Left Atrial Fibrosis: Role in Atrial Fibrillation Pathophysiology and Treatment Outcomes

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Abstract

The mechanisms of atrial fibrillation are complex, and have been the subject of intensive study for over fifty years. There is likely a complex interplay between triggers and substrate that mediates the initiation and maintenance of AF. Increasingly, atrial fibrosis has been recognized as a key component of that substrate, playing a critical role in conduction abnormalities in the left atrium that appear necessary to maintaining AF. In the last several years, our abilities to quantify left atrial fibrosis – both through catheter- and MRI-based techniques – has shed important light on the underlying mechanisms of AF, and on therapeutic strategies to treat AF. Whether our increased appreciation of the role of atrial fibrosis in AF translates into improved efficacy of catheter ablation or anti-arrhythmic therapy, though, remains to be seen. The aim of this review is to summarize clinical investigations of atrial fibrosis as a factor in the development and treatment of atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained tachycardia encountered by physicians. The prevalence of AF increases with age. In the US, roughly 6% of patients over 65yo and 10% of patients over 85yo have AF. The burden of AF in the US, in terms of total number of patients (currently roughly 2.2 million), total health-care expenditures, and associated morbidity and mortality, is likely to rise as the population ages.

While Harvey first identified fibrillating atrial tissue almost four centuries ago, it has only been in the last sixty years that we have developed an appreciation of the mechanisms underlying AF. While that mechanistic understanding remains incomplete, it has contributed to radical new therapies – principally catheter-based – in the treatment of AF. The purpose of this review is to summarize what is known about atrial fibrosis, and specifically, how atrial fibrosis contributes to the pathogenesis of AF and how that fibrosis impacts current therapies used to treat AF.

Basic Mechanisms

As clinicians we tend to regard AF as a single disease. This is probably not the case. Indeed, it seems strange to attribute lone AF in a 20yo and chronic AF in an octogenarian with advanced CHF to common underlying mechanisms. The relative importance of triggering foci and maintenance substrate, for instance, is likely to be different in disparate patient populations. However, there are some basic electrophysiologi-
cal principles that are likely important in most patients with AF. Over a 5 year period from 1959 to 1964, Gordon Moe published a series of papers hypothesizing that AF was due to functional reentry of multiple wavelets, rather than to rapidly firing ectopic foci.\textsuperscript{5,7} Reentry, either functional or anatomic, has several prerequisites. First, there must exist a substrate allowing for unidirectional block, with concomitant conduction over a discreet limb of the circuit. Second, the wavelength of the depolarization during tachycardia (as defined by the product of conduction velocity and refractory period) must fit in the excitable, repolarized tissue available. Conditions that reduce the wavelength of depolarized tissue, either by shortening atrial effective refractory period and/or reducing atrial conduction velocity, are likely to contribute to sustained arrhythmia.

In subsequent work by Allessie and others, the multiple wavelet hypothesis put forth by Moe was largely confirmed.\textsuperscript{8-10} AF induced by rapid pacing was shown to shorten atrial refractory periods, leading to ever-increasing predisposition for AF induction and maintenance and demonstrating the observation that AF begets AF.\textsuperscript{8} In his initial study of pacing-induced AF in goats, Allessie did not find significant changes in atrial conduction velocity. Subsequent investigators have found, however, that conduction velocity in atrial tissue prone to sustained fibrillation is significantly compromised.\textsuperscript{11} There are likely a number of factors that contribute to deranged activation propagation in diseased (and fibrillation-prone) atria, including alterations in gap junction protein expression,\textsuperscript{12-15} attendant changes in myocyte coupling, and the development of interstitial fibrosis and atrial scarring.\textsuperscript{11} Together, these factors conspire to reduce conduction velocity, generate regions of anisotropic conduction and lines of frank conduction block, and thus contribute to the initiation and maintenance of functional reentry.

The contributory role of left atrial scar in the genesis of AF has been shown in a variety of animal and human models.\textsuperscript{16-22} Olgin and colleagues demonstrated increased atrial fibrosis and AF propensity in a mouse model of TGF-B1 overexpression.\textsuperscript{16} Mice engineered to overexpress ACE have also been shown to have increased atrial fibrosis and AF.\textsuperscript{17} In larger models, atrial and ventricular tachypacing,\textsuperscript{18,19} aging,\textsuperscript{20,21} and mitral regurgitation\textsuperscript{22} have all been shown to result in atrial fibrosis which in turn may increase the likelihood of sustained AF.

In humans, there have been a wide variety of studies identifying increased atrial fibrosis and scar in

\textbf{Figure 1}: Schematic of the Posterior Left and Right Atria, Showing (A) Autonomic Ganglia, (B) Abnormal Patterns of Conduction, (C) Triggering Foci from the PVs (red) and other Ectopic Sites (green), and (D) the Superimposition of each of these Components as Contributors to AF.
patients either at increased risk for AF, or in AF patients per se. This includes increased atrial fibrosis seen in patients with advanced CHF, valvular heart disease, and ischemic heart disease. Increased atrial scar has also been seen in patients with lone AF, suggesting that even in those relatively healthy patients, there are fundamental changes in atrial conduction properties necessary for the maintenance of fibrillation.

The precise mechanism by which fibrosis contributes to the origination and maintenance of fibrillation in atrial tissue is not fully understood. AF is thought to depend on an interplay between triggers and substrate. Traditionally, triggers are thought to be localized to the PV ostia, though increase in fibrosis may give rise to new, non-PV localized trigger sites. Increased fibrosis almost certainly changes the conduction properties of the tissue activated by triggered beats (PV-focused and otherwise), such that fibrosis is an important contributor to AF maintenance. Animal models of tachycardia-mediated cardiomyopathy suggest that regions of left atrial fibrosis result in increased conduction heterogeneity through the left atrium, with both large patches of fibrosis and pulmonary vein ostia serving as anchors reentrant circuits and impediments to conduction that result in delays, wavebreaks, and lines of block.

Catheter Mapping of Scar

As mechanisms underlying AF have been determined, strategies to treat AF with catheter ablation have evolved in parallel. Early ablative procedures consisted of linear lesion sets in the right atrium, left atrium, or both and were delivered with the goal of interrupting reentrant circuits. These strategies, designed to alter the substrate by parsing left and right atrial tissue into regions small enough to be incapable of supporting sustained AF, were of limited efficacy. The linear lesions applied to modify the substrate with this strategy were long and complex, with complete lines of block difficult to deliver. With Haisseguerre’s seminal report that AF is triggered by PV foci, ablative strategies targeting triggers located in PVs were adopted. Initially, focal ablation of the PV foci themselves was performed, but focal ablation gave way to segmental and eventually to circumferential lesions designed to isolate, rather than eliminate, PV targets. Most procedures today combine some combination of circumferential and segmental isolation, with the goal of isolating each of the pulmonary veins. In patients with persistent AF, some operators deliver additional lesion sets to further divide atrial tissue, eliminate rotors, or destroy ganglia. Catheter ablation for AF has provided unique opportunities to investigate in situ atrial fibrosis, with the aim of understanding the mechanisms of AF induction and maintenance more completely, as well as determining whether there exists a relationship between AF scar burden and patient prognosis. The Michigan group performed an analysis of bipolar atrial electrograms in 47 patients undergoing PVI for persistent AF. Patients in the cohort had LA diameters of 46 +/- 5 mm, and had been in persistent AF for 2 +/- 1 years prior to ablation. The authors found that atrial fibrosis correlated strongly with patient age, and that age (and associated fibrosis) correlated inversely with AF cycle length. These findings mirrored investigational and ex vivo studies (referred to above) correlating age with atrial fibrosis. Natale and colleagues investigated LA scar, as assessed during catheter ablation, in a much larger series of patients (700) undergoing initial PVI. Patients included in the study underwent mapping of LA scar using a decapolar lasso catheter, with scar defined as absence of electrograms on all 10 catheter poles in three distinct lasso positions. LA scar was noted to be present in 42 patients (6%). There was apparent correlation between scar and LA size, low EF, and increased plasma C-reactive peptide levels. The incidence of AF recurrence was significantly higher (57%) in patients with LA scar than in patients without scar (19%). LA scar was the only predictor of AF recurrence on multivariate analysis. In patients with LA scar who underwent CARTO electroanatomical mapping, scar area averaged 21 +/- 11% of LA surface area, and was associated with large regions of low voltage electrograms. The authors postulated that scarring likely contributes to AF etiology by providing abnormal patterns of LA conduction that allow for triggers of AF (from the PVs or elsewhere) to successfully initiate fibrillation, and that myopathic, diseased tissue itself may provide triggered beats. Olgin and colleagues studied regional patterns of LA fibrosis in patients with AF versus those with focal atrial tachycardia. They found that in both patient...
populations, the anterior LA and appendage had highest bipolar voltage electrogram amplitudes, and that scar (as assessed by voltage amplitude) was most often found in the posterior and septal LA. In patients with AF, there was greater regional variability in voltage amplitude, perhaps suggesting increased heterogeneity of conduction. Similar to the findings of Morady and colleagues, the authors also found that low voltage and scar correlated strongly with patient age. In summary, there have been a number of systematic analyses of LA scar, as defined by low-voltage bipolar atrial electrograms, in patients undergoing catheter ablation for AF. Generally these studies support data from ex vivo studies or experimental models that LA scar burden correlates with age, left atrial size, and with reduced cardiac function. LA scar burden appears to be a negative prognostic indicator of long-term freedom from AF after initial PVI. While this information is clinically helpful, there are obvious disadvantages to catheter-based scar mapping of the LA: such maps are by definition invasive, laborious, and must be performed during the procedure (rather than informing decisions about whether to proceed with AF ablation at all). For these and other reasons, a number of centers have developed imaging techniques – predominantly MRI-based – to analyze LA scar in pre- and post-ablation patients.

MRI Assessment of LA Scar

The use of delayed enhancement MRI (DEMRI) to determine burden and patterns of LA fibrosis in AF patients has largely been championed by two groups, the Marrouche lab in Utah and the Peters lab in Boston. Other centers, including our own, are beginning to investigate the technique. DEMRI assessment of cardiac scar (in either the ventricles or atrium) takes advantage of the different kinetics of contrast (typically gadolinium) loading and washout in blood, healthy myocardium, and myocardial scar. Typically patients undergo non-contrast cardiac MR imaging, followed by contrast loading and reimaging shortly thereafter. Comparison of the two sets of images allows regions of tissue enhancement (i.e. scar) to be identified. DEMRI in AF patients has been used for two principal aims: to characterize patient substrate (LA scar burden) prior to AF treatment for prognostic purposes, and to characterize post-ablation lesion burden, both for prognosis and for planning redo ablation procedures.

Assessment of LA Scar in AF Patients Pre-procedure

Initial investigations of LA scar imaging by DEMRI were performed in patients who had undergone catheter ablation for AF. In 2007, the Peters group reported on a series of 23 patients who underwent PV isolation, with 15 patients getting pre-procedure MRIs and 18 patients getting post-procedure MRIs. The authors reported that 0% (0/14 with adequate MRI images) of patients were found to have atrial scarring on pre-procedure MRI; data about the nature and duration of AF (i.e. paroxysmal versus persistent; AF burden) were not provided. In 2008 the Marrouche group reported on a series of 46 patients undergoing PV isolation. All patients underwent pre- and post-procedure MR imaging. Pre-procedure MRI detected LA fibrosis in only 4 patients (8.7%).

The Utah group refined their pre-procedure assessment of LA scar in patients referred for PVI, and introduced the Utah scoring system in a 2010 investigation of LA fibrosis in patients with lone AF. The Utah system categorizes patients by LA area showing enhancement, dividing patients into four groups: I (<5%), II (5-20%), III (20 – 35%), and IV (>35%). The investigators report that procedural outcomes were predicted by LA scar burden, with a 100% freedom from AF (mean f/u 324 +/- 234 days; AF assessed by ECGs and Holter monitors at f/u visits; AF recurrence defined as episode > 30s) in the Utah I group, contrasted with a 96% recurrence rate in the Utah IV group. The authors conclude that, in their hands, MRI provides a powerful pre-procedure assessment that can help determine whether a patient should be referred for catheter ablation. Subsequently, the same group has proposed that the strategy used during AF ablation (i.e. simple PV isolation versus isolation coupled with more extensive ablation) be informed by scar burden as assessed by DEMRI. Whether that sort of tailored therapy will result in improved long-term outcomes remains to be seen.

LA Scar Assessment Post-Ablation

A number of studies have been performed inves-
tigating the utility of DEMRI imaging of LA scar post-ablation. What is immediately obvious is that the “scar” that is being imaged after PV isolation is not only endogenous, pathological atrial fibrosis, but also the ablation lesion set (typically from RF ablation). The implications, then, of scar burden in post-PVI imaging are quite different than in pre-procedure imaging. Several groups have reported that increased density of LA scar after AF ablation correlate with improved procedural outcomes. The Utah group has reported such a correlation in 144 patients undergoing PV isolation. Total LA scar burden and the degree of circumferential isolation of PV ostia (as seen by DE MRI) were directly proportional with freedom from AF after the procedure. PV circumferential lesions were seen in a distinct minority of patients (all 4 PVs isolated in only 7% of patients), confirming by MRI what is unfortunately well known by AF ablationists – that achieving durable PV isolation is remarkably difficult. The Utah group and others have proposed that post-procedure MRI can be used to assess adequacy of the lesion set, that ablated regions on MRI correlate well with RF lesion sets recorded on electroanatomical mapping systems during the procedure, and that repeat ablation strategies can be informed by DE MRI performed after the initial procedure. Whether these assertions will translate into widespread clinical practice is not clear.

Other novel uses for MRI-based LA scar assessment have been proposed, including augmenting stroke risk profile scoring systems (CHADS and CHADS-VASC) with LA scar burden, assessment of LA transport function post-ablation, and evaluation of collateral damage to structures abutting the LA in PVI patients.

There are a number of limitations to DE-MRI based analysis of LA scar that must be acknowledged. First, there are only two centers that have published extensively on the use of DEMRI to assess LA scar burden. The degree to which meaningful analysis is dependent on indigenous knowledge and image processing techniques remains to be seen. Even at the most experienced centers, it is routine (in published series) for a large percentage of scans to be tossed out because of inadequate imaging quality. This is sobering. Other groups, including our own at Johns Hopkins, have begun using MRI to assess fibrosis in LA tissue. The results, for our group and others, has been less promising to date than the results from the Utah and Boston groups. This, too, is sobering, and may reflect the highly specialized nature of image acquisition and post-image data processing that is required to generate images of LA scar. However, MRI clearly has become a powerful and alluring technique to provide non-invasive, pre-procedure assessment of LA fibrosis in patients considering catheter ablation.

Conclusions

From the initial work of Moe to the confirmatory studies of Allessie, from the observation of PV triggers by Haisseguerre to the more recent descriptions of focal rotors, our collective understanding of the mechanisms underlying AF has progressed remarkably over the last several decades. One aspect of the pathophysiology underlying AF that almost certainly comprises a critical part of the substrate is LA scarring and fibrosis. Basic principles of electrophysiology predict that scar, with conduction block and slowing, is required for arrhythmia initiation and maintenance. And indeed, a wide array of studies including experimental animal models, human ex vivo studies, human catheter-based scar mapping, and novel non-invasive assessment of LA scar by DEMRI, all seem to validate those basic electrophysiological principles. How we use that information to guide clinical choices, how we differentiate “good” scar post-ablation from pathological scar contributing to arrhythmogenesis, and how we can target fibrotic processes before the onset of clinical AF, these and other questions remain, for now, unanswered.

Disclosures

No disclosures relevant to this article were made by the author.

References

41. Calkins H, Kuck KH, Cappato R, Brugada J, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012; 9(4): 632 – 96.
57. Meng J, Peters DC, Hsing JM, Chuang ML, Chan J, Fish A, Josephson ME, Manning WJ. Late gadolinium enhancement of the esophagus is common on cardiac MR several months after pulmonary vein isolation: preliminary observations. Pacing