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Lone AF – Etiologic Factors and Genetic Insights into Pathophysiolgy

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Abstract

Ever since atrial fibrillation (AF) was first recognized in young people (so called "lone" AF) over 4 decades ago, there has been increasing focus on determining the underlying pathophysiology of the condition. Although lone AF is presumed to be a highly heterogeneous disease, recent studies have identified novel risk factors such as inflammation, oxidative stress, endurance sports and genetics, for the arrhythmia. This monograph aims to highlight some of the recent advances in our understanding of the molecular pathophysiology of lone AF especially insight provided by contemporary genetic studies. These insights may provide novel therapeutic targets for treatment of this challenging arrhythmia in young patients.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, representing a growing epidemic with significant health consequences and affecting more than two million adults in the U.S.[1] The mean age of individuals with AF is 75 years; disease prevalence increases with age (2.3% age > 40 years; 5.9% age > 65 years) and with the presence of structural heart disease such as ischemic, hypertensive, myocardial, or valvular disease.

AF in young patients or so called "lone" or idiopathic AF is characterized by the presence of the arrhythmia in the absence of structural heart disease or other identifiable causes such as hypertension, coronary artery disease, valvular heart disease, hyperthyroidism, or alcohol use. Lone AF typically occurs in young and middle-aged adults (mean age at diagnosis ~ 44 years).[2] The prevalence of lone AF, depending on the age of the population under consideration, ranges from 2% to 11% [3, 4, 5]. Although novel risk factors for this arrhythmia have recently been described,[6, 7] the etiology of an individual's condition often remains unknown.[8]

The term lone auricular fibrillation was first introduced by Evans and Swann[9] in 1953. Since then it has been suggested that a diagnosis of lone AF should be restricted to patients <60 years of age[10]; although there is no evidence of any threshold values by age for stroke risk in patients with AF.[9] Recently, several novel epidemiological associations with AF have emerged. Conditions such as obesity, sleep apnea, diabetes, metabolic syndrome, increased alcohol consumption, anger and hostility (in men), pulse pressure, and subclinical atherosclerosis (assessed by carotid intima–media thickness) have all been associated with AF.[11, 12, 13, 14, 15, 16] Atrial and ventricular structural changes, increased atrial stretch, autonomic imbalance, systemic inflammation, oxidative stress, and others have been some of the underlying pathophysio-

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logic mechanisms identified.[14, 15, 17, 18] Nevertheless, a cause–effect relationship has not clearly been established.

Pathophysiology

Inflammation and Oxidative Stress

Several lines of evidence support a strong association between inflammation and the pathogenesis of AF. Inflammatory infiltrates, myocyte necrosis and interstitial fibrosis were found in atrial tissue from patients with lone AF but not in control patients.[19, 20, 21, 22] Furthermore, a number of studies have shown that concentrations of inflammatory mediators or markers, such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP), are increased in patients with AF.[20, 23, 24, 25] One mechanism that may mediate the effects of inflammation in AF is oxidative stress.

Emerging evidence implicates oxidative stress in the initiation and maintenance of AF.[26] Carnes et al[27] have shown that AF induced by rapid pacing in dogs decreases tissue ascorbate levels and increases protein nitration, a marker of oxidative and nitrosative stress. Biochemical evidence of oxidation by peroxynitrite and hydroxyl radicals, both downstream products of oxygen radical generation, has also been demonstrated in experimental models of AF.[28] Coronary artery bypass surgery, a procedure often complicated by AF, is associated with an increase in oxidized glutathione and lipid peroxidation.[29, 30, 31] However, in vivo studies have been difficult to perform because of the lack of reliable methods to quantify oxidative stress. Although a number of assays are available, they are primarily of use to measure oxidation in vitro and are inaccurate when applied to the in vivo assessment of oxidative stress in humans.[32] Recently, the development of methods to quantify F2-isoprostanes (IsoPs), prostaglandin-like compounds derived from the free radical-catalyzed peroxidation of arachidonic acid, has allowed a facile and accurate assessment of oxidative stress in vivo.[33, 34] Recently, we showed that inflammatory markers were associated with AF and elevated inflammatory mediators varied according to the different sub-types of the arrhythmia.[35] Surprisingly, in the same large cohort of AF patients, levels of urinary F2-IsoPs, a sensitive index of oxidative stress in vivo, were not increased.

Triggering Factors

Lone AF appears to be more prevalent among males of relative young age presenting with paroxysmal AF.[36, 37] Several factors such as sleep, exercise, alcohol use, eating, duration of physical activity, and alteration in autonomic nervous system[38] have been implicated in triggering AF episodes. Fluctuations of the autonomic tone could be operative in several forms of lone AF such as exercise- induced (sympathetic), and sleep-induced (parasympathetic).[37, 39] Most of the available data support the association between sport practice and lone AF implicating increased vagal tone as the principal underlying mechanism.[40, 41] It is also of clinical importance to recognize that certain drugs may trigger an episode of AF.[42] Several classes of drugs including cardiac stimulants, antiarrhythmics, cholinergics, sympathomimetic inhalants, xanthines, cytostatics, central nervous system drugs, and others have been known to induce AF in patients without apparent heart disease, although the relative evidence is largely based on individual case reports.[42]

Endurance Sports

Some studies have documented long-lasting endurance sport practice as a risk factor for lone AF[41, 43] These studies have shown that subjects who practice endurance sports are at approximately five times higher risk of lone AF than those who are sedentary.[41, 44] Although AF is a commonly studied arrhythmia in athletes, accurate data on the true incidence of lone AF among sport practitioners is limited.[45] Some underlying mechanisms implicated in the pathophysiology of AF in athletes include high vagal tone, presence of atrial ectopic beats, and changes in left atrial size (atrial remodeling).[45, 46] It is well known that the athlete's heart, although assumed to be a physiological adaptation, has increased atrial size and ventricular mass and altered diastolic function which, may in the long run create fibrosis and a substrate for AF.[45, 47] Although Pelliccia et al.[45] showed that left atrial enlargement (defined as a transverse antero-posterior diameter >40 mm) was common among competitive athletes (20%), this was not associated with higher incidence of lone AF. In contrast, a

small prospective study showed that the 10-year cumulative incidence of lone AF in 300 top-ranked runners was 5.3% compared with 0.9% in 495 healthy controls.[44] This was supported by another study that showed that left atrial enlargement in a cohort of 252 marathon runners was associated with increased risk for lone AF.[40] A recent study assessed the association between frequency of vigorous exercise and risk of developing AF in 16,921 apparently healthy men in the Physicians' Health Study.[48] During 12 years of follow-up, 1,661 men reported developing AF. This study showed that the frequency of vigorous exercise was associated with an increased risk of developing AF in young men and joggers. However, this risk decreased as the population aged and was offset by known beneficial effects of vigorous exercise on other AF risk factors.

Genetic Basis of Atrial Fibrillation

The underlying pathophysiology of AF especially lone AF remains poorly understood. Recent advances in genetics and molecular biology have provided important insights into the underlying molecular mechanisms of AF. Although familial AF was first reported in 1943,[49] it is only recently that the genetic basis for the arrhythmia has been recognized.

Heritability of lone AF

Heritability of AF is suggested by two recent population-based studies demonstrating that the presence of AF in first-degree relatives was associated with an increased risk of developing AF.[50, 51] In fact, the relative risk of AF is estimated at 85% in individuals with at least one parent with a history of AF.[50] We and others have confirmed that a family history of AF is present in one-third of patients with lone AF indicating that familial AF is more common than previously recognized.[52, 53]

Genes associated with AF

Studies of kindreds with AF suggest a genetic basis for the condition, especially in younger subjects
with lone AF. Several genes and loci have now been described for Mendelian AF [Table 1]. A gene locus for AF was first reported in 1997, based on genetic mapping in three Spanish families.[6] However, the gene responsible for AF in these kindreds has not yet been identified. A second locus for AF on the proximal long arm of chromosome 6 was identified in 2003.[54] Three additional AF loci have subsequently been identified on chromosomes 20q12-13,[55] 5p13[56] and 10p11-q21.[57] We recently identified a novel AF locus on chromosome 5p15 by genome-wide linkage analysis of a 4-generation family with familial AF.[58] Importantly, our study established an abnormally prolonged P-wave determined by signal-averaged ECG analysis as an intermediate or 'endophenotype' that improved statistical power of the linkage study in this family.

Table 1 Genes and loci implicated in familial atrial fibrillation (AF).

Chromosome	Gene	Function	Inheritance	Reference
11p15.5	KCNQ1	Increases I_{ks}; expected to shorten AP	AD	[59]
21q22.1	KCNE2	Increases I_{ks}	AD	[60]
17q23.1	KCNJ2	Increases I_{ks}; expected to shorten AP	AD	[67]
12p13	KCNA5	Loss of I_{Kur}; prolongs AP	AD	[62]
3p21	SCN5A	Reduces I_{Na}; expected to shorten AP	AD	[63]
1p36-p35	NPPA	Mutant ANP; shortens AP	AD	[75]
5p13	NUP155	Affects transport of hsp70	AR	[87]
Genetic loci				
10q22-24	unknown	Overlaps with locus for DCM	AD	[6]
6q14-16	unknown	Overlaps with locus for DCM	AD	[54]
10p11-q21	unknown	unknown	AD	[57]
5p15	unknown	Associated with P-wave prolongation	AD	[88]

AD, autosomal dominant; ANP, atrial natriuretic peptide; AP, action potential; AR, autosomal recessive; hsp70, heat shock protein; DCM, dilated cardiomyopathy

In one such family of Chinese descent, Chen and coworkers[59] identified a mutation in KCNQ1, which encodes a potassium channel that underlies the slowly repolarizing current in cardiomyocytes known as IKs. The investigators were able to map the locus to a 12-Mb region of chromosome 11p15 in a 4-generation family with early-onset lone AF and long QT syndrome. The KCNQ1 gene lies within this region and resequencing identified an S140G mutation in all affected family members. Functional analysis of the S140G mutant revealed a gain-of-function effect in KCNQ1/KCNE1 and KCNQ1/KCNE2 currents, which contrasts with the dominant negative or loss-of-function effects of KCNQ1 mutations previously associated with congenital long QT syndrome. The same group also established a link between KCNE2 and AF by identification of a mutation in two families with AF.[60] The mutation (R27C) also caused a gain-offunction when co-expressed with KCNQ1. Interestingly, there is a high incidence of atrial arrhythmias in patients with the short QT syndrome caused by gain-of-function mutations in IKs, IKr, or IK1[61] and this suggests an important role for shortening of the action potential in the development of AF. More recently, a truncating mutation in KCNA5, encoding a voltage-gated potassium channel (Kv1.5) underlying the ultrarapid delayed rectifier current (IKur) was associated with familial AF.[62]

Another set of single-gene-based abnormalities cause AF by impairing conduction through effects on the cardiac sodium channels that carry fast inward Na+ current (INa), via loss-of-function gene variants in the α-subunit pore-forming subunit gene, SCN5A. These can present predominantly as AF occurring alone,[63] in association with dilated cardiomyopathies,[64] or in the context of life-threatening ventricular arrhythmias with Brugada syndrome. Finally, a series of patients has recently been described with loss-of-function mutations in the CACNA1C and CACNB2 genes, encoding α-subunit and β2-subunit genes of the cardiac L-type Ca2+-current (ICaL), producing features of both Brugada syndrome and short QT syndrome accompanied with a high incidence of AF.[65]

AF Candidate Genes

A candidate gene can be any gene that is hypothesized to cause a disease. Based on the work relating KCNQ1 to AF, investigators have considered other potassium (and ion) channels as potential candidate genes for AF and screened for mutations in these genes in cohorts of subjects with lone AF. Otway and colleagues[66] examined 50 kindreds with AF and amplified the genes for KCNQ1 and KCNE1-3, which encode accessory subunits of KCNQ1. They found a single mutation (R14C) in KCNQ1 in only one family. Unlike the S140G mutation discovered by Chen and colleagues,[59] R14C had no significant effect on KCNQ1/KCNE1 current amplitudes in cultured cells at baseline. However, upon exposure to hypotonic solution, mutant channels exhibited a marked increase in currents compared with wild-type channels. Interestingly, only those with left atrial dilatation had AF, leading the authors to speculate a "two-hit" hypothesis for AF. They also identified a mutation in KCNE2 in two of the kindreds. Like the S140G mutation in KCNQ1 the mutation in KCNE2 (R27C) dramatically increased the amplitude of IKs. Additional studies suggest that the relationship between potassium channels and AF extends beyond IKs. The work of Xia and colleagues[67] also implicates KCNJ2 which encodes, an inward rectifier potassium channel that underlies IK1 in AF. In their work, a V931I mutation was found in all affected members in one kindred with familial AF. The mutation also leads to gainof-function in KCNJ2 channels, which increased potassium current amplitudes. However, there is still an incomplete understanding of how an increase in the background current IK1 might lead to AF.

The genes that encode connexins, gap-junction proteins that mediate the spread of action potentials between cardiac myocytes, have also been examined as potential candidates for AF. Prior work has shown that mice with null alleles of GJA5, the gene for connexin-40, exhibit atrial reentrant arrhythmias. From this work, Gollob and colleagues[68] considered this gene as a potential candidate in individuals with lone AF who underwent pulmonary vein isolation surgery. An analysis of DNA isolated from their cardiac tissue showed that 4 of the 15 subjects had mutations in GJA5 that markedly interfered with the electrical coupling between cells. In three of the patients, DNA isolated from their lymphocytes lacked the same mutation in GJA5 indicating that the connexin-40 mutation had been acquired after fertilization or was a somatic mutation. One of the four individu-

als carried the mutation in both cardiac tissue and lymphocytes consistent with a germline rather than somatic mutation.

Association studies

Most patients with AF have one or more identifiable risk factors, but many or even most patients with these same risk factors do not develop AF. Thus, a working hypothesis is that genetic determinants favor AF in some individuals with identifiable risk factors. Studies comparing cases of non-familial AF to age-related and gender-matched controls (association studies) have provided some insight into the genetic basis of acquired AF. Over the last decade, many case-control and cohort studies have been performed in subjects with AF, leading to the identification of variants associated with the disease. These studies have typically tested a small number of variants and have been directed at candidate genes previously believed to be involved in AF. Examples include genes encoding the renin-angiotensin-aldosterone system (RAAS), and calcium handling, as well as neurohormonal and lipoprotein pathways. Additionally, genes encoding gap junction proteins, ion channels, interleukins, signaling molecules, and mediators of other molecular pathways have been examined. Unfortunately, these studies have been limited by a low prior probability of any polymorphism truly being associated with AF. Further complicating these analyses are the small sample sizes and a lack of replication in distinct populations, as well as phenotypic and genetic heterogeneity.

In recent years, genome-wide association studies (GWAS) have been made possible by advances in genotyping technology that allow investigators to assay hundreds of thousands of single nucleotide polymorphisms (SNPs) spread over the entire human genome. In the first GWAS of AF, involving replication studies in three distinct European and a Chinese population, a strong association was discovered between AF and two SNPs on chromosome 4q25.[69] About 35% of individuals of European descent have at least one of the DNA sequence variations and the risk of AF increases by 1.72 and 1.39 per copy. The stronger variant is carried by 75% of the Chinese population, in whom it increases the risk of AF by 1.42 per copy. Although the mechanism for this observed association remains unknown, both variants are adjacent to the PITX2 gene, which is critical for cardiac development. In knockout mice, pitx2c was implicated in the formation of the extension of left atrial myocardium into the pulmonary veins[70]; since abnormal automaticity in this region is now implicated as a common driver for many forms of AF,[71] PITX2 is an obvious candidate gene. We worked with others to replicate this association in a study of 4 large AF populations,[72] and showed that the association also holds in post-cardiac surgery AF,[73] a setting thought to be related to inflammation.

Genetic insight into the pathophysiology of lone AF

One prevailing conceptual model proposed for AF pathogenesis describes reduced atrial refractory period as a substrate for re-entrant arrhythmias.[74] This model is supported by reports of gain-of-function mutations in genes encoding subunits of cardiac ion channels responsible for generating IKs (KCNQ1/KCNE2] and IK1 (KCNJ2) which are predicted to decrease action potential duration.[59, 60, 67] We recently identified mutations in KCNQ1 and NPPA (which encodes for atrial natriuretic peptide [ANP]), in two moderate-sized Caucasian kindreds with early onset familial lone AF and normal QT intervals. Although both these genes have previously been linked with familial AF,[59, 75] this is the first study to demonstrate that augmented potassium current is the shared phenotype across these diverse genetic defects causing familial AF.[76] IKs gain-of-function mutations have previously been reported for potassium channel defects, but the notion that mutations in disparate genes, KCNQ1 and NPPA, lead to the same arrhythmia phenotype raises the possibility of subtype specific therapy for familial lone AF. Interestingly recent studies have established that loss-of-function mutations are also associated with lone AF. Mutations in KCNA5, a voltage-gated potassium channel expressed solely in human atria, have been associated with familial AF.[62, 77] The mutated channels fail to generate the ultrarapid delayed rectifier current IKur and lead to atrial action potential prolongation, early afterdepolarizations and increased vulnerability to stress-induced triggered activity. This is a novel mechanism for lone AF that does not invoke shortening of the action potential duration. Such improved understanding of familial AF mechanisms provides a therapeutic rationale for either prolonging or shortening the atrial refrac-

tory period for the treatment of familial lone AF with antiarrhythmic drugs.

Management of lone AF

Management strategies in patients with lone AF include rhythm or rate control as well as anticoagulation. Recent randomized trials in minimally symptomatic patients have argued against vigorous attempts to maintain sinus rhythm.[78] However in such trials, patients maintaining sinus rhythm have improved outcomes[79] and many patients are highly symptomatic with AF.

Maintaining sinus rhythm with antiarrhythmic drugs or left atrial ablation remains an important goal for many patients especially those that have highly symptomatic paroxysmal or persistent lone AF. However a cardioselective beta-blocker e.g. metoprolol, may also be tried first.[10] Other membrane-active drugs such as flecainide, propafenone
and sotalol are also moderately effective at maintaining sinus rhythm. In adrenergically-mediated lone AF,[37, 39] beta-blockers represent the first line therapy, followed by sotalol and amiodarone.

Safety and efficacy of drug therapy and catheter ablation

The limited efficacy of membrane-active drugs and
the potential for proarrhythmia combined with poor ventricular rate control with AV nodal blocking agents, has encouraged many electrophysiologists to consider left atrial catheter ablation at an early stage in the management of patients with lone AF.[10] However, it should be appreciated that patients with lone AF have excellent long-term survival[5] and the risks of serious adverse events with long-term antiarrhythmic drugs or ablation should be carefully weighed against the superb prognosis without any risk associated with such treatment. Nonetheless, the value of catheter ablation for improvement of symptoms in patients with lone AF is well established and is recommended according to published guidelines.[10] A 30 year follow up study[5] established a low risk of progression to permanent AF in young patients. Hence invasive therapies should be reserved for highly symptomatic patients. With aging and development of secondary comorbidities such as hypertension, heart failure, or diabetes, thromboembolic risk increases. Apart from left atrial catheter ablation, several surgical techniques have been proposed for the management of patients with lone AF, including the Cox maze III surgery, beating-heart pulmonary vein isolation and minimally invasive surgical approach via small right inframammary incisions or video assisted thoracoscopic approach.[80, 81, 82]

Targeting therapy based on genetic subtypes

The rare ion channel and other variants that we and others have identified in patients with AF have obvious (but as yet untested) therapeutic implications. A gain of function potassium channel mutation would be predicted to respond to a potassium blocking drug, while sodium channel blockers would be predicted to be ineffective in subjects with AF arising from slow conduction or decreased sodium current. It is also possible that common genetic variants identify AF subtypes with differing drug responses. For example, recognizing that renin-angiotensin activation is implicated in AF,[83, 84] we examined the impact of the common ACE ID polymorphism on response to antiarrhythmic therapy. An analysis of 213 subjects treated with rhythm control showed that lone AF and DD/ID genotypes were highly significant predictors of failure of drug therapy.[85] By contrast, we found no relationship between common SNPs in the β1-adrenergic receptor (resulting in G389R; rs1801253 and S49G; rs1801252) and response to ventricular rate control therapy in a group of 279 patients managed with rate control.[86] We have also examined the role of clinical variables and two common SNPs at the 4q25 locus (rs2200733, rs10033464) as predictors of response to antiarrhythmic drug therapy in AF. Among these, only rs10033464 genotype was associated with successful rhythm control (OR; 1.48, 95% CI: 1.01-2.19), and this association persisted after correction for clinical factors (OR 2.39; 1.25-4.59).

Conclusions

Currently lone AF is considered a nosographic entity, only when clinical and echocardiographic evidence of cardiovascular or pulmonary disease has been ruled out. Although a consistent definition is lacking, lone AF should be considered a separate en tity from AF associated with under-

lying cardiovascular disease. Recent studies have identified novel risk factors for the disease that provide important insight into the underlying pathophysiology of the condition. Furthermore, improved understanding of the genetic basis for lone AF will not only help define clinical sub-types but will also provide new therapeutic targets for the prevention and treatment of this challenging arrhythmia in young patients.

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