

Structural And Functional Remodeling Of The Left Atrium: Clinical And Therapeutic Implications For Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. Despite advances in our understanding of the pathophysiology of this complex arrhythmia, current therapeutic options remain suboptimal. This review aimed to delineate the atrial structural and functional remodeling leading to the perpetuation of AF. We explored the complex changes seen in the atria in various substrates for AF and the therapeutic options available to prevent these changes or for reverse remodeling. Here we also highlighted the emerging role of aggressive risk factor management aimed at the arrhythmogenic atrial substrate to prevent or retard AF progression.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. Currently it affects approximately 2.7 million people in the USA alone and its prevalence is expected to rise to between 5.6 and 12 million by 2050.¹⁻³ AF is a major public health problem through its association with an increased risk of stroke, heart failure, reduced quality of life, cognitive dysfunction and death.⁴⁻⁷ In addition, recent data demonstrates that there has been an exponential rise in hospitalizations due to AF that already exceeds those for congestive heart failure (CHF).^{8,9} Current rhythm control pharmacotherapies for AF are limited by poor efficacy and potentially serious adverse effects profile.¹⁰ Catheter ablation of AF has evolved as an effective therapy for drug-refractory or intolerant AF. Despite recent advances in ablative techniques, post-ablation freedom from AF has not improved proportionately, especially in those with the more persistent form of the arrhythmia.¹¹ These limitations of the currently available treatment modalities have stimulated further interest into the mechanisms of genesis and perpetuation of AF, with the hope to find a better and more definitive treatment for the future.¹² In this review, we focused on different aspects of atrial remodeling

and highlight the implications of structural and functional changes on therapeutic strategies for this complex arrhythmia (Fig.1)

Atrial Electrical and Ionic Remodeling

Significant advances have been made in our understanding of the fundamental pathophysiological mechanisms underlying AF, although the complexity of how these interact in the individual patient to maintain AF remains poorly understood.¹³ AF arises as a result of a complex interaction between triggers, perpetuators, and substrate.¹⁴ There are dynamic adaptive changes in the atria in response to persistent AF, which enhances the ability of the arrhythmia not only to sustain itself, but also to recur (i.e. "AF begets AF"). In brief, the intra-cellular calcium (Ca^{2+}) increases due to persistent tachycardia, which eventually leads to down-regulation of L-type Ca^{2+} channels and a resultant decrease in action potential duration. Other repolarization abnormalities have also been described with changes in various potassium currents to contribute to the shortening of atrial refractoriness. Also, there is reduction in inward Na^+ current leading to reduction in conduction velocity and shortening of reentry wavelength.^{12,13,15-18} More recent work on calcium homeostasis such as intracellular calcium handling, spontaneous calcium release from the sarcoplasmic reticulum and increased diastolic calcium concentrations have added further complexity to our understanding of the ionic mechanisms involved in the initiation and maintenance of AF.¹⁹⁻²¹

Atrial Functional Remodeling

AF is associated with progressive atrial mechanical remodeling, which is implicated in the development of thrombo-embolic stroke.^{22,23} Studies have demonstrated that the degree of mechanical remodeling correlates strongly with the duration of AF and the

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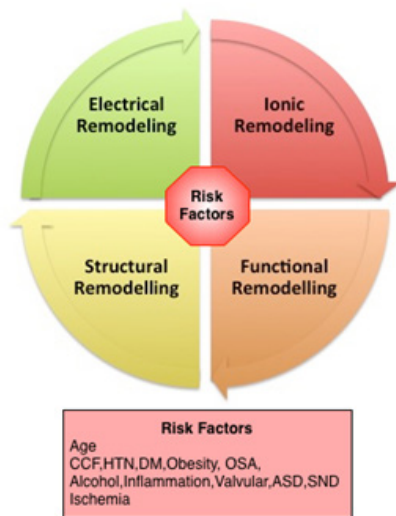


Figure 1: Vicious Cycle of remodelling and Impact of Risk Factors

underlying electrical and ionic remodeling at the cellular level are also known to contribute to mechanical remodeling.²⁴⁻²⁶ In patients with AF for > 3 years, mechanical function during AF is significantly impaired and atrial stunning is more pronounced as compared to patients with shorter duration AF.²⁷ Altered atrial function after a short paroxysm of AF is likely to be the result of transient changes in cellular metabolism. In contrast, long-lasting AF may induce more stable changes such as depressed L-type Ca^{2+} channels and up regulation of $\text{Na}^+\text{-Ca}^{2+}$ Exchanger (NCX).^{26,28,29} This altered Ca^{2+} handling is responsible for the “atrial stunning” seen post cardioversion which relates more to the properties of the preceding arrhythmia rather than the mode of cardioversion.^{27,30} Additionally, the decreased contractile function leads to increased atrial compliance to result in atrial stretch and subsequent structural remodeling.³¹ Although the ionic changes underlying electrical and mechanical remodeling can in part explain how AF promotes its own maintenance, it does not account for the substrate that further maintains AF. Li et al provided the seminal observations of the importance of “structural remodeling” in creating a substrate for arrhythmia in a rapid ventricular pacing model of heart failure to highlight the importance of “additional factors”.³²

Atrial Structural Remodeling

Left atrial (LA) structural remodeling refers to adaptive or maladaptive changes in cardiac architecture in response to “external stressors”.³³ These changes occur at both macro- and microscopic levels and are time and etiology dependent. The hallmark of macroscopic change is “atrial dilation”.³⁴ Significant microscopic changes include cellular hypertrophy, myolysis, dedifferentiation, fibrosis, apoptosis, mitochondria and sarcoplasmic reticulum disruption.³⁵⁻³⁸ More recent work has also highlighted the importance of endomyocardial fibrosis within the epicardial layer rather than the absolute quantity of atrial fibrosis as contributors to AF complexity.³⁹

While electrical and functional dysfunction can lead to structural remodeling, this can also occur independently. The external stressors or “modulating factors” can directly lead to structural remodeling and help to initiate and maintain AF.⁴⁰ Modulating factors can be non-modifiable (age, genetics) or modifiable such as hypertension, obstructive sleep apnea (OSA), obesity, valvular heart disease,

congestive heart failure (CHF), ischemia, endocrine abnormalities, inflammation and infective states. Most of these conditions can directly or indirectly cause pressure or volume overload of the atria.⁴¹ The augmented atrial load leads to atrial dilatation and stretch. Indeed, acute atrial stretch has been shown to increase the dispersion of atrial refractoriness, slow atrial conduction, increase AF vulnerability and pulmonary vein ectopy.⁴²⁻⁴⁴ Chronic atrial dilatation or stretch has also been demonstrated to result in direction-dependent conduction block thereby increasing the anisotropic properties of the atrial myocardium leading to increased AF inducibility.^{45,46} [Fig.2]. This may be due to activation of ion channels, which are sensitive to increased volume and wall stretch, including Cl^- , K^+ and non-selective cation channels, $\text{Na}^+\text{-Ca}^{2+}$ Exchanger (NCX) and other non-specific stretch-sensitive channels.⁴⁷⁻⁴⁹ Here we detail the various conditions known to be associated with atrial stretch and structural remodeling.

Aging

Early epidemiological data from the Framingham study had found sharp increases in the incidence of AF with aging. The estimated odds ratio for developing AF was 2.1-2.2 with each decade of advancing age.^{50,51} Many investigators have since studied the substrate for AF with senescent in both experimental and clinical settings. Spach et al. elegantly demonstrated the progressive electrical uncoupling of the side-to-side connections between groups of atrial fibers due to collagen deposition in the aging atria. This resulted in reduced transverse conduction velocities and an environment conducive to the reentry mechanism of AF.⁵² Both increased atrial fibrosis and myocyte hypertrophy had been demonstrated in the aging atria to result in electrical changes of atrial conduction slowing, increased conduction heterogeneity and electrogram fractionation.^{53,54} Similar changes have also been documented in more recent clinical studies with electroanatomic mapping showing reduced voltage, conduction slowing and increased electrogram fractionation with senescence.^{55,56} Together, these structural changes are responsible for the increased propensity for AF with increasing age.

Congestive Heart Failure

CHF is an established risk factor for AF with odds ratio of 4.5 to 5.9 as seen in the Framingham study.⁵¹ This relationship can be explained by the presence of common risk factors in both conditions.⁵⁷ In addition, the prevalence for AF in CHF is known to increase with increased severity of pump failure.⁵⁸ In the canine rapid ventricular pacing model, Li et al found that 5 weeks of induced heart failure resulted in increased atrial interstitial fibrosis and conduction heterogeneity leading to more sustained AF.³² Similar atrial structural changes due to heart failure have since been confirmed in chronic (4 months) rapid ventricular pacing model in dogs and doxorubicin-induced non-ischemic cardiomyopathy model in sheep.^{59,60} In patients with both ischemic and non-ischemic cardiomyopathy, significant electro-anatomic remodeling with areas of low voltage (scar), conduction slowing, site-specific conduction blocks and increased atrial refractoriness.⁶¹ Also, significant structural remodeling with atrial interstitial fibrosis has also been demonstrated in autopsied hearts of patients with dilated and hypertrophic cardiomyopathy.³²

Hypertension

Hypertension (HTN) is the most prevalent, independent, and potentially modifiable risk for atrial fibrillation.^{62,63} In the Manitoba

Follow-up study, prevalence of HTN was 53%, and the risk of AF was 1.42 times higher in hypertensive.⁶⁴ HTN is associated with structural changes in the left atrium that are associated with atrial fibrillation. They include left atrial enlargement, changes in left atrial mechanical function, altered left atrial electrophysiology, and increased atrial ectopic activity.⁶⁵ These changes occur in different time domains making early and aggressive management of HTN prudent. Structural changes such as atrial dilatation and hypertrophy develop early and are an important step in the progression from HTN to AF.^{66,67} With prolonged HTN these changes worsen and are characterized by increased atrial fibrosis, atrial hypertrophy, scarring and apoptosis.⁶⁸⁻⁷⁰ Indeed, the magnitude of LA enlargement is proportional to the degree of HTN. In the Framingham study, the risk of developing AF increased by 39% for each 5mm increase in left atrial size.⁶³ Changes in atrial electrical properties occur early in hypertensive heart disease with higher refractoriness, progressive conduction slowing and anisotropy.^{67,69} These progressive structural and electrophysiological changes lead to functional impairment with reduced atrial ejection fraction.⁶⁹ This impaired contractile function of the left atrium has also been shown to predict the development of atrial fibrillation.⁷¹

Diabetes

Diabetes mellitus (DM) is a recognized risk factor for AF. In the Framingham Heart Study, the presence of diabetes conferred a 1.4-increased risk of AF in men and 1.6 in women.^{51,57} AF commonly coexists with cardiovascular risk factors that may predispose to AF. However in a meta-analysis, after adjusting for multiple risk factors for AF, the RR of AF in patients with DM was still 1.24.⁷² DM-related cardiac structural, functional and electrophysiological changes predispose the atria to fibrillate. Possible pathophysiologic mechanisms of these structural changes include oxidative stress, cellular apoptosis, interstitial fibrosis, mitochondrial dysfunction and myocardial hypertrophy. In a DM rat model, widespread fibrotic deposit has been seen in the atria. This was associated with longer intra-atrial activation time due to decreased conduction velocity.⁷³ Decreased phosphorylation of connexin-43 can also result in impaired intercellular electrical coupling and atrial arrhythmia.⁷⁴ Oxidative stress and activation of the AGE-RAGE (advanced glycation end product/AGE—receptor for AGE) system mediate the diffuse interstitial fibrosis of the atrial myocardium via up-regulation of circulating tissue growth factors and by pro-inflammatory response resulting in formation of hyperglycemia associated AF substrate.^{75,76}

Obesity

Obesity increases the risk of developing AF. Obese individuals have an associated 49% increased risk of developing AF compared to non-obese individuals (RR 1.49, 95% CI 1.36-1.64).⁷⁷ Additionally, there is a graded risk relationship between body mass index and progression from paroxysmal to permanent AF.⁷⁸ This association is likely mediated through LA enlargement.⁷⁹ Abed et al demonstrated in ovine model that progressive weight gain results in atrial structural, functional and electrophysiological remodeling. This was associated with spontaneous and more persistent AF. Obesity was associated with increased atrial volume, pressure, and pericardial fat volume. Also, there were micro architectural changes such as atrial interstitial fibrosis, inflammation, and myocardial lipidosis. These changes were associated with significant electrical remodeling characterized by slowing of atrial conduction and increased conduction heterogeneity.⁸⁰

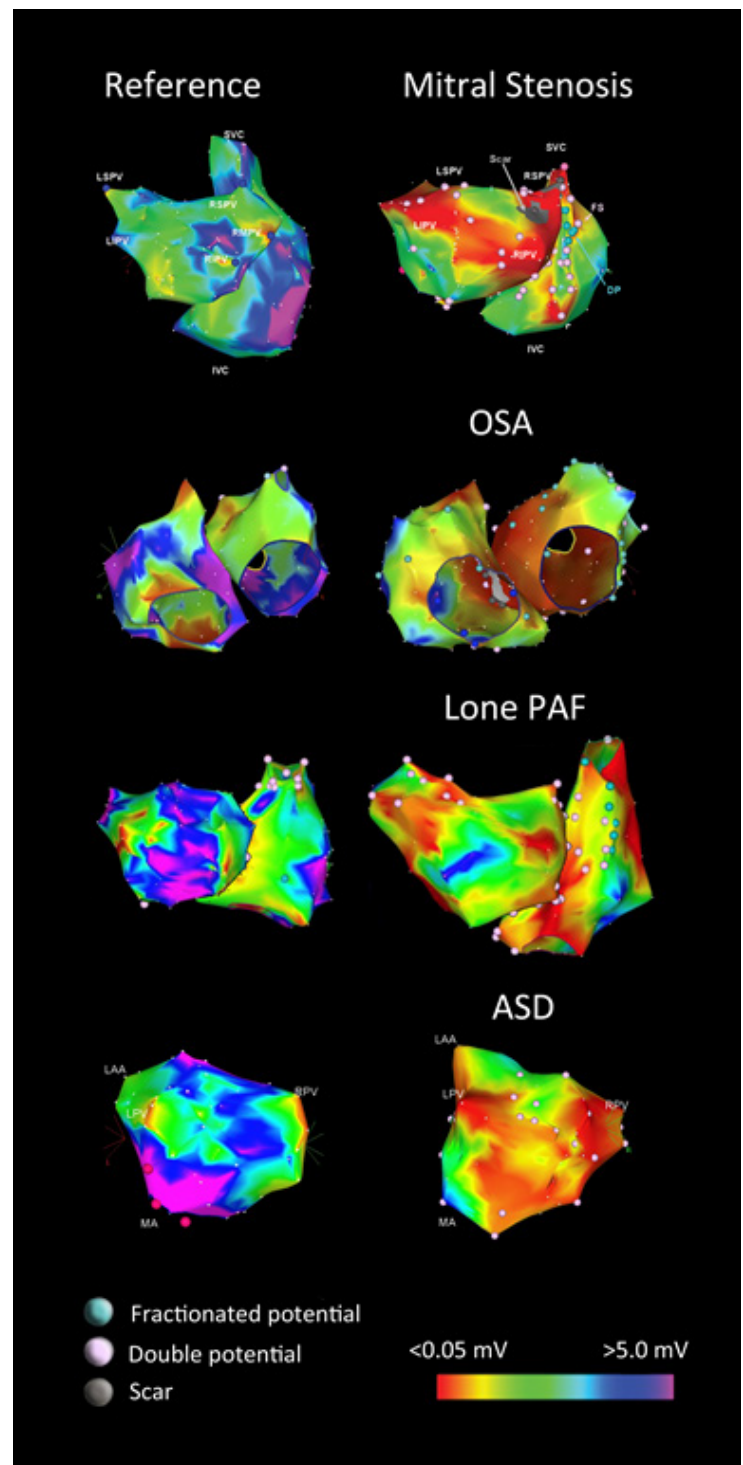


Figure 2: Example Electroanatomic Bipolar Voltage Maps: Representative CARTO maps of patients with atrial fibrillation and various modulating factors compared to control patients.

Similar findings were also seen in obese AF patients.⁸¹ Moreover, increased visceral adiposity due to obesity such as pericardial fat volume has been shown to be associated with AF incidence, severity and adversely effects ablation outcome.^{82,83}

Sleep Apnea

Considerable evidence links AF and sleep apnea with high prevalence of sleep disordered breathing found in AF patients.⁸⁴ Gami et al reported that obstructive sleep apnea (OSA) was a strong

predictor of incident AF (hazard ratio 2.18) and that the measures of OSA severity were also strong predictors of incident AF.^{85,86} Patients with moderate-to-severe OSA have impaired LV diastolic function and increased LA size independent of obesity. Furthermore, prolonged atrial electromechanical activation time as measured by tissue Doppler imaging was evident in subjects with severe OSA as compared to controls with similar body mass index. Therefore, OSA itself may induce cardiac changes that could predispose to AF independent of obesity.^{87,88} Detailed electrophysiological study and electroanatomic mapping by Dimitri and co-workers had found significant atrial remodeling characterized by atrial enlargement, prolonged sinus node recovery time, reduction in voltage, site-specific and widespread conduction abnormalities in patients with OSA. These factors may account for the development and maintenance of AF in patients with OSA.⁸⁹ [Fig.2]. Further insights into the link between OSA and AF can be gained from various pre-clinical studies. In sheep with induced hypercapnia, lengthening of atrial refractoriness and conduction time was observed. However, AF vulnerability was only documented in the period on return to eucapnia due to differential recovery in atrial refractoriness and conduction.⁹⁰ In a pig model of OSA, negative tracheal pressure during obstructive episodes led to shortened atrial refractoriness and increased AF susceptibility that were prevented by vagotomy or atropine, implicating a mechanistic role of vagal activation in OSA related AF.⁹¹ Other AF inducing mechanisms include hypoxemia and atrial stretch during apneic episodes as well as sympathetic activation with acute hypertension on arousals.⁹¹⁻⁹⁴

Inflammation

Inflammation is purported to be among one of the primary causal factors of AF initiation, perpetuation as well as the pro-thrombotic state associated with AF.⁹⁵ This temporal relationship is supported by the fact that AF is frequently associated with inflammatory states such as myocarditis,⁹⁶ pericarditis,⁹⁷ post cardiac surgery⁹⁸ and systemic infections. Also, the findings of marked inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF support this hypothesis.⁹⁹ These micro-architectural changes could explain the bi-atrial electrical and structural remodeling characterized by volumetric change, conduction abnormalities and sinus node dysfunction seen in lone AF.^{100,101} [Fig.2]

Ischemia

Coronary artery disease is also recognized as an independent risk factor for AF.^{57,62} In contemporarily managed patients with acute coronary syndrome, new onset AF remains commonly encountered to result in increased short and long term complications.^{102,103} However, the mechanistic link between myocardial ischemia and the development of AF remains incompletely understood. Detailed assessment of coronary angiography in patients has shown that coronary artery disease affecting the atrial branches is associated with AF in the setting of acute myocardial infarction.^{104,105} Experimentally, atrial ischemia due to acute occlusion of atrial arterial branch in dogs resulted in significant conduction slowing which can promote re-entry that can maintain AF.¹⁰⁶ In dogs with chronic atrial ischemia, increased atrial fibrosis was seen in infarct border zone as substrate for increased conduction heterogeneity, sustained re-entry and even increased spontaneous ectopy.¹⁰⁷ Indeed, recent work by Alasady and co-workers have demonstrated that direct atrial ischemia played a dominant role in the substrate for AF over and above hemodynamic

and neurohumoral changes during acute myocardial infarction.¹⁰⁸

Valvular Heart Disease

Valvular heart disease is one of the common causes of AF. In addition, it is well recognized that the risk of stroke due to AF in this population is increased to a greater extent.¹⁰⁹ The concept of atrial fibrosis, myocyte hypertrophy and degeneration in AF was initially studied by Thiedemann et al in humans with mitral valve disease whereby cellular contractile function was found to be impaired with these structural changes.¹¹⁰ In an animal model, Verheule et al demonstrated that volume overload and atrial stretch due to mitral regurgitation was associated with increased atrial volume, interstitial fibrosis, chronic inflammation and glycogen accumulation.¹¹¹ In patients with mitral stenosis, John et al found significant bi-atrial remodeling characterized by atrial enlargement, loss of myocardium, and areas of electrical scarring associated with widespread and site-specific conduction abnormalities. These abnormalities were associated with a heightened vulnerability for AF.¹¹² [Fig.2]. Examinations of atrial appendage tissues from patients with valvular heart disease undergoing open-heart surgeries have demonstrated that increased atrial endothelin-1 and decreased matrix metalloproteinases were associated with increased atrial fibrosis.^{113,114} Furthermore, increased atrial amyloid deposition has also been seen in biopsies from patients with rheumatic valve disease and long-standing AF.¹¹⁵

Atrial Septal Defects

AF is one of the well-documented sequelae of atrial septal defects (ASD) that appear to be minimally altered by ASD closure.^{116,117} Although the precise pathogenesis of arrhythmias in ASD patients is unclear, both electrical and structural remodeling due to chronic atrial stretch appear to play a major role. Chronic atrial stretch resulting from ASD causes electrical remodeling with anatomically determined conduction delay at the crista terminalis, a trend toward an increase in right atrial ERP, and impaired sinus node function.¹¹⁸ Additionally, significant structural remodeling due to volume overload leads to marked bi-atrial enlargement and left atrial scarring evidenced by regions of low voltage amplitude and electrical silence.¹¹⁹ [Fig.2]

Sinus Node Disease

Sinus node disease (SND) is a common indication for permanent pacemaker insertion in the community. One recent study has shown that new AF was detected in 22% of patients who received permanent pacing for sick sinus syndrome over a mean follow-up period of 7 years.¹²⁰ SND has been associated with an atrial myopathy with a number of atrial structural and electrical changes being described.¹²¹ Early necropsy data has demonstrated widespread structural abnormalities such as diffuse atrial fibrosis and fatty infiltration in patients with chronic sino-atrial disorder.¹²² Detailed evaluation by Sanders et al in patients with SND confirmed these structural changes with electro-anatomical evidence of regions with low voltage and spontaneous scarring together with increased electrogram fractionation and significant conduction abnormalities.¹²³ These findings were consistent with other indirect measures of atrial conduction changes reported in patients with SND such as prolonged P wave duration.¹²⁴ The atrial changes described above may contribute to the high prevalence of atrial fibrillation seen in patients with SND.

Reversal of LA Remodeling: Therapeutic Implications

Long-term maintenance of sinus rhythm is difficult to achieve in

AF patients. Factors such as underlying etiology and its duration, extent of atrial remodeling and management of risk factors collectively determine the success of AF therapy.^{125,126} Although atrial remodeling can be reversible, it is time critical and early intervention is prudent. Both electrical and contractile remodeling were seen from the first few minutes of acutely induced AF and could be completely reversible following cardioversion in a goat model. However, the recovery time increased with longer duration of remodeling.¹²⁷ Other examples of reverse atrial remodeling were seen in mitral stenosis patients undergoing mitral commissurotomy¹²⁸ and in VVI paced patients when atrioventricular synchrony was restored with DDD pacing.¹²⁹ More recently, we have demonstrated that weight loss and risk factor management can result in beneficial cardiac remodeling and improved AF symptoms.¹³⁰ However, a smaller degree of reversibility is expected in subjects with longer AF duration due to progressive remodeling. This was seen in the attenuated reversal of atrial mechanical stunning following cardioversion in patients with longer duration of AF (more than 3 years) as compared to those with short-duration AF (1 to 6 months).²⁷ Similarly, structural remodeling, which occurs over weeks to months of AF, is more long-standing and may be very slow to reverse or even irreversible.^{31,131} Markers of extent of structural remodeling such as LA volume and LA strain at baseline are independent predictor of reverse remodeling.¹³² Similarly, extent of atrial fibrosis as seen via delayed-enhancement magnetic resonance imaging and AF disorganization can also provide insight into the progress of disease and ability of the LA to reverse remodel.^{133,134}

Thus managing the risk factors of AF needs to be timely to prevent or maximize the chance of reverse structural remodeling in the long-term management of AF. To what extent prevention and reversal of atrial remodeling will translate into a reduction in the burden of AF remains to be seen. Recent studies have tested the efficacy of various strategies that can reverse atrial structural and electrical remodeling in various stages of atrial remodeling. However, much work still needs to be done to ascertain the impact of these strategies and their role in reducing AF as a public health problem.

Anti-Arrhythmic Therapy

Most of the anti-arrhythmic drugs work by direct inhibition of ion channels. Amiodarone, in addition to its polypharmacology has been shown to affect atrial electrical remodeling in an experimental animal model. Shinagawa et al. have shown that amiodarone, but not flecainide or dofetilide, prevented tachycardia-induced ERP shortening in canine atria by preventing L-type Ca^{2+} channel down regulation. Moreover, amiodarone treatment after the induction of atrial tachycardia was able to reverse remodeling.¹³⁵ Similar finding were shown by Ashikaga et al in canine atria. In this study, Amiodarone also suppressed the increases in MMP-2 activity and fibrosis induced by long-term rapid atrial pacing. Amiodarone therefore reversed both electrical and structural remodeling and suppressed the inducibility of sustained atrial fibrillation.¹³⁶ Although it is unclear whether amiodarone has similar effects in patients, such effects could potentially contribute to its clinical efficacy. However, the clinical value of amiodarone is limited by its wide range of side effects.

Electrical Cardioversion and Radiofrequency Ablation

Restoration of sinus rhythm whether by electrical cardioversion or radiofrequency ablation has been shown to facilitate 'reverse' atrial

remodeling with a resultant decrease in atrial size and improvement in atrial function.¹³⁷⁻¹³⁹ In a meta-analysis by Jeevanantham et al, a significant decrease in LA diameter and volume was seen at post ablation follow-up especially in patients without AF recurrence in comparison to those with AF recurrence. Although reverse atrial functional remodeling was not evident in this meta-analysis, patients without AF recurrence showed no decline in LA ejection fraction and LA active emptying fraction as opposed to those with AF recurrence.¹⁴⁰

Drugs targeting Renin Angiotensin Aldosterone System (RAAS)

Both ACE-inhibitor (ACE-I) and angiotensin receptor blocker (ARB) have been shown to be effective in the prevention of AF in a recent meta-analysis although this effect appears to be most clearly seen in patients with systolic LV dysfunction and left ventricular hypertrophy.¹⁴¹ Recently, there has also been increased awareness on the role of aldosterone in atrial ionic remodeling and fibrosis.^{142,143} Several pre-clinical studies have demonstrated the beneficial role of ACE-I, ARB and aldosterone antagonists in preventing the substrate for AF in pacing models of AF and CHF. For example, in animal models of CHF, ACE-I pre-treatment reduced left atrial dilation, contractile dysfunction, fibrosis and shortening of the atrial effective refractory period to result in shorter induced AF duration.^{144,145} However, the role of ACE-I/ARB in the secondary prevention of AF is non-conclusive with divergent results. When AF recurrence was examined in patients with HTN and AF, a randomized study has shown no difference in AF frequency between patients with HT and paroxysmal AF treated with candesartan or amlodipine.¹⁴⁶ Furthermore, several secondary prevention trials have reported that inhibitors of the RAAS may not reduce the risk of arrhythmia recurrence in AF patients.^{147,148}

Other Therapies

HMG-CoA Reductase Inhibitors

The exact mechanisms by which statins may prevent AF are not well established although their anti-inflammatory and antioxidant properties, membrane stabilizing effect and effect on endothelial and neurohormonal activation are thought to be contributory.¹⁴⁹ In animal experiments with sterile pericarditis, rapid atrial pacing, and ventricular tachypacing AF models, statins have been shown to attenuate electrical and structural atrial remodeling and reduced vulnerability to AF.¹⁵⁰⁻¹⁵² However, the beneficial effects of statins in human AF have not been convincingly demonstrated in large randomized control trials.¹⁵³

Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

Several population-based studies have shown conflicting results regarding the role of n-3 PUFAs in preventing AF.¹⁵⁴⁻¹⁵⁷ Similarly, its role in AF and in associated conditions such as post open-heart surgery and AF prevention following cardioversion remains uncertain given recent contradictory findings.¹⁵⁸⁻¹⁶² In contrast, n-3 PUFAs have been associated with reduction in incident CHF, fewer CHF hospitalizations and associated mortality. In animal CHF models, several groups have demonstrated that n-3 PUFAs use was protective against adverse atrial remodeling in CHF by preventing atrial enlargement, fibrosis, and conduction abnormalities to result in shorter induced AF episodes.¹⁶³⁻¹⁶⁵ More importantly, it has been suggested that its protective role can be reduced if n-3 PUFAs was

not given prophylactically.¹⁶⁶ The anti-arrhythmic mechanisms of n-3 PUFAs can include anti-inflammatory, anti-fibrotic, anti-sympathetic, anti-oxidative and pro-autonomic. Specifically, it has been shown to inhibit Ito, IKur and INa in human atrial myocytes, modulate Connexin 40 in canine atria and prolong refractoriness in human pulmonary vein and left atria.¹⁶⁷⁻¹⁶⁹ Perhaps, the beneficial effects of n-3 PUFAs are limited to specific underlying atrial substrate and at the right therapeutic window.

Anti-Fibrotic Drugs

Atrial fibrosis is an important substrate in AF and an attractive therapeutic target. This fibrosis is responsible for conduction abnormalities to favor re-entry and maintenance of AF. Pirfenidone have been shown to have broad anti-fibrotic and anti-inflammatory effects. In canine CHF atria, it reduced atrial conduction heterogeneity, fibrosis and AF vulnerability by inhibiting pro-fibrotic mediators such as TNF- α and TGF- β 1.¹⁷⁰ More recently, prevention of adverse atrial remodeling by another anti-fibrotic agent, Tranilast, has been shown in a different canine model of rapid atrial pacing and left ventricular dysfunction.¹⁷¹ However, clinical evidence are still lacking with the above-mentioned agents.

Anti-Inflammatory Agents

Inflammation is frequently implicated in different substrates of AF. However, both glucocorticoids and non-steroidal anti-inflammatory agents are also known to be pro-arrhythmic in humans.^{172,173} This is despite solid experimental evidence regarding the beneficial effects of prednisolone in rapid atrial pacing and sterile pericarditis models.^{174,175} More recently, a randomized control trial has shown that transient corticosteroids treatment after AF ablation procedure could reduce both immediate and mid-term AF recurrences as compared to placebo.¹⁷⁶ Certainly, further work is needed to define the utility of these agents in AF patients.

Role of Aggressive Risk Factor Management

In light of the limitations with current therapeutic options such as anti-arrhythmic agents, catheter ablative options and other upstream therapies, there appears to be a role for aggressive risk factor management. The same factors that underlie adverse atrial remodeling leading to AF must be actively targeted to limit progression of the abnormal substrate and reduce AF recurrence independent of standard rhythm management strategies. Here, we highlight some of these avenues available to clinicians managing patients with AF.

Weight loss

There is limited published data available currently regarding impact of weight loss on AF. In an animal study, Mahajan et al demonstrated that weight reduction was associated with reduction in total body fat, atrial size, atrial fibrosis and improved hemodynamics and atrial connexin-43 expression to result in reduced AF vulnerability.¹⁷⁷ Likewise, our group has recently presented data showing that weight loss and risk factor modification in overweight and obese patients is associated with reversal of atrial dilation, left ventricular hypertrophy and a marked reduction of AF symptoms and arrhythmia burden from Holter monitoring.¹⁷⁸

Hypertension

Antihypertensive therapy has been shown to prevent left atrial dilatation and favorable reverse remodeling. It is associated with reduction in the left atrial size and left ventricular hypertrophy

leading to a lower relative risk of AF.^{179,180} Although current consensus statements have not provided strict guidelines on blood pressure targets and evidence remains lacking regarding usage of specific class of anti-hypertensive agents, close monitoring and titration of anti-hypertensive agents to control this risk factor remain prudent.

Glycemic control

Aggressive treatment of diabetes and adequate glycemic control may prevent or delay the occurrence of AF despite little direct evidence of the effects of anti-diabetic drugs on AF. Peroxisome proliferator-activated receptor- γ agonists can offer protection against AF beyond glycemic control, due to their anti-inflammatory, antioxidant, and anti-fibrotic effects. In an animal model of AF, pioglitazone attenuate structural remodeling and had significant anti-inflammatory effect by reducing transforming growth factor TGF- β 1, TNF and extracellular signal-regulated kinase expression.⁽¹⁸¹⁾ At present, clinical data is limited to only case reports for the beneficial atrial effects of these drugs in humans.¹⁸²

Sleep Apnea

Current evidence suggests that continuous positive airways pressure (CPAP) therapy directed at OSA can lead to a reduction in AF burden. In patients with OSA, Oliveira et al demonstrated that long-term effective CPAP therapy significantly increased LA passive emptying volume and improved left ventricular diastolic dysfunction.¹⁸³ Recent studies have also shown that CPAP therapy in OSA patients was associated with higher success with pulmonary vein ablation and lower subsequent AF recurrences as compared to those not receiving CPAP therapy.^{184,185}

Conclusions:

Despite the advances in our understanding regarding the structural substrate underlying AF in various conditions, the translation of this knowledge to effective anti-AF therapy remains a challenge. Although the cure of AF remains elusive due to its complex pathophysiology, it appears that a multi-dimensional approach that include risk factors management and substrate specific therapy are necessary in addition to standard rhythm control strategies.

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