have also been identified to influence AF incidence.81 Hypertension may be still occult while already damaging the atrial tissue. At present, it is unknown whether these factors result in a substrate comparable to
that of AF in the setting of underlying heart disease or these factors are solely leading to electrophysiological changes that trigger AF without concomitant structural changes of the atria. Consequently, one can only speculate whether these forms of ‘not-so-lone’ AF carry an increased risk for thrombo-embolic complications and other adverse events. Therefore, all patients with these forms of AF should be offered follow-up and the development of risk factors for thrombo-embolic events, left atrial diameter, and/or symptoms should be monitored. Finally, little is known about the effect of lifestyle modification on AF burden in these patients. Future research is warranted to address these issues.

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References


