Lone AF: is There a Rationale?

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Abstract

Although atrial fibrillation (AF) development has been demonstrated to be associated with underlying cardiovascular conditions such as hypertension, valvular heart disease or diabetes mellitus; in a subset of relatively younger patients, no cardiopulmonary disease diagnosis can be established. AF patients younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease are defined as lone AF patients. Despite the decrease in lone AF prevalence due to advances in understanding of AF pathogenesis, there are still issues yet to be resolved. Future studies are needed to demonstrate the cost-effectiveness of the routine use of more advanced diagnostic tools, such as non-invasive assessment of endothelial function, autoimmune markers or genetic screening and whether they would have clinical implications on treatment of lone AF.

This review focuses on the suggested mechanisms in lone AF initiation and maintenance.

Introduction

Although atrial fibrillation (AF) development has been demonstrated to be associated with underlying cardiovascular conditions such as hypertension, valvular heart disease or diabetes mellitus; in a subset of relatively younger patients, no cardiopulmonary disease diagnosis can be established. AF patients <60 years without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus are defined as lone AF patients. This term was first introduced by Evans and Swann in 1954. Due to advances in understanding of AF pathogenesis, prevalence of lone AF has decreased in a significant way from 30% to 5%.5

A recent survey has reported that AF patients without conventional cardiovascular risk factors were not further evaluated for other possible risk factors for development of AF. Results of the survey, which was conducted in thirty-two European centers, all members of the EHRA electrophysiology research network, has shown that assessment for sleep apnea, obesity, and intensive sports activity in lone AF was performed at 27 (84%) centres.5 According to the survey, number of centers where exercise testing, coronary angiography and a computed tomography were performed were 8 (25%), 2 (6%), and 1 (3%), respectively. The work-up typically included screening for known risk factors but not genetic testing.5

10 (31%) centers did perform genetic testing only when there was a family history of AF. Therefore, some of the patients diagnosed with “lone AF” are actually under-evaluated.

Atrial Structural and Functional Changes

Atrial fibrosis has been regarded as the hallmark of the structural changes in the atria in AF patients. Atrial fibrosis was found to be prominent in the tissue samples of patients with history of AF when compared to those without. Extent of fibrosis was found to be comparable in patients with paroxysmal vs. persistent AF, or in lone AF patients vs. those with AF accompanied with mitral valve disease.8

Atrial fibrosis was previously demonstrated with electroanatomic voltage mapping in clinical electrophysiological studies. Stiles et al. have shown that even after maintenance of sinus rhythm for 10 days, lone AF patients had biatrial low voltage values when compared to control patients without AF. More recently, studies have focused on quantification and grading of atrial fibrosis with delayed-enhancement magnetic resonance imaging (DE-MRI). These studies, on the other hand, have shown that there was no profound difference in the degree of atrial remodeling between lone AF patients and those with AF and an accompanying cardiopulmonary disease, and that the extent of atrial remodeling poorly correlated with AF duration, even in lone AF patients.

Rather than just a pathologic finding on atrial specimens, atrial fibrosis has therefore led to a novel definition of the disease. The term “fibrotic atrial cardiomyopathy (FACMP)”, which was originally proposed by Kottkamp et al., is being used to describe a specific, primary form of biatrial pathology, characterized by extensive fibrosis as the substrate underlying atrial arrhythmias and thromboembolism.
According to this hypothesis, multifactorial insults to the atrium may contribute to the development of an atrial cardiomyopathy, and subsequently to the “symptom” of AF. Therefore, lone AF has been proposed to be actually one of the arrhythmic manifestations of a structural atrial disease defined as FACMP. The utility of screening patients for a FACMP has been highlighted by several studies examining the substrate of lone AF. Indeed, Han et al. have stated that they had adopted the approach of using DE-MRI to diagnose true lone AF in patients who were younger than 60 years, lacked comorbidities, and had < 10% LA fibrosis.

In addition, isolated atrial myocardial perfusion abnormalities and coronary flow reserve impairment indicative of microvascular dysfunction have been reported in patients with lone AF.

Autoimmune Biomarkers

Emerging evidence has suggested that autoimmunity may contribute to the development of AF. Although the association between AF and several autoantibodies, including the anti-myosin heavy chain autoantibody, anti–M2-muscarinic receptor autoantibody (anti-M2-R), anti-B1-adrenergic receptor autoantibody (anti-B1-R) and the anti-heat shock protein autoantibody have been demonstrated, data on the relationship between autoimmunity and lone AF is limited. A recent study has reported that anti-M2-R and anti-B1-R levels were significantly elevated in lone AF patients when compared to age- and gender- matched control subjects. Autoantibody levels were also found to be correlated with the left atrial diameter and hs-CRP levels.

Exact pathophysiological mechanisms underlying this relationship have not been fully elucidated yet. Hong et al. have demonstrated that anti-M2-R positive rabbits had longer intra-atrial activation times, shorter atrial effective refractory periods and significantly increased atrial arrhythmogenicity compared to control rabbits possibly due to activation of acetylcholine-gated potassium channel IKCh. Anti-M2-R levels in paroxysmal lone AF patients were found to be strongly correlated with the extent of LA fibrosis in another study, suggesting that severe LA fibrosis may be speculated to be the underlying mechanism for the role of anti-M2-R in the development and maintenance of lone AF in humans. As for anti-B1-R, it has been suggested to promote the passage of calcium through L-type calcium channels by increasing production of cAMP and protein kinase A, which is followed by myocyte destruction, fibrotic repair and electrical instability of the heart, causing atrial inflammation and maintenance of AF.

Genetic Factors

Heritability of AF has been evaluated in several studies. However, although successful linkage studies in AF have been reported, the majority of studies have relied on the candidate gene approach in small families followed by functional studies of identified putative mutations.

A family history of lone AF has been found to expose individuals to a 3.5-fold greater risk of developing arrhythmia. Mutations and polymorphisms in genes coding ion channels involved in cardiac repolarization and connexins in the atria have been found to be associated with the development of lone AF.

Coronary Artery Disease

Weijs et al. have reported that actually insidious coronary artery disease may be present in AF patients with no documented cardiovascular disease. Coronary computed tomographic examination showed that half of the patients had concealed and sometimes advanced coronary artery disease while patients were evaluated for AF. Therefore, asymptomatic coronary artery disease may be suggested as a factor in pathogenesis of lone AF.

Subclinical Atherosclerosis and Endothelial Dysfunction

Increased intima-media thickness, which is an established indicator of subclinical atherosclerosis, has been shown to predispose to AF. Chen et al. have demonstrated that increased carotid intima-media thickness and arterial stiffness were associated with lone AF. Another study has also reported impaired endothelial function in patients with lone AF compared to control subjects reflected with lower FMD.

Variations in Autonomic System Abnormalities

Although both sympathetic and parasympathetic components play a role in AF, the cholinergic component appears to be important for spontaneous initiation of AF. In the experimental setting, electrical stimulation of the left atrial ganglionic plexi or the autonomic nerve endings with retrograde activation of the ganglia has been shown to induce spontaneous firing from pulmonary veins followed by AF. Lone AF patients more frequently have paroxysmal AF in the setting of increased vagal tone, especially during sleep.

Vigorous Physical Activity

Several studies have demonstrated that long-lasting endurance sport practice was associated with an increase in the risk of lone AF. Molina et al. have reported that marathon running and the practice of >1500 lifetime hours of sport have been associated with a higher risk of lone AF when compared with sedentary men. Accompanying left atrial dilatation or increased vagal tone have been suggested to contribute to the pathogenesis of lone AF. However exact electrophysiological mechanisms underlying this association have not been elucidated fully yet.

Social Characteristics

The type of personality (type A behavior), anger, hostility and acute life stress have been shown to be associated with incident AF. Excessive sympathetic activity has been proposed to mediate these effects. Increased circulating catecholamines in acute life stress and the observation that beta-adrenergic blockade prevents the arrhythmogenic effects of acute life stress support this hypothesis. Same changes may also apply in the pathogenesis of lone AF.

Alcohol and Other Stimulants

A ‘holiday heart syndrome’ of paroxysmal AF after occasional excessive alcohol intake was described over 30 years ago. Alcohol is known to have a direct toxic effect on cardiomyocytes and cause a hyperadrenergic state with impaired vagal tone.

Several case-control studies have found relatively similar odds of AF among abstainers and moderate drinkers, but significantly higher odds of AF among heavier drinkers, finding confirmed in a prospective analysis of the Copenhagen City Heart Study. Another study has reported higher risks of AF associated with the 3 highest quintiles of alcohol intake, when compared with the lowest quintile, but only among men. Similarly, heavy alcohol consumption may also have a role in lone AF pathogenesis.

Caffeine consumption and nicotine have also been associated with AF.

Air Pollution

Air pollution has been suggested to predispose to AF. A study has shown that an interquartile increase in NO2 was associated with an increase in the percentage of time in atrial fibrillation of 4.39% among those ≤ 50 years old, and 7.1% among males.
had suggested the influence of air pollutants on new-onset atrial fibrillation, with a 26% increase in the risk of arrhythmic incidence for each 6-μg/m³ increase in particulate matter aerodynamic diameter. Underlying mechanisms include endothelial dysfunction secondary to direct translocation; pulmonary oxidative stress and inflammation; alterations in the autonomic nervous system and secondary repolarization abnormalities. Further studies are needed to identify the link between air pollution and lone AF, since study population in aforementioned previous studies had co-morbidities.

Anatomic Abnormalities

Tran et al. have reported an association of AF with pectus excavatum. Pectus excavatum is known to result in right atrial and right ventricular compression with potential effects on stroke volume and heart rhythm. They have reported that patients with lone AF were significantly more likely to have mild, moderate, or severe pectus excavatum as defined by the pectus severity index compared to those with non-lone AF and controls.

Unclarified Points

Some clinicians consider an isolated left atrial enlargement as a sign of heart disease which excludes the diagnosis of lone AF. Same also applies for left ventricular diastolic dysfunction. However, there is still no consensus on the definition for the extent of these echocardiographic abnormalities.

Treatment of Lone AF

Anti-arrhythmic medications are not well studied in lone AF patient population in randomized controlled trials. However, inferences can be made from studies that mainly included paroxysmal AF patients, suggesting that anti-arrhythmic medications are useful in maintenance of sinus rhythm and probably improve quality of life in lone atrial fibrillation. PV isolation may be combined with linear lesions in the left atrium; ablation of non-PV triggers, complex fractionated atrial electrograms or ganglionated plexi and focal impulse and rotor modulation. Surgical treatment of AF using the Cox–Maze procedure has not been accepted due to its complexity. Surgical AF ablation has been reported to be indicated in asymptomatic AF patients who prefer a surgical approach; who have failed one or more attempts at catheter ablation or who have contraindications for catheter ablation.

Some authors have suggested that treatment should be personalized based on LA structural remodeling quantified by the degree of LA fibrosis determined with DE-MRI. Akoum et al. have previously suggested that PV isolation strategy was effective for patients in Utah stages I and II. Furthermore, they have reported a low success rate of ablation for Utah stages III and IV. Extent of fibrosis detected on DE-MRI pre-procedurally has been shown to be a predictor of AF ablation success in lone AF patients.

Prognosis

A study with a 12-year follow-up, including 346 newly diagnosed lone AF patients, has shown that these patients had a favorable prognosis as long as they had truly ‘lone’ arrhythmia. However, with aging and/or the occurrence of cardiovascular comorbidities, the risk of AF-related complications, including thromboembolism and heart failure have been shown to increase. Furthermore, also when compared to healthy control subjects, patients diagnosed with lone AF developed cardiovascular disease more often, at younger age and with a more severe disease profile.

In the original description of lone AF, the authors had emphasized that there was no increase in the left atrial size during follow-up, but this assessment was done using chest radiography. More recently, it has been shown that lone AF patients with increased left atrial volume (>32 ml/m²), either at diagnosis or during the follow-up, subsequently experienced adverse cardiovascular events including stroke.

Therefore, although lone AF occurs in relatively younger patients with no documented cardiopulmonary disease, long follow-up studies have demonstrated that half of lone AF patients develop cardiovascular disease over time.

Conclusion

Lone AF patients should regularly undergo a clinical follow-up dedicated to the primary prevention of cardiovascular disease and AF-related complications.

Future studies are needed to demonstrate the cost-effectiveness of the routine use of more advanced diagnostic tools, such as non-invasive assessment of endothelial function, autoimmune markers and genetic screening and whether they would have clinical implications on treatment.

References

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