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Epidemiology of atrial fibrillation

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Summary

Atrial fibrillation is the most common sustained cardiac arrhythmia in the general population. Unfortunately, current treatment strategies aiming at the elimination of atrial fibrillation have limited long term success rates and significant risks. In this context, recent publications have provided many insights on potentially treatable risk factors for the occurrence of atrial fibrillation, such as alcohol, blood pressure, obesity, inflammation and nutritional factors. In this review, we summarise the current evidence on these risk factors and indicate areas in need of further investigation. The current evidence shows that blood pressure, hypertension and obesity seem to play a key role in the pathogenesis of atrial fibrillation. Preliminary evidence also suggests that inflammation is an important mediator of these associations. Knowledge of these interrelationships may eventually help to develop new treatment strategies and decrease the burden of atrial fibrillation in the general population.

Key words: atrial fibrill ation; epidemiology; bood pressure; inflammation; risk factors

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia in the general population [1–3], and its prevalence is strongly dependent on age. While atrial fibrillation is a rare disorder among individuals aged <60 years (prevalence <1%), the prevalence of atrial fibrillation increases to >7% among individuals aged 80 years and older [1]. Recent estimates suggest that over 10% of the population will develop atrial fibrillation by the age of 75 years [2]. Framingham Heart Study investigators also estimated that the lifetime risk for the development of atrial fibrillation was one in four at age 40 and was one in six even in the absence of preceding heart failure or myocardial infarction [4]. For as yet unknown reasons, men have a higher risk of developing atrial fibrillation than women [5].

The prevalence and incidence of atrial fibrillation have substantially increased over time, even after adjustment for age [2, 3]. Possible reasons for this rise may be the increasing obesity burden in the population, but also the availability of improved diagnostic tools for the detection of atrial fibrillation. The importance of atrial fibrillation as a public health problem is further underscored through its association with an increased risk of stroke, heart failure, death, cognitive dysfunction and a reduced quality of life [6–10]. For example, patients who have been diagnosed with atrial fibrillation have a 5-fold increased risk of stroke compared to those without atrial fibrillation [11]. Unfortunately, treatment strategies aiming at the elimination of established atrial fibrillation have limited long-term success rates and significant risks [12, 13]. Furthermore, stroke risk in patients with atrial fibrillation may never be significantly reduced due to persistence of asymptomatic atrial fibrillation [14]. For all these reasons, characterising potentially treatable risk factors for atrial fibrillation has substantial clinical relevance.

Although atrial fibrillation frequently occurs in individuals with underlying structural heart disease, such as valvular heart disease or left ventricular dysfunction [5, 15, 16], many recent publications have provided more detailed insights on other important risk factors for the occurrence of atrial fibrillation. In this review, we would like to summarise the current evidence on these risk factors and indicate areas in need of further investigation. For this purpose, we performed a compre-

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hensive, but not systematic review of the literature in PubMed, asked experts in the field about other potentially relevant articles and reviewed the reference lists of retrieved articles for additional studies. Although genetic risk factors are certainly involved in the pathogenesis of atrial fibrillation, we did not consider this topic for this review given the rapidly changing knowledge in this field.

Blood pressure and hypertension

Many studies have shown that individuals with hypertension have an increased risk of developing atrial fibrillation compared with normotensive individuals [5, 15, 17]. Given the high prevalence of hypertension worldwide, elevated blood pressure has become the most common risk factor for atrial fibrillation. For example, data from the Framingham Heart Study suggested that 14% of the atrial fibrillation risk in both men and women was attributable to hypertension [5].

Recent studies provided more detailed insights into this relationship by assessing the relative importance of the individual blood pressure components in the development of atrial fibrillation [15, 18, 19]. For example, in elderly individuals with a high baseline prevalence of cardiovascular diseases, systolic blood pressure was a stronger predictor of incident atrial fibrillation than a history of hypertension [15]. Recent data from the Framingham Heart Study confirmed the importance of systolic blood pressure and provided important additional insights in the pathogenesis of atrial fibrillation [18]. Mitchell et al. found that diastolic blood pressure provided important additional information to the effect of systolic blood pressure, suggesting that pulse pressure may be even more predictive of subsequent atrial fibrillation than systolic blood pressure alone [18]. These findings provided some evidence that aortic stiffness may be an important factor in the pathogenesis of atrial fibrillation.

Our own data from the Women's Health Study partially confirmed these findings [19]. Within a large cohort of initially healthy women, we confirmed that systolic blood pressure was a better predictor of incident atrial fibrillation than diastolic blood pressure. We also found that diastolic blood pressure may provide some additional information to systolic blood pressure, again supporting hypotheses on the potential importance of pulse pressure. Furthermore, this study also showed that blood pressure values considered as normal are associated with an increased risk of incident atrial fibrillation, and that there was no evidence of a threshold below which the risk of incident atrial fibrillation was not increased. Women with systolic or diastolic blood pressure values between 130–139 mm Hg or 85–89 mm Hg had a 28% and 53% increase in risk compared with women who had systolic or diastolic blood pressure below 120 mm Hg or 65 mm Hg, respectively. These findings suggest that even slightly elevated blood pressure levels impose some degree of increased risk and that a lower blood pressure treatment target for patients suffering from atrial fibrillation may help to reduce the growing atrial fibrillation burden in the community.

Prior studies have established several potential mechanisms in addition to arterial stiffness that could underlie the relationship between blood pressure and incident atrial fibrillation. Elevated systolic blood pressure is associated with increases in left atrial fibrosis [20, 21], which in turn is related to prevalent atrial fibrillation [22]. Some studies suggest that left ventricular hypertrophy and increases in left atrial size may also mediate the relationship between blood pressure and incident atrial fibrillation [16, 23]. However, while these factors probably play an important role in the pathogenesis of atrial fibrillation, prior studies have found independent blood pressure effects even after taking into account some of these structural variables [18].

Obesity, metabolic syndrome and physical activity

Obesity is another major risk factor for the development of atrial fibrillation. Multiple studies have documented a strong and independent association between body mass index and incidence of atrial fibrillation [24–26]. Given the increasing incidence of both atrial fibrillation and obesity in the general population, obesity may be an important factor for the increasing burden of atrial fibrillation [2, 3]. Investigators from the Framingham Heart Study found a 45–50% increased risk of incident atrial fibrillation among obese participants (defined as body mass index ≥30 kg/m^2) compared with those who had a normal body mass index; a relationship that was independent of age and other cardiovascular risk factors [25]. In addition to increasing the susceptibility of developing atrial fibrillation, a recent publication also suggested that obesity may be an important factor of disease progression in an individual patient, as obesity was found to be an independent predictor

of progression from paroxysmal to permanent atrial fibrillation [27]. Finally, while a Danish study has provided some evidence that even overweight individuals may be at increased risk of incident atrial fibrillation [24], these results were not confirmed in other cohorts [25]. Thus, more studies are needed to describe in detail this important relationship and provide potential mechanistic insights.

Obesity is closely related to the metabolic syndrome, a cluster of metabolic abnormalities occurring in individuals at increased risk of developing type 2 diabetes [28, 29]. Many studies have demonstrated that individuals with the metabolic syndrome have an increased risk of developing cardiovascular events [30–34]. Recent evidence from Japan also supports a significant relationship between the metabolic syndrome and incident atrial fibrillation [35]. In this study, participants with the metabolic syndrome had an 88% increased risk of developing atrial fibrillation compared with those without the metabolic syndrome. However, it is currently unclear whether this association is also present in different population groups and whether the presence of the metabolic syndrome provides additional information that is independent of its individual components. Further studies are needed to clarify these issues.

Obstructive sleep apnoea is a sleep related disorder associated with episodes of repetitive and prolonged hypoxaemia, exaggerated intrathoracic pressure oscillations with increased cardiac wall stress and increased sympathetic activity, all factors that promote the occurrence of atrial fibrillation. It is therefore not surprising that studies have consistently shown a strong link between atrial fibrillation and obstructive sleep apnoea [36–38]. While obstructive sleep apnoea is strongly related to obesity, a recent study suggested that its effect on atrial fibrillation may even be independent of obesity, at least in younger individuals [36]. Future studies should investigate in more detail the pathogenic mechanisms that increase the risk of atrial fibrillation among patients with obstructive sleep apnoea and whether these mechanisms are truly independent of obesity.

While physical inactivity has been associated with an increased risk of incident coronary heart disease even after taking into account other cardiovascular risk factors [39, 40], differential findings have been demonstrated with regard to incident atrial fibrillation. Small studies have suggested an increased risk of atrial fibrillation after vigorous exercise [41, 42], but the role of chronic moderate physical activity in the development of atrial fibrillation has long been unclear. A recent study among elderly individuals found that leisure-time physical activity was related to a reduced risk of incident atrial fibrillation during follow-up [43]. These results were maintained after multivariable adjustment, suggesting that promoting light to moderate physical activity may reduce the incidence of atrial fibrillation in the general population.

Other cardiovascular risk factors

Compared to the factors described above, much less is known about the relationship between other established cardiovascular risk markers such as smoking, diabetes or dyslipidaemia and the development of new-onset atrial fibrillation. Although diabetes was a significant risk factor for the development of atrial fibrillation in the entire Framingham population, this association was not significant among participants with non-valvular atrial fibrillation [5]. Similarly, smoking has been associated with a somewhat increased risk of atrial fibrillation in some, but not all studies [5, 15, 44].

The relationship between lipid levels and atrial fibrillation is also poorly understood. Unexpectedly, high levels of cholesterol have been repeatedly associated with a reduced risk of developing atrial fibrillation [15, 24]. In one study, women with high cholesterol levels had a 43% reduced risk of incident atrial fibrillation compared with those with normal cholesterol levels [24]. It has been suggested that low levels of high density lipoprotein cholesterol may affect atrial vulnerability and cause atrial fibrillation [45], but much more data are needed with regard to this relationship. Areas of particular interest for future research include the differential influence of different lipid sub fractions or the effect of statin therapy on the risk of atrial fibrillation.

Alcohol consumption

Consuming moderate amounts of alcohol has been consistently associated with reduced risks of coronary heart disease, stroke, and congestive heart failure [46–50]. Conversely, acutely ingesting excessive amounts of alcohol ("binge drinking") has been related to increased risks of myocardial infarction [51], stroke [52] and atrial fibrillation [53–55]. Many years ago, Ettinger et al were the first to use the term holiday heart to describe an increased incidence of atrial arrhythmias

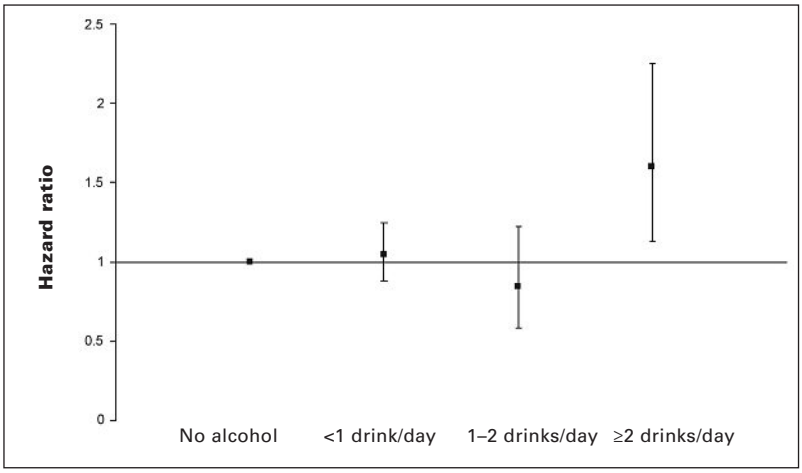

Figure 1

Risk of incident atrial fibrillation according to the amount of alcohol consumption in women.

after week-ends and holidays [53]. Since then, many cohorts have consistently documented that men consuming at least 35 alcoholic drinks per week on a regular basis had an increased risk for the subsequent development of atrial fibrillation compared with non-drinking men [50, 56, 57]. This relationship was independent of other cardiovascular risk factors.

We recently found a similar relationship between elevated amounts of alcohol consumption and the risk of developing atrial fibrillation among women participating in the Women's Health Study [58]. In the group of women consuming at least two alcoholic beverages per day (i.e., 14 drinks per week), there was a 60% increased risk of incident atrial fibrillation compared with non-drinking women (fig. 1). We concluded that consuming moderate amounts of alcohol is not associated with an increased risk of atrial fibrillation, but that excessive amounts of regular alcohol consumption may induce atrial fibrillation. Our findings also suggest that the risk threshold for the development of atrial fibrillation is substantially lower in women than in men.

Fatty acid intake

In cultured rat atrial myocytes, n-3 fatty acids reduce induced asynchronous contractile activity, suggesting that they may have antiarrhythmic effects on atrial muscle [59]. They also decrease excitability and cytosolic calcium fluctuations of ventricular myocytes via inhibition of sodium and L-type Calcium channels, thereby inhibiting automatic and re-entrant arrhythmias [60, 61]. A beneficial effect of n-3 fatty acids may also be mediated through a lowering of blood pressure, a reduction in systemic inflammation or an improvement in left ventricular diastolic function [62, 63].

Consistent with these mechanistic considerations, a prospective cohort study among elderly participants found a reduced risk of incident atrial fibrillation in participants with high intake of baked or broiled fish [64]. In this study, consuming fish at least five times per week was associated with a 31% reduced risk of developing atrial fibrillation compared with those who consumed fish less than once per month. Unfortunately, these promising results have not been confirmed by two other publications from European cohorts [65, 66], such that more studies are needed to assess the role of n-3 fatty acids and other nutritional factors in the pathogenesis of atrial fibrillation.

Inflammation

Plasma levels of the acute-phase reactant C-reactive protein (CRP) have been consistently associated with the occurrence of cardiovascular events in multiple populations [67–69]. The concept that inflammation also contributes to the occurrence of atrial fibrillation is supported by several lines of evidence, including the frequent occurrence of atrial fibrillation after cardiac surgery in 25% to 40% of these patients. Furthermore, postoperative complement-CRP complex levels have been associated with the occurrence and timing of post-operative supraventricular arrhythmias [70]. Patients with high baseline CRP levels are at higher risk of having postoperative atrial fibrillation in both on-pump and off-pump surgery [71]. Also from a histological perspective, studies have documented inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with both lone [72] and nonvalvular atrial fibrillation [73].

Currently, two prospective studies have evaluated whether elevated levels of CRP are associated with an increased risk of atrial fibrillation [74, 75]. In the Cardiovascular Health Study for example, baseline CRP predicted a higher risk of incident atrial fibrillation among 5806 participants aged 65 years or older over a median follow-up of 7.8 years. Compared with participants in the first quartile of CRP levels, subjects in the fourth quartile had a significant 31 percent increased risk of incident atrial fibrillation during follow-up, even after adjustment for multiple other risk factors [74]. However, these observed associations between CRP and atrial fibrillation in observational studies could be due to well-established associations between inflammation and conditions that

predispose to atrial fibrillation [76–78]. Although the above study attempted to control for these conditions in multivariable analyses, it is possible that incomplete control for these co-morbidities and/or severity of disease accounts for at least part of the observed association. On the other hand, it is also possible that inflammation may be an important mediator between some established risk factors and the development of atrial fibrillation. For example, the increased risk of incident atrial fibrillation associated with elevated body mass index or blood pressure may be mediated by an increased inflammatory burden among obese [79] or hypertensive individuals [80].

Taken together, inflammation may be an important factor or mediator in the pathogenesis of atrial fibrillation. Studies among younger and healthier individuals, who have a low burden of cardiovascular disease, may shed more light in this potential association. Further studies are also needed to assess whether modulation of the inflammatory process influences the risk of new-onset atrial fibrillation among individuals at risk.

Oxidative stress

One potential link between atrial fibrillation, tachycardia and atrial remodelling is oxidative stress. Increased oxidative stress may also underlie the early electrophysiological remodelling associated with atrial fibrillation. Consistent with this hypothesis, rapid atrial pacing in dogs has been shown to increase myocardial peroxynitrite formation and lead to a shortening of the atrial effective refractory period, both of which are reversed by treatment with the antioxidant and peroxynitrite decomposition catalyst ascorbate [81]. In patients undergoing cardiac surgery, oxidative modification of myofibrillar proteins is increased in atrial myocytes from atrial fibrillation patients undergoing the Maze procedure, and this modification appears to contribute to the loss of fibrillar protein function in atrial fibrillation [82]. Markers of oxidative stress have been associated with persistent or paroxysmal atrial fibrillation in one small case control study [83], and in small randomized studies of cardiac surgery patients, the antioxidants ascorbate [81] and N-acetylcysteine [84] have lowered risk of postoperative atrial fibrillation. However, there have been no large prospective associations reported for markers or therapies that could potentially reduce oxidative stress, and more studies are needed to fill this gap.

Conclusion

Multiple recent publications have provided important insights on risk factors for the development of new-onset atrial fibrillation. Blood pressure, hypertension and obesity all seem to play a key role in the pathogenesis of atrial fibrillation, in addition to the importance of structural heart disease. Preliminary evidence suggests that inflammation may be an important mediator of these associations. Due to the current obesity epidemic worldwide, we have to expect a further rise in the incidence of atrial fibrillation in the near future. Given the relative ineffectiveness of current treatment strategies, trials assessing alternative intervention strategies are urgently needed.

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