

The Progressive Nature of Atrial Fibrillation: A Rationale for Early Restoration and Maintenance of Sinus Rhythm

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Abstract

Atrial fibrillation (AF) is the manifest outcome of a multifactorial, progressive disease process, secondarily or primarily involving the atrial chambers. The slowly progressive electrostructural alterations diffusely involve the atrial substrate and lead to persistent and permanent forms of AF. Although the progression of the AF disease process is variable and associated with the development of comorbid conditions, rhythm restoration therapies, particularly catheter ablation, provide higher acute and long-term success rates in paroxysmal than non-paroxysmal AF. This review of literature aims to discuss how early restoration and maintenance of sinus rhythm especially using novel approaches can influence the progressive nature of atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiovascular rhythm disorder in clinical practice. AF can present and prevail in different forms varying from insidious and unnoticed to overtly acute and troublesome. AF is the manifest outcome of a multifactorial, progressive disease process secondarily or primarily involving the atrial chambers. The gravity of fibrillatory rhythm lies in its potential to cause seriously debilitating but preventable complications like stroke and heart pump failure.

This review of literature aims to discuss the progressive nature of atrial fibrillation as a rationale towards early restoration and maintenance of sinus rhythm.

Clinical Classification of AF

Conventionally, AF is classified into paroxysmal, persistent and permanent categories to guide its management. When a patient has had 2 or more episodes (each lasting through the electrocardiographic recording period or at least 30 seconds, continuously), AF is considered recurrent. If the arrhythmia episode terminates spontaneously within 7 days or by electrical/pharmacological cardioversion within 48 hours of its onset, recurrent AF is designated paroxysmal; when sustained beyond 7 days or terminated by electrical/pharmacological cardioversion after 48 hours of sustenance, AF is designated persistent. The category of persistent AF also includes cases of long-standing AF where AF has lasted for 12 months uninterruptedly. In

the current era of ablative therapy, the term permanent AF is applied to clinical AF when the attempts of restoration of sinus rhythm are not contemplated.¹

Most frequently, AF occurs in the setting of underlying heart disease, which includes coronary artery disease, hypertension, valve disease, congestive heart failure, and thyroid dysfunction.¹ AF occurring in the absence of structural heart disease is called lone AF. Of note, genetic forms of AF have also been described.

Experimental Evidence for Progressive Nature of AF:

Multiple Wavelet Hypothesis

A The multiple-wavelet hypothesis as the mechanism of reentrant AF was advanced by Moe and colleagues, who proposed that fractionation of wavefronts propagating through the atria results in self-perpetuating “daughter wavelets.”² In the computer-based mathematical model, the fibrillatory activity was not the result of fixed impulse generators or circuits, but was sustained by irregular drifting eddies (wavelets), which varied in position, number and size. The number of wavelets at any time depends on the refractory period, mass, and conduction velocity in different parts of the atria. A large atrial mass with a short refractory period and delayed conduction increases the number of wavelets, favoring sustained AF.^{3,4}

Focal-Source Theory

No experiential model exists for focal source theory for AF as like multiple wavelet hypothesis. However, there is a clinical evidence that AF arises from focal sources. Paroxysmal form of lone AF is triggered by rapidly firing impulses originating from focal sources in the majority of patients. These focal sources have been identified to be lying surprisingly outside the atrial cavity and most commonly in the pulmonary veins.⁵ In contrast to paroxysmal AF, atrial tissue

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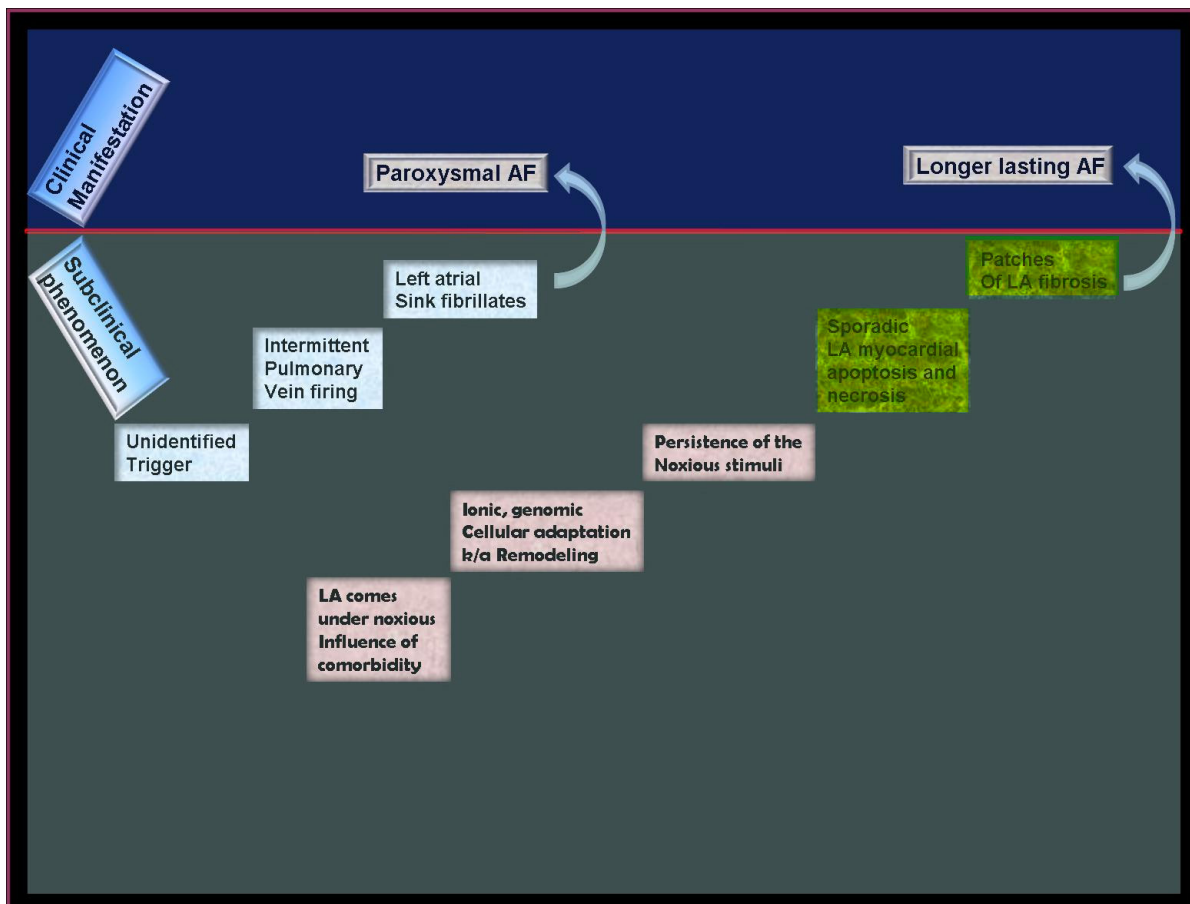


Figure 1:

Different pathogenetic mechanisms (displayed one in each box shown as subclinical phenomenon) occur progressively over time and culminate into clinically manifested rhythm disorder - AF. These mechanisms are interlinked subclinically and surface as paroxysmal and longer lasting AF depending on the interplay between the provocative factor(s) and tissue response

undergoing widespread electrostructural alterations is considered to sustain persistent and permanent forms of AF.⁶ The development of such changes in the atrial substrate occurs due to oxidative stress, inflammation and atrial fibrosis.

These changes harbingers the onset of persistent AF (Figure 1).^{7,8} In paroxysmal AF, there are a few sources responsible for the onset of the arrhythmia but for persistent AF, the number of sources may be higher and involve the atrial tissue. It appears more logical to believe that a typical patient beginning to have AF will have a few sources to start with, which will increase in number in due course of progression rather than that patient having 5-6 sources at the AF-beginning itself.

Although AF is a progressive disorder and the basic research has led to the hypothesis "AF begets AF", its clinical impact is not yet proven as up to 30% of paroxysmal AF patients progress to permanent AF and some patients present directly with permanent AF. In an individual with AF, the frequency and rapidity of progression are not predictable. Some studies have reported that the progression of paroxysmal AF occurs at a rate of 5% to 9% annually.⁹⁻¹¹ It has been clinically observed that progression of paroxysmal AF to more sustained forms is marked by structural alterations in the atrial tissue (substrate) brought about by comorbidities like aging, diabetes and hypertension.^{9,12} Besides progression, the risk of stroke in AF is also due to the same comorbidities and additionally, to those like heart pump dysfunction and previous stroke, which together determine

the risk of stroke in patients with non-valvular AF based on the most prevalent CHADS₂ and increasingly utilized CHA₂DS₂-VASc scoring systems.¹³ This risk remains the same across all clinical types of AF.

Lone AF Without Any Comorbidities: A Small Fraction of AF Population

In a population-based study, 3623 residents of Olmsted County, MN, with the diagnosis of atrial fibrillation were followed up for 30 years at the Mayo Clinic between 1950 and 1980. Out of them, 76 patients (age : 44.2±11.7 years; 50% of patients were ≥45 years of age, and 78% were male) were identified to have lone atrial fibrillation without any of the CHADS₂ comorbidities : paroxysmal in 34, persistent in 37, and permanent in 5 at diagnosis.⁹ Among 71 patients with paroxysmal or persistent atrial fibrillation, who were followed for a 30-year period, 22 received treatment with a class I or III antiarrhythmic agent and 63 received an atrioventricular node-slowing agent. Twenty-two (29%) patients had progression to permanent atrial fibrillation in 30 years. Most of them progressed within 15 years after diagnosis and on multivariate analysis, age was the sole independent predictor of progression in this group of patients. Also, while 2 patients with paroxysmal AF progressed to persistent AF, 25 patients with persistent AF at diagnosis reversed to paroxysmal AF during the follow-up. In comparison with the age- and sex-matched population without AF, the overall survival

of patients with lone atrial fibrillation was not different at 15 and 30 years ($p=0.12$) follow up. While considering survival free of congestive heart failure, the patients with lone AF tended to be slightly but not significantly worse than expected at 30 years ($p=0.051$).

The risk for stroke/transient ischemic attack was similar to that of the expected population risk during the initial 25 years of follow-up but increased thereafter to be significantly worse at 30 years. Of note, all of the 17 patients (age: 73.6 ± 10.7 years) who had a cerebrovascular event had developed one or more risk factors for thromboembolism (hypertension in 12, heart failure in 4, diabetes mellitus in 3).

Looking at the natural course of lone AF, this study provides strong evidence that comorbidities significantly modulate progression of lone AF as a disease process and its resultant complications^{12,13}. Importantly, because the risk of progression to permanent atrial fibrillation appears low in young patients, rhythm restoration and in particular invasive therapies should be reserved for highly symptomatic patients. After a young patient with lone atrial fibrillation ages or develops hypertension, heart failure, or diabetes, the thromboembolic risk increases. Therefore, screening for comorbidities is essential in patients with lone AF. Importantly, lone AF without comorbidities constitutes about 2% of the total study population. Thus, a large part of the population of AF may not be lone AF, in reality.

Outcomes of Ablation Therapy

Short- and Medium-Term Outcomes

In a meta-analysis of the studies reporting medium-term (not more than 4 years) outcomes of AF ablation, AF disappeared with antiarrhythmic drugs in 52% of patients, with catheter ablation in 57% to 71% of patients and with the combination of the two in 77% of patients. Importantly, the clinical type of AF influenced acute and long-term success. Ablation was found to be successful in 70–85% of

patients with paroxysmal lone AF but in only 38% of patients with long-lasting persistent AF.^{21,22}

Long-Term Outcomes (≥ 55 mon)

Recently, the data on long-term (about 5 years) outcomes of AF ablation have been published from several centers across the world. In concurrence with the short- and medium-term results, the long-term data (presented in Table) consistently concluded that the success rate was higher when the ablation involved paroxysmal AF versus persistent AF. This is true not only for the patients who underwent only one ablation procedure but also for those who had multiple ablations and across various different ablation strategies in paroxysmal and persistent AF. The long-term multiple-procedure success rate was higher in paroxysmal AF than the persistent AF by 15–20%. Not only did persistent AF patients experienced reduced efficacy of the ablation procedure(s), the presence of persistent AF predicted recurrence in the patients undergoing AF ablation. Not to mention the obvious impact of comorbidities on higher recurrence rate.

Recurrence of arrhythmia following pulmonary vein isolation is most commonly attributed to recovery of impulse conduction to and from pulmonary vein at the previously ablated site in the antrum. This entails ablation of limited sites (most of which are previously ablated) during the repeat procedure. This is not the picture in patients who have additional lesions to PV isolation. Since pulmonary vein isolation, the cornerstone therapy of AF ablation, suffices for paroxysmal AF but not for persistent AF and the ablation extends beyond it in the latter, the total procedural, fluoroscopic and radiofrequency ablation (RF-based procedures) times are longer in persistent AF patients than their paroxysmal counterparts. The burden of ensuing recurrent atrial tachycardia depends largely if not only on the extent

Table 1: Long-term (≥ 55 -mon) Outcomes of Catheter Ablation

Investigator	Year	N	Paroxysmal	Persistent	Technique	Single procedure success	Multiple Procedure Success	Progression to Persistent AF	Relevant Comment
Shah et al ⁴⁶	2008	264	87%	13%	PVI	74.5%			
Sawhney et al ⁴⁷	2009	71	100%	0%	Segmental PVI	56%	84%	11.2%	Success rate is lower persistent than AF paroxysmal AF
Bhargav et al ⁴⁸	2009	1404	52%	48%	Antral PV and SVC Isolation	77.6%(Paroxysmal) 67.2%(persistent)	92.4%(paroxysmal) 84%(persistent)		
Quyng et al ⁴⁹	2010	161	100%	0%	PVI		79.5%	2.4%	Persistent AF predicated Recurrence
Tzou et al ⁵⁰	2010	123	85%	15%	PVI+Non PV trigger ablation	71%			Persistent AF reduced long-term ablation efficacy
Wokhlu et al ⁵¹	2010	774	55%	45%	WACA or PVI		71%(paroxysmal) 61%(persistent)		
Weerasooriya et al ⁵²	2011	100	63%	37%(14% longstanding)	Segmental PVI+Linear ablation	29%	63%		
Dayl et al ⁵³	2011	187	72%	28%	PV ablation		74%(paroxysmal) 56%(persistent)		paroxysmal AF did better than persistent AF
Hussien et al ⁵⁴	2011	831	69%	31%	PVI		79.4%		Persistent AF predicated Recurrence
Tilz et al ⁵⁵	2012	202	0%	100%(longStanding)	Sequential Hamburg	20%	45%		
Scherr et al ⁷	2013	160	0%	100%	Stepwise		67%		

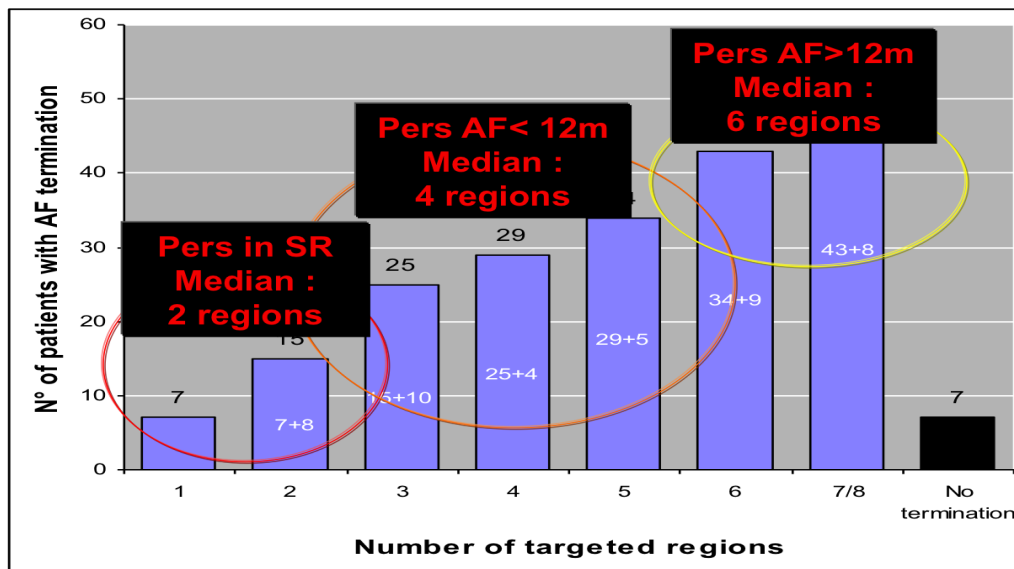


Figure 2: Number of Arrhythmogenic regions targeted to achieve AF termination of PsAF depends on the duration of continuous AF

of ablation lesion. The incidence of AT after PV isolation has been variably reported from 2.9% to 10%.²³⁻²⁷ Notably, the incidence rises to 40% to 57% in patients wherein electrogram based atrial ablation accompanies PV isolation and linear ablation.²⁸⁻³⁰

Although this has not been specifically reported, the rate of complications for longer procedures involving wider extent of ablation than PV isolation can be expected to be higher than for the shorter procedures involving ablation of limited sites.

Catheter Ablation of Persistent AF in Sinus Rhythm: Evidence for the Reversal of Progressive Remodelling

In an elegant study, the investigators divided consecutive patients with persistent AF into 2 groups of 40 patients each.³¹ In group-1, SR was restored for at least 1 month prior to ablation and in group 2, patients matched by age, sex, and AF duration were ablated in AF. A stepwise catheter ablation was performed in AF for both groups (induced and spontaneous, respectively). During the index ablation procedure, AF cycle length was longer in the SR group than in the AF group, suggestive of reverse electrical remodeling. In the SR group, AF more frequently terminated during ablation and required less extensive ablation of complex fractionated electrograms and linear lesions. The mean procedural, fluoroscopy, and radiofrequency energy delivery times were shorter in the SR group. Clinical success rates were similar between groups for first and last procedures, during similar follow-up periods of about 2 years.

From our ongoing work on AF ablation guided by non-invasive mapping system, the number of AF sources were found to vary directly with the duration of persistent AF. The number of sources targeted to terminate persistent AF were median 2 when the presenting rhythm was SR and AF was induced during ablation versus median 4-6 when the presenting rhythm was AF (Figure 2). The AF termination rates and the duration of RF delivery to achieve that varied proportionally to correlate with the duration of persistent AF such that they were optimum when the presenting rhythm was SR (Figure 3). Restoration of SR prior to catheter ablation for persistent AF possibly reverses the progressive electrostructural remodeling of the substrate, at least

partially, and decreases the need for extensive ablation to achieve the same high clinical efficacy as observed with the stepwise approach.

Early Management of AF

Rationale

1. Current treatment of AF using antiarrhythmic drugs, ablation and antithrombotic therapy is still not satisfactory. These treatment modalities are also associated with mild to severe adverse events. The response to rhythm control therapy is highest in paroxysmal AF patients whereas persistent and long-standing persistent AF patients do not respond as well. Since AF is a temporally progressive disorder, treating it earlier in its course (paroxysmal versus persistent) may improve outcomes with new and currently available modalities.

2. In paroxysmal AF, which is predominantly a trigger-based arrhythmia, the extent of involvement of the atrial myocardium (substrate) in the fibrotic disease process as imaged using late gadolinium enhanced MRI is reported to be significantly lesser than in persistent AF.³² With an increasing extent of diseased substrate in the biatrial tissue, the rate of successful outcome of ablation therapy reduces such that at one stage when the disease (fibrosis on MRI) is extensive, the ablation therapy may not be recommended. While focal sources can be easy therapeutic targets with high likelihood of long-term maintenance of sinus rhythm, the successful outcome of ablation in extensively diseased persistent AF is not shown to be similarly high, despite ablating higher amount of tissue.

3. Persistent AF develops under the influence of comorbid conditions which exert stress on the atrial myocardium. Atrial remodeling is a process of ionic, genomic and cellular adaptation to such external stressors manifested clinically as progressively longer lasting form of AF. Timely removal of the stressor can reverse the progression of the disease. But, if left untreated, irreversible changes manifested as atrial fibrosis ensue as early as 1 month.²⁰ Early management of AF can break the chain of pathological events shown in Figure 1 and possibly retard, if not halt, the AF progression.

4. Although the predictors of recurrence of atrial arrhythmias post AF ablation are not uniform in all the studies, the time spent

Total RF delivery terminating AF depends on duration of continuous AF

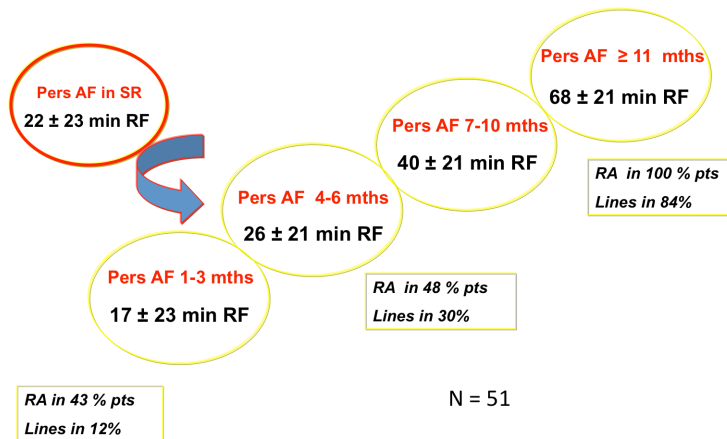


Figure 3:

I The duration of RF delivery terminating AF varies directly with the duration of continuous persistent AF

in persistent AF and left atrial diameter have been very consistent. Therefore, many operators are reluctant to consider patients with a left atrial diameter >5 cm, although the thresholds of operators are continually decreasing as experience increases.³³

Challenges

1. The relevance of external stressors in the progression of AF can be estimated by the association of persistent and permanent AF with a variety of clinical conditions.^{6,34,35} These conditions and their variable contribution towards modifying atrial substrate add to the complexity of AF. This pathophysiological diversity hampers the development of both adequate preventive strategies as well as effective therapies for AF.

2. The roles of atrial tachycardia, heart failure, age, hypertension, and diabetes as independent risk factors for AF are well established but the mechanisms by which these factors increase AF susceptibility are less clearly defined.³⁶⁻⁴⁰

3. There is also a high variability in the electrophysiological mechanisms directly

promoting AF (variability in trigger activity and substrate complexity). Electrophysiological characteristics of arrhythmogenic pulmonary veins have been elucidated⁴¹⁻⁴³ But, the cause of such arrhythmogenicity has not been identified.

Current therapeutic regimes are most often chosen based on clinical symptoms, the duration of AF (paroxysmal or persistent AF), and simple clinical factors such as left atrial size. These categories do not necessarily reflect the degree of electrophysiological changes resulting in AF. For example, in patients with persistent AF, the relative contribution of abnormal impulse formation or the severity of the electrophysiological substrate is usually unknown and is not taken into account during the therapeutic decision-making process. Therefore, an effective AF management requires novel therapeutic targets. These can be identified by searching for novel AF-causing and AF-perpetuating factors.

4. Ultrastructural alterations are certainly accelerated by AF itself, but usually begin before the onset of AF, and certainly before the arrhythmia becomes persistent. Early recognition of this process and identification of patients at risk for progression to persistent

AF would be desirable in order to strengthen secondary preventive approaches.

5. Catheter ablation of AF has been shown to better restore and maintain sinus rhythm than antiarrhythmic drugs with complications ranging from 3-5%.⁴⁴ While this may still be acceptable, the goal to achieve rapid and permanent PV isolation / blocked linear lesion preferably in a single shot and a single procedure, although desirable, is associated with high risk. The alarm is raised by clinically silent adverse events like MRI-detectable embolic cerebral lesions, which can occur in up to 40% cases depending on the ablation technique and tool to achieve this goal. Although smaller lesions disappear a few months later, the delayed clinical significance of these silent lesions is unknown so far.⁴⁵ It also raises the possibility of the occurrence of both clinically silent as well as undetectable lesions with its manifestations likely to occur at a later stage.

Comprehensive Therapy

Since AF, as a disease process, takes variable course; it is difficult to generalize the therapeutic approach. Treatment should be individualized based on one's symptoms, comorbidities and expectations. Prevention/early control of common comorbidities like hypertension, obesity, alcoholism, sleep apnea can not be undermined.

Early initiation of rhythm control strategy is a reasonable approach and justifies controlled trials with long term follow-up to detect its impact on delay in the progression of AF.

Since the catheter ablation's role is not completely established in the prevention of progression of paroxysmal AF and is far from satisfactory in a large population of persistent AF patients, efforts should not be exclusively directed towards non-pharmacological therapies. Besides evolving appropriate AF mapping and ablation tools and techniques, research involving novel drug therapies should be equally entertained. This may involve drugs which specifically act on the triggers like pulmonary veins. Since sinus rhythm maintenance rates are higher in AF ablated patients on antiarrhythmic drugs than in patients treated with any one of these two strategies, we may consider that there is a room for hybrid approach in the early management of AF

Besides achieving acute subjective improvement in patient's symptomatic status, objective benefits of sustained normal rhythm like improvement in death, stroke and heart failure rates and the absence of deleterious impact on left atrial function and long-term quality of life are clinically vital criteria advocated for gauging the success of any AF abolition strategy.

Upcoming Role of Electrostructural Imaging

The inadequacy of clinical classification of AF into broad paroxysmal and persistent varieties is realized when viewed from AF-therapeutics' standpoint. New diagnostic tools are being developed to differentiate various types of AF non-invasively and understand the structural changes occurring within the atria. The ultimate aim is to devise appropriate therapy and prognosticate the disorder on an individual basis by combining non-invasively obtained structural (tissue-level) and electrical (functional) information maps.

With advancements in imaging and mapping techniques, it is possible to infer and plot the multilead surface ECG information on to the computerized tomogram derived cardiac chamber geometry using inverse mathematics. It is feasible to non-invasively generate electrical maps of the cardiac chambers during organized arrhythmias

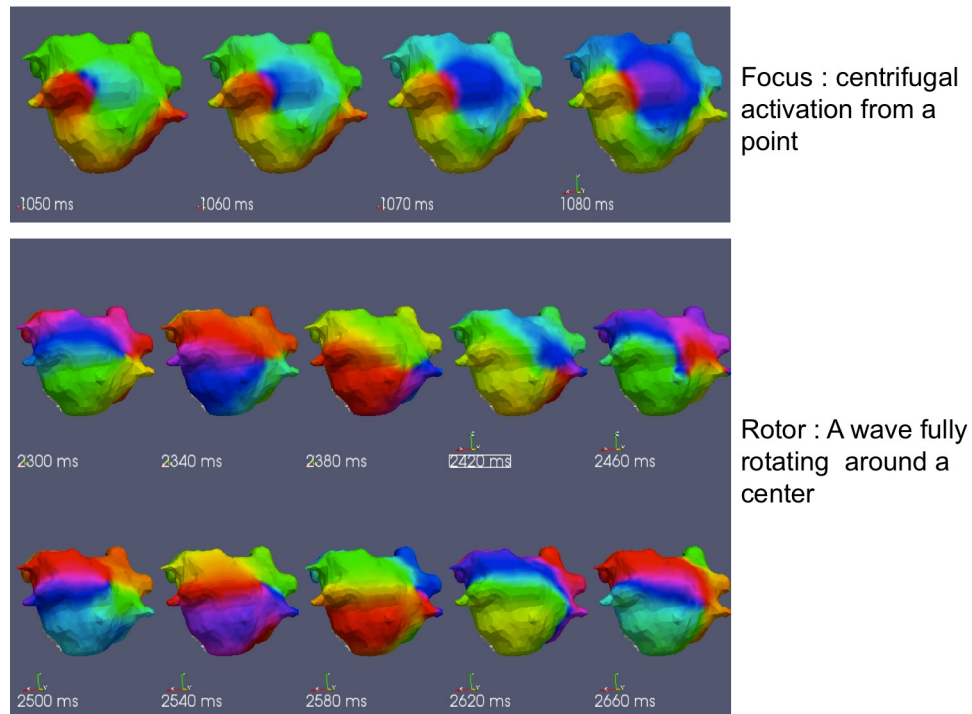


Figure 4:

Non-invasive mapping showing posterior view of left atrium during paroxysmal AF. Panel A shows serial snapshots of a single wave emerging out of the left inferior PV (white star) and reaching right veins in 30ms while it expands radially to the roof and inferior walls. Panel B shows serial snapshots of two successive rotations (white arrows) of a rotor located near the ostia of right veins. The core of the rotor (white star at the center of rainbow-coloured phases of rotor) is seen meandering in a small region in this example. The blue wave indicates the depolarizing front, which makes one full rotation in 160ms.

The phases of wave propagation are color-coded using rainbow scale. The blue colour represents depolarizing wave and the green represents the end of repolarization. The wavefront can be read by following the blue colour. The time (ms) at the bottom of each snapshot represents the moment in the time-window when the snapshot was taken

and fibrillation. Such a technique including the indigenously developed AF mapping softwares, tools and algorithms has been evaluated in paroxysmal and persistent AF with promising results of non-invasive mapping guided ablation at our center. This tool provides panoramic view of the ongoing fibrillatory rhythm elucidating coexisting AF sources and passive activity spread across the biatrial substrate (Figure 4), besides displaying the electrograms, isochrones and scar areas within the substrate.

A Delayed contrast enhancement (DE) on cardiac magnetic resonance imaging (MRI) represents areas of myocardial fibrosis and scar. Recently, the extent of delayed enhancement in the left atrium has been associated with the clinical type of AF, procedural success and recurrence after pulmonary vein isolation procedure. All patients with extensive (mean 50% of left atrial wall) enhancement presented with persistent AF. Limited areas of DE (confined to the posterior left atrium and septum) were associated with higher success rates and lower recurrence after pulmonary vein isolation than the widespread enhancement. Pre and post ablation comparative DE MRI can quantify the areas of ablative scar and help visualize the gaps in linear ablation and circumferential pulmonary vein isolation. The advantage over electroanatomic systems includes the non-invasive nature of MRI and the spatial accuracy of localization. Respiratory artifacts interfere with the detection and quantification of fibrosis using the algorithms which are limited by the need for an experienced observer.³²

These non-invasive imaging tools will be helpful in tracking the changes occurring in the atria along the course of AF. This could

have an impact on deciding the right time for instituting therapy early in AF.

Conclusions:

The slowly progressive electrostructural alterations diffusely involve the atrial substrate and lead to persistent and permanent forms of AF. Although the progression of the AF disease process is variable and associated with the development of comorbid conditions, rhythm restoration therapies, particularly catheter ablation, provide higher acute and long-term success rates in paroxysmal than non-paroxysmal AF. Besides, laying emphasis on preventive/early management of comorbid conditions, the growing experience on pulmonary vein isolation in paroxysmal AF will reveal how this strategy modifies the progression to persistent AF. Non-invasive electro-structural imaging/mapping-guided safe rhythm restoration modality targeting specific and limited atrial tissue on an individual basis at the right time can set a new paradigm in the timely management of AF in near future.

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