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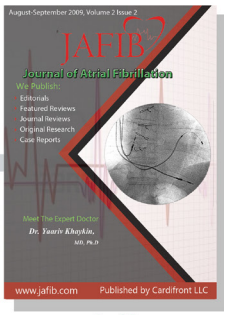

Paroxysmal Lone Atrial Fibrillation Is Associated With An Abnormal Atrial Substrate: Characterizing The "Second Factor"

Charles R. Mitchell, MD and Mithilesh K. Das, MD

Krannert Institute of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

Introduction

Stiles et al, [1] recently published a study titled "Paroxysmal Lone Atrial fibrillation is associated with an abnormal atrial substrate: Characterizing the Second Factor" in The Journal of The American College of Cardiology." Authors demonstrated structural and electrophysiological abnormalities in the atria of patients with paroxysmal lone atrial fibrillation (AF). The authors postulate that these factors are likely contributors to the "second factor" that predisposes to the development and progression of AF.

AF is the commonest arrhythmia encountered in clinical practice. It is associated with a poor clinical outcome and a high healthcare cost. It is classified as paroxysmal, persistent or permanent AF. Although each clinical class is distinct, a majority of patients with paroxysmal AF ultimately may suffer from the persistent or permanent AF due to lack of appropriate therapy and continued remodeling of the atria. Lone AF has been defined as AF in an individual less than 60 years of age with no classic cardiac risk factors. [2] Although lone AF is associated with a low incidence of morbidity, the natural history is that of a progressive increase in incidence and duration of episodes of AF, with many becoming permanent .[3] Present therapeutic approaches to AF have major limitations, including limited efficacy and significant adverse effect liability. Although, in the recent years, AF ablation has been shown to have a substantially improved success rate over antiarrhythmic drug, [4-7] it has not been completely successful, and has been associated with adverse events. The realization of AF progression in otherwise healthy subjects, coupled with the limitations of therapy mandate researchers to improve the understanding of the mechanisms underlying AF, with the premise that better mechanistic insights will lead to innovative and innovative therapeutic approaches. As such, there has been a wealth of research attempting to elucidate the causes of the onset of AF and its progression.

In the study by Stiles et al, [1] the authors electrophysiologically characterized the atrial substrate of 25 highly symptomatic patients with documented paroxysmal lone AF, who were undergoing first-time ablation for AF. They compared these patients with a reference group of 25 patients with no history of AF, who had atrioventricular re-entry tachycardia, and were undergoing ablation of a left-sided pathway. All of the patients had structurally normal hearts and no known risk factors for cardiac disease. In an attempt to isolate the chronic, underlying abnor-

Corresponding Address :Mithilesh K. Das, MD, MRCP, FACC, Associate Professor of Medicine, Krannert Institute of Cardiology, 1800 North Capitol Avenue, Indianapolis, IN 46202.

mality from any acute electrophysiologic effects of AF, only patients with no AF documented on continuous monitoring for the week prior to the study were enrolled. During electrophysiologic study, four catheters were positioned in the atria of these patients, including a coronary sinus catheter, a 10-pole "crista" catheter, a 20-pole catheter along the lateral right atrium, and a 10-pole roving catheter positioned at sites in the left atrium via a sheath across the atrial septum. Effective refractory period (ERP), conduction velocity (CV), and site-specific conduction abnormalities along the crista terminals were measured. Electroanatomical mapping was conducted, with creation of voltage and activation maps of the atria. The proportion of fractionated electrograms, including fractionated signals and double potentials, were recorded as well. There are two major findings of this study as discussed below:

1.Structural Remodeling and Electrophysiological Properties of the Atria in Lone AF

The study demonstrated that when compared with reference group, lone AF is associated with significant structural abnormalities characterized by atrial dilation and loss of endocardial voltage. The patients with AF had significantly larger left atrial size at baseline than the reference group (41 ± 7 mm vs. 34 ± 4 mm P<0.001). The left and right atrial volumes were enlarged by 27% and 36%, respectively. There were lower mean atrial voltage (right atrial and left atrial voltages were lowered by 41% and 48%) in lone AF patients, suggesting the loss of atrial myocardium.

Lone AF is associated with significant P-wave prolongation by 35%, atrial refractoriness lengthening by 10%, intra-atrial conduction decrease between 21% and 45%, and a significantly higher proportion of fractionated and complex electrograms, when compared to the reference group. The mean ERP of the patients with AF was significantly increased over the reference patients (at 600 ms: 255 ± 25 ms vs. 222 ± 16 ms, p<0.001; at 450 ms: 234 ± 20 ms vs. 212 ± 14 ms, p=0.004) with no significant difference in the heterogeneity of refractoriness.

Electroanatomical mapping showed larger volumes, lower mean bipolar voltage, a slower mean conduction velocity, and a prolonged total atrial activation time in the AF group as compared to the reference group. Evaluation of complex electrograms showed significantly greater proportion of points with double potentials or fractionated signal in the AF group than the reference group (27 ± 8% vs. 8 ± 5%, p<0.001).

Since the early models of AF, it has been shown that the arrhythmia itself causes electrophysiological changes in the atrial substrate, including a shortening and heterogeneity of the atrial refractory period, and prolongation of the sinus node recovery time, which can lead to further AF .[8-10] These studies yielded the conclusion that "AF begets AF, [10]" however, aggressive attempts at cardioversion or antiarrhythmic drugs to maintain sinus rhythm may slow but has failed to prevent the progression of this disease. [11] Therefore, authors suggested that "sinus rhythm does not beget sinus rhythm" in lone AF. Mechanistically AF is thought to be due to the interaction between a trigger and atrial substrate. In 1972, Zipes et al. demonstrated electrical activity within the thoracic veins .[12] Twenty seven years later, Haissaguerre et al. identified a focal source of electrical discharges within the pulmonary veins as a source of AF [13] and opened the door to a new potential treatment modality and new mechanisms of AF. However, treatment of triggers has not been successful in all patients with paroxysmal or lone AF. On the contrary, substrate modification along with the treatment of triggers of persistent and permanent AF has been effective, at least, in few patents. Several studies try to investigate the substrates and associated risk factors involved the pathogenesis of paroxysmal AF. A familial predisposition for AF has been frequently seen clinically. Mutations in potassium channels, sodium channels as well as connexins have been implicated in rare forms of monogenic AF, although no more common genetic link has been found. [14,15] Multiple other risk factors such as obesity and weight gain, obstructive sleep apnea, inflammation, excessive endurance exercise, and toxins ranging from alcohol to caffeine have been shown to be associated with AF. Lone AF patients do not have any known risk factor for AF, yet sinus rhythm does not beget sinus rhythm in them. Of the electrophysiological findings of this study the one that stands out is a prolongation of the atrial ERP in patients with AF. Heretofore, evaluations of the ERP have been performed in the acute period, soon after conversion of AF, and have dem-

onstrated a shortening of the ERP. However, it is unclear in the study what the burden of reciprocating tachycardia the reference group had, and whether it may have abnormally shortened the refractory period in the reference group. It could be that, although the arrhythmogenicity of a shortened atrial ERP after conversion to sinus is the cause of acute recurrence of AF, a prolonged ERP and CV characterizes the underlying arrhythmogenic substrate in initiation and maintenance of AF. This was a small and select subgroup of patients with highly symptomatic AF and no cardiac risk factors or structural heart disease, on the other hand, so caution must be maintained when generalizing to the AF population as a whole.

2.Abnormal Sinus Node Function

The study evaluated the baseline sinus cycle length,sinoatrial conduction time (SACT), and corrected sinus node recovery time (CSNRT). Patients with AF have an impaired sinus node function (the corrected sinus node recovery time was prolonged by 43%). AF patients had a longer baseline sinus cycle length (975 ± 131ms, vs. 762 ± 129 ms, p<0.001), longer SACT (154 ± 58 ms vs. 83 ± 31ms, p<0.001), and longer CSNRT at 600 ms (265 ± 57ms vs. 185 ± 60 ms, p = 0.002), but not at 450 ms (261 ± 96 ms vs. 241 ± 76 ms, 9=0.6). These findings confirm an abnormal sinus node function in lone AF, although it cannot be defined as a clinically significant sinus node dysfunction (SND). With the progression of the disease to persistent AF, sinus node function can worsen. SND is an abnormality involving the generation of the action potential by the SAN and is characterized by an atrial rate inappropriate for physiological requirements. SND occurs in 1 in every 600 patients with heart disease above 65 years of age and accounts for approximately half of implantations of pacemakers in the United States. Several intrinsic or extrinsic factors may influence sinus node function, although age-dependent primary degenerative fibrosis of the tissues of the sinus node is thought to be the primary cause of SND. [16] Manifestations of SND include symptomatic sinus bradycardia, sinus pauses, sinus node exit block, sinus arrest and chronotropic incompetence. [17] A subset of patients with AF suffer from sinus node dysfunction (SND), which is defined as tachy-brady syndrome. [18-22]

The tachy-brady syndrome is a common manifestation of SND and is the combination of abnormal automaticity (bradycardia) and abnormal conduction properties of the atrium which predispose patients to AF and other atrial arrhythmias. Conversely, proportion of patients with SND who receive a pacemaker suffer from AF during follow-up .[23]This study, like others, has demonstrated that AF is associated with significant electrophysiological and structural remodeling [24] Furthermore, SND encountered in patients with paroxysmal or persistent AF, can reverse with catheter ablation of AF [18]. It is possible that SND and AF are interrelated and may be the two spectrums of the same disease or at least share some common mechanisms, with clinical symptoms that depend upon severity of these two arrhythmias.

The main limitation of the study is that patients with persistent AF were not studied; however, many patients with persistent AF start with paroxysmal AF initially and possibly the same "second factors" continue to work in this stage of the disease. Furthermore, patients were monitored only for a week before the procedure to ensure that the evaluation was remote from an episode of AF; nevertheless, an effect of rate-related remodeling from previous episodes cannot be excluded.

The study by Stiles et al, has shown that lone AF is associated with structural and electrophysiological remodeling of atria and the SAN. Whether "second factors," are the result of progressive fibrosis, inflammation, or any of a number of other mechanism is still remains to be elucidated. The authors, by studying patients remote in time from the arrhythmia itself, have been able to show that the predominant underlying substrate in patients with lone AF is structural and electrophysiological remodeling, perhaps accounting for the progression of the disease. Future strategies to treat paroxysmal or lone AF should, therefore, also focus on atrial substrate. It may be valuable since pulmonary vein isolation is currently considered to be only moderately successful (success rate 70-85%) for the majority of patients with paroxysmal AF. It is often difficult to predict which patient will have a recurrence of the arrhythmia after catheter ablation. This study showing an abnormal substrate in lone AF raises the possibility of progressive disease continuing despite early procedural success. Further study is needed to define the role of substrate

in recurrence of paroxysmal AF despite achieving a good pulmonary vein isolation and substrate modification. A combination of detailed noninvasive evaluation of atrial dimensions and function with echocardiography and/or enhanced magnetic resonance imaging techniques along with a high density mapping of the electrophysiological substrate (fractionated electrograms, dominant frequencies, CV, ERP, etc) as well as triggers (pulmonary vein and non-pulmonary vein sources) may be needed to improve the long-term success rate of AF ablation. The study provides an encouragement to find a "cure" for AF by identifying "second factors" and its role in disease progression.

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