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Atrial Fibrillation: Mechanisms, Therapeutics, and Future Directions

Jason Pellman[1] and **Farah Sheikh**[*,1]

[1]Department of Medicine, University of California, San Diego, La Jolla, California, USA

Abstract

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting 1% to 2% of the general population. It is characterized by rapid and disorganized atrial activation leading to impaired atrial function, which can be diagnosed on an EKG by lack of a P-wave and irregular QRS complexes. AF is associated with increased morbidity and mortality and is a risk factor for embolic stroke and worsening heart failure. Current research on AF support and explore the hypothesis that initiation and maintenance of AF require pathophysiological remodeling of the atria, either specifically as in lone AF or secondary to other heart disease as in heart failure-associated AF. Remodeling in AF can be grouped into three categories that include: (i) electrical remodeling, which includes modulation of L-type Ca^{2+} current, various K^{+} currents and gap junction function; (ii) structural remodeling, which includes changes in tissues properties, size, and ultrastructure; and (iii) autonomic remodeling, including altered sympathovagal activity and hyperinnervation. Electrical, structural, and autonomic remodeling all contribute to creating an AF-prone substrate which is able to produce AF-associated electrical phenomena including a rapidly firing focus, complex multiple reentrant circuit or rotors. Although various remodeling events occur in AF, current AF therapies focus on ventricular rate and rhythm control strategies using pharmacotherapy and surgical interventions. Recent progress in the field has started to focus on the underlying substrate that drives and maintains AF (termed upstream therapies); however, much work is needed in this area. Here, we review current knowledge of AF mechanisms, therapies, and new areas of investigation.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting 1% to 2% of the general population (8, 64, 78, 90, 110, 143, 159, 187, 201, 253). It is characterized by rapid and disorganized atrial activation leading to impaired atrial function, which can be diagnosed on an EKG by lack of a P-wave and irregular QRS complexes. AF is associated with increased morbidity and mortality and is a risk factor for embolic stroke and worsening heart failure (26). AF can be defined as paroxysmal (converts to normal sinus rhythm within 7 days), persistent (converts to normal sinus rhythm after 7 days), or permanent (does not spontaneously convert to normal sinus rhythm) (25). As in the case of paroxysmal AF, the intermittent nature of the arrhythmia suggests there may be a higher prevalence than is

[*]Correspondence to fasheikh@ucsd.edu.

clinically observed. Numerous risk factors are associated with development of AF, though age and sex are the strongest with 2 times risk per decade and 1.5 times risk for males (8). The lifetime risk for individuals of 40 to 55 years of age is estimated between 22% and 26% (78,90).

Large-scale epidemiological studies have highlighted differences in AF presentation between men and women. Women tend to be older with a higher proportion in the 75 years or older age group and are more symptomatic at first AF presentation than men (76, 100, 145). Thus, presentation of AF in women is associated with a higher risk of stroke (42, 145). There is also evidence for sex-related differences in response to treatment. Rhythm control treatment in women is found to lead to increased morbidity and mortality compared to rate control treatments, which is not observed when treating men (200). In spite of the evidence pointing to significant sex-related differences in AF, the factors underlying these differences are still unknown and require further investigation.

The high prevalence of AF may be attributable to the various mechanisms contributing to development of the arrhythmia. Current research on AF support and explore the hypothesis that initiation and maintenance of AF requires pathophysiological remodeling of the atria, either specifically as in lone AF or secondary to other heart disease as in heart failure-associated AF. Remodeling associated changes in AF can be grouped into three categories that include: (i) electrical remodeling, which includes modulation of L-type Ca^{2+} current, various K^{+} currents, and gap junction function; (ii) structural remodeling, which includes changes in tissues properties, size, and ultrastructure; and (iii) autonomic remodeling, including altered sympathovagal activity and hyperinnervation. Electrical, structural, and autonomic remodeling all contribute to creating an AF-prone substrate which is able to produce AF-associated electrical phenomena including a rapidly firing focus, complex multiple reentrant circuit, or rotors (162). The purpose of this review is to summarize current knowledge of the mechanisms contributing to the development and maintenance AF with an emphasis on recent progress, particularly in therapy and diagnosis as well as future directions.

Historical Perspectives on Atrial Fibrillation

Numerous milestones have been achieved in understanding AF etiology and mechanisms. A number of these achievements are of particular relevance to the AF mechanisms presented in this review. A more detailed history of AF research milestones that encompass topics not in this review has been reviewed in detail elsewhere (142, 168). Since the early 20th century, AF has been recognized as the most common cardiac arrhythmia in the general population (168). The electrical conduction abnormalities associated with AF were first described by Garrey in 1924, which include the same electrical patterns currently examined today (72). In the following years, the mechanisms underlying these phenomena in AF have been more directly established. AF electrical modeling methods were vastly improved by work by Moe and colleagues in 1964 who developed the first computer based mathematical model of AF using the multiple-wavelet concept of AF which acted as a fundamental tool for analyzing electrical defects in AF (157). Starting in 1978, Coumel and colleagues established the importance of the autonomic nervous system in AF (41). Renma and colleagues established

the role of shortened conduction wavelength in 1988 which is calculated as the refractory period multiplied by the conduction velocity, for reentry in occurrence of AF (199), which serves as the basis for more recent models of reentry including the “leading circle model” and “spiral wave” concept (40). In 1995, Wijffels and colleagues made the observation that AF begets AF, which uncovered the importance of worsening atrial remodeling in AF (252). In the following years, knowledge of the role of atrial remodeling in AF has quickly expanded and is reviewed in subsequent sections.

Various experimental (Table 1) and transgenic (Table 2) animal models have been generated to investigate AF, which have been summarized in this review. Early models have depended on the use of large animal models to induce AF via electrical or surgical intervention, while more recent studies have included use of numerous transgenic mouse models to investigate specific pathways identified in AF. Although transgenic mouse models have paved the way to determining the specific contributions of relevant pathways in AF, limitations imposed by the lack of atrial specific promoters to drive gene ablation and overexpression in the heart have tempered the conclusions within these models.

Genetics Play a Role in Atrial Fibrillation

Numerous risk factors contribute to AF, including genetics. Lone AF was first documented within a family in 1936 by Orgain and colleagues who described three brothers presenting with AF (178), and in 1943 AF was first documented in a heritable autosomal dominant pattern by Wolff (255). It was not until 1997 until direct evidence of familial AF was established using linkage analysis identifying a locus between D10S1694 and D10S1786 at 10q22-q24 in families with early onset AF, although the causative gene at this locus is still unknown (20). In 2003, Chen and colleagues identified the first mutation in a gene associated with familial AF, as a gain of function mutation in KCNQ1 which codes for the α-subunit of the slowly repolarizing potassium current, I_{KS} (36). Since these initial discoveries, multiple genes associated with development of AF have since been identified.

Numerous potassium channel mutations have now been associated with AF. These include KCNQ1 (14,15,48,88,116,148), KCNA5 (39,176,261,262), KCND3 (174), and KCNJ2 (52,258). In addition to mutations in the channels themselves, mutations in channel accessory proteins are also associated with AF, including KCNE1 (173), KCNE2 (263), KCNE3 (147), and KCNE5 (196). The majority of mutations in these proteins are thought to increase channel activity, which would decrease action potential duration and refractoriness in the atria (250). Mutations that reduce channel activity can prolong atrial action potentials and lead to early afterdepolarizations and AF (131).

Mechanisms Underlying Atrial Fibrillation

AF occurrence is dependent upon complex electrical defects in the atria which include a rapidly firing focus, complex multiple reentrant circuit, or rotors (162). Alterations in after-depolarization, both early and late, can contribute to ectopic atrial foci (185, 247). Reentrant waves can occur due to reduced refractoriness, slow conduction, and conduction barriers (162,212,247,250). Rotors, or localized electrical spiral waves, are a result of complex

substrate changes leading to a stable disease wave. These electrical defects are dependent upon remodeling mechanisms, which can be grouped into electrical, structural, and autonomic remodeling that allow for initiation and maintenance of AF (Fig. 1). In the following sections, we describe the prevailing mechanisms leading to AF in relation to the aforementioned electrical defects.

Electrical remodeling

One of the most characterized mechanisms driving AF is the electrical remodeling occurring in atrial cardiomyocytes. Various types of ionic currents have been found to change in AF and, through animal models, to contribute to its development. The ionic currents include the L-type Ca^{2+} current (35, 56, 163, 164, 214, 245, 250) and inward rectifier K^+ currents (55, 111, 132, 183, 246, 248). Gap junction function, specifically connexins 40 and 43, has also been linked to lone AF, though this may have broader effects on conduction (82,102).

Alterations in Ca^{2+} handling in the atria can contribute to both development and worsening of AF. Numerous studies have shown the connection between altered calcium handling and delayed afterdepolarizations, which contribute to formation of ectopic foci and AF initiation. In cardiomyocytes, intracellular calcium is stored in the sarcoplasmic reticulum (SR) until its release is triggered by specific stimuli. In AF, unwarranted calcium release can be triggered by ryanodine receptor (RyR) hypersensitivity or SR Ca^{2+} overload. Both RyR hyperphosphorylation and mutations have been shown to increase Ca^{2+} sensitivity. Data from mouse models also support the role of excessive RyR activation in development of AF (35, 214). This is also reflected in patients harboring activating mutations in RyR that exhibit catecholaminergic polymorphic ventricular tachycardia and AF (114, 232, 269). Mice specifically lacking the RyR stabilizing subunit FKBP12.6 exhibit SR Ca^{2+} leaks and increased susceptibility to AF (228). AF itself can also promote calcium handling defects, as has been observed in chronic AF patients who display activation of the Ca^{2+} calmodulin-dependent protein kinase type II (CaMKII) leading to phosphorylation of RyRs (56,164,245,250). Studies in isolated canine atrial cardiomyocytes have revealed detrimental effects of tachypacing on calcium handling (191). As atrial depolarization rates increase, intracellular Ca^{2+} begins to accumulate, leading to activation of calcineurin/NFAT signaling, which in turn leads to reduced transcription of Cav1.2 L-type calcium channel (CACNA1C), ultimately leading to reduced L-type Ca^{2+} current (191). Animal models have shown this leads to a reduced action potential duration and atrial effective refractory period, which favors reentrant waves (210, 267). Similar results have also been observed in isolated human atrial myocytes (38, 242), supporting the role for reduced L-type Ca^{2+} current in human AF.

Increased K^+ currents are intimately associated with electrical remodeling in AF. The inward rectifier K^+ currents (I_{K1}, and $I_{K,AcH}$, basal, and acetylcholine dependent, respectively) are increased in AF which alters resting potential and phase 3 activation, leading to reduced atrial refractoriness and wavelength (55, 77, 111, 132, 246, 248). This mechanism has also been supported by in vitro data showing increased magnitude of inward rectifier K^+ currents stabilizing reentrant currents (183). The elevated K^+ currents observed in AF are likely due to upregulation of the Kir2.1 channel, a major channel protein for I_{K1} current, which has specifically been shown to be affected in AF (33, 59, 70, 246). It has been hypothesized that

regulation of Kir2.1 is controlled by miRNA targeting Kir2.1, specifically miR-1 and miR-26, which are reduced in AF (77, 149). Thus in AF, loss of miR-1 and miR-26 would lead to increased K^+ channels and current, leading to reduced atrial refractoriness and wavelength and ultimately allowing for reentrant waves.

Gap junction function is also affected in AF (102). Gap junction function is directly related to conduction velocity, which is a known determinant of AF. Specifically, slower conduction velocity favors reentry, allowing for initiation and maintenance of AF. From clinical studies, GJA5, which codes for connexin 40, has been linked to idiopathic AF (82). Heterogeneous connexin 40 distribution has also been observed in large animal models of AF, specifically in goats undergoing endocardial burst pacing, suggesting that connexin 40 remodeling is involved in maintenance of AF (241). In dogs undergoing atrial tachypacing, connexin 40 has been shown to decrease in the pulmonary vein (270), a region shown to be an important site for reentrant waves. Furthermore, mutations in the GJA5 promoter sequence have been associated with AF vulnerability through human clinical studies (67). Somatic mutations in GJA1, which codes for connexin 43, have been observed specifically in the atria, a phenomenon referred to as genetic mosaicism (237). The mutant connexin 43 contributes to heterogeneous electrical conduction, which favors reentrant waves and ultimately leads to AF. The gap junction inhibitory peptide, rotigaptide, has been used in dog models of AF to varying degrees of success. Rotigaptide was shown to have beneficial effects on AF in the setting of acute ischemia but not when caused by ventricular or atrial tachypacing (222), suggesting that gap junction inhibition may only be necessary for specific stages or etiologies of AF, as reflected in its varying roles in different experimental models of AF.

Electrical changes in the heart, as would be expected based on the principles of excitation-contraction coupling, lead to secondary changes in contractile function in the atria (85, 211). This is broadly demonstrated by the association of chronic AF with atrial contractile dysfunction (18), which has been observed as a reduction in maximum tension as well as in the rates of tension activation and relaxation. These effects have been linked to increased myofilament sensitivity to Ca^{2+}, possibly due to changes in myofilament phosphorylation (251). These effects are also accompanied by a reduction in myofibril passive tension, potentially caused by upregulation of slow beta-myosin heavy chain isoform and the more compliant titin isoform N2BA (251). However, these myofibril alterations may be related to specific mechanisms of AF development, as a dog model of AF induced via atrial tachycardia developed hypocontractile atria (251) while other models of AF have reported no changes in myofibril properties (101). Recent studies have also identified a role for inositol-1,4,5-trisphosphate-receptor (IP3R)-mediated $Ca2^+$ release in AF-related contractile defects which may represent a mechanism independent of myofibril alterations (138, 140).

Structural remodeling

Structural remodeling is perhaps the most obvious change in the atria that occurs in AF. These effects are characterized by changes is tissue properties (most notably fibrosis), atrial size, and cellular ultrastructure. These types of changes predispose the atria to defects in conduction predominantly contributing to reentry and rotor formation.

Various factors contribute to the fibrosis underlying AF, including cell stretch, neurohumoral activity, oxidative stress, and even AF itself can contribute to worsening tissue properties (32, 119, 264). Atrial fibrosis is a salient feature of a majority of animal models of AF, including aging (57), myocardial infarction (MI) (169), volume overload (53), endurance exercise training (84), and tachypacing-induced HF (21,29,134,231). Conversely, numerous animal models of atrial fibrosis exhibit increased susceptibility to AF (160,259). Specific profibrotic signaling molecules are associated with atrial fibrosis and AF including Angiotensin II, aldosterone, and TGF-β1 (60,83,197).

Angiotensin II functions in the renin-angiotensin-aldosterone system (RAAS) and increases in activity have previously been associated with increased cardiac fibrosis (118). Goette and colleagues showed increased levels of angiotensin-converting enzyme (ACE) in AF and corresponding increased levels of activated extracellular signal-regulated kinase 1 and 2 (ERK1/2), consistent with increased RAAS activity (80). Conversely, treatment with candesartan, an angiotensin receptor blocker, reduces the profibrotic effects of rapid atrial pacing induced AF and reduces propensity for AF (125). Similar results were also observed with the ACE inhibitor enalapril. In dogs with ventricular tachypacing-induced congestive heart failure (CHF), atria exhibit conduction slowing, fibrosis, and propensity for atrial burst-pacing induced AF, which occur along with increased atrial concentration of angiotensin II. With enalapril treatment, all of these features are attenuated, supporting the importance of RAAS signaling in developing AF features (29,135,220).

Aldosterone, another important mediator of RAAS signaling that binds to the mineralocorticoid receptor (MR), has also been linked to atrial fibrosis and AF (19, 233, 240). Blockade of aldosterone signaling at the MR via spironolactone improved morbidity and mortality in AF patients (188), suggesting an important role for aldosterone in AF. Another MR blocking drug, eplerenone, has also been successfully used to prevent recurrence of AF after catheter ablation (103). The effects of MR blockade on atrial fibrosis have not been directly examined in patients; however, data from animal and cell-based models of AF have demonstrated reductions in cardiac fibrosis following treatment with MR blockers (120,126,127,274).

TGF-β1 is another profibrotic molecule upregulated in AF, as demonstrated in animal models of AF (30,129) as well as in clinical studies on patients with AF (139,193). TGF-β1 is an established positive regulator of cardiac fibrosis and its specific overexpression in the heart leads to atrial fibrosis and increased susceptibility to AF (54, 58), suggesting that TGF-β1 is sufficient for developing an AF-prone substrate (193). However, the determinants of increased TGF-β1 expression in the heart during AF are still unknown.

Evidence from genetic models of cardiac fibrosis suggest that the atria are particularly sensitive to profibrotic signaling potentially due to increased response of atrial fibroblasts compared to ventricular fibroblasts (22). This may be related to the cases of atrial fibrosis without ventricular fibrosis in patients with lone AF (68). This has been further explored in transgenic mouse studies overexpressing either ACE or a constitutively active TGF-β1 mutant protein in the heart (160, 259). Both of these models lead to fibrosis only in the atria.

MicroRNAs have also been linked to control of atrial fibrosis leading to AF. miR-21 knockdown suppressed the development of an AF substrate in a rat model of post-MI HF (28). This is hypothesized to occur via miR-21's role in regulating Sprouty-1 levels, which negatively regulate ERK 1/2 activity, which then inhibits fibroblast density (28,238).

The mechanism by which fibrotic tissue serves as a substrate for AF has been examined in detail. Cardiomyocytes in fibrotic atria are more distantly separated than those in nondiseased atria, with the fibroblasts and ECM essentially forming a physical conduction barrier (21). This reduces electrical coupling between cardiomyocytes and provides susceptibility to reentry (21, 134, 230). There is also an increase in fibroblast proliferation in AF and as with other disease states, their proliferation in AF is linked to increases in myofibroblast phenotype (268). Interactions specifically between myofibroblasts and cardiomyocytes have previously been shown in cocultures to negatively affect conduction organization leading to increased propensity to ectopic activity and reentrant arrhythmias (155,277). Fibroblast-myocyte interactions increase, which in turn alter conduction via fibroblast's function as electric sinks and paracrine activity (268), leading to conduction slowing, depolarization of cardiomyocyte resting potential, variable effects on action potential duration, and the induction of spontaneous phase-4 depolarization all of which predispose to reentry and ectopy (104,150).

From early on in the history of AF research, increased atrial size has been known to favor AF (71, 92). Reentrant circuits form more readily with larger atrial size, potentially due to the additional area available for rotor formation as demonstrated in computer modeling studies (278). Animal models (50, 123, 165), as well as clinical data support this idea (51,95,153). Atrial size may also indirectly affect tissue properties, since it can be a sign of increased atrial stretch, which is generally associated with increased tissue remodeling in the atria (108).

Structural remodeling changes in AF also occur at the ultrastructural level. Numerous defects in cardiomyocyte ultrastructure have been observed in AF including myolysis, glycogen accumulation, as well as changes in nuclear chromatin, mitochondrial disruption and redistribution as well as SR alterations (12,13). Gap junction localization heterogeneity, specifically of connexin 40, is also observed in AF models (241). Interestingly, many of these changes can partially revert back to normal after restoration of sinus rhythm. In a goat model of burst pacing-induced AF, typical ultrastructural defects appear after 4 months of AF, but after restoration of normal sinus rhythm for 2 months myolysis, glycogen accumulation, and mitochondrial defects are improved and nuclear chromatin defects are completely normalized (12).

Autonomic remodeling

The autonomic nervous system exerts significant control of cardiac electrophysiology, and defects in autonomic function have been associated with AF (217). The heart is extensively innervated by the autonomic nervous system by both extrinsic (ganglia outside the heart) and intrinsic (ganglia inside the heart) nervous tissue. The extrinsic nerves include the vagal nerve and nerves arising from the paravertebral ganglion, which includes the thoracic

ganglion, cervicothoracic ganglion, middle cervical ganglion, and the superior cervical ganglion (10,106,113).

There is extensive evidence of autonomic dysfunction reflected as increased sympathetic activity in AF observed in various types of large animal AF models. In a dog model of pacing-induced AF, heterogeneous increased sympathetic enervation has been observed in the atria (34,107). In ventricular MI-associated AF, atrial nerve sprouting and sympathetic hyperinnervation have been observed (6,11,166,167,243). In a pacing-induced CHF model of paroxysmal AF, increased autonomic nerve activity was observed (172). Sympathetic innervation of the atria appears to be particularly sensitive to pacing, as observed in an intermittent left atrial tachypacing model which causes sympathetic hyperinnervation, paroxysmal AF, and paroxysmal atrial tachycardia (235). The role of sympathetic innervation is further supported by the observation that simultaneous sympathovagal discharge commonly precedes AF (215, 235). Autonomic changes have also been observed in smaller model systems such as in rats where endurance exercise increased AF susceptibility in the context of autonomic changes, atrial dilation, and fibrosis (84). This effect is also paralleled in humans by the increased prevalence of AF in endurance athletes (229). Though there is much evidence of autonomic remodeling occurring, there is less data directly testing the role of autonomic remodeling on development and progression of AF, though there is suggestion that the increased sympathetic activity leads to heterogeneous changes in atrial refractoriness which in turn favor reentrant waves (117,175).

Ablation of various autonomic innervation sites has revealed the necessity for their function in the maintenance of AF. Cryoablation of atrial sympathetic nerves has been used in a dog model of pacing-induced heart failure as well as in patients with long QT syndrome to moderate success (213, 235). Vagal nerve stimulation has been effective in suppressing induction of AF in an induced model of AF (137, 218, 219, 266). Innervation by nerves beside the vagal nerve has also been explored to similar results. Ablation of the ganglionated plexus can also improve long-term AF symptoms (112,189,209,272,275). This has also been shown with specific denervation of the pulmonary vein (184). Renal sympathetic denervation has also been shown to improve AF features, however this may also affect nonautonomic mechanisms such as RAAS signaling (4, 96, 141). Somatic sensory modulation via low level stimulation to the tragus nerve of the ear has also been shown to improve early stages of AF; however, the mechanism by which this occurs is currently unknown (265). Based on these studies, autonomic innervation appears to function as an exacerbating factor in AF as ablation improves AF severity and delays onset; however, it is unable to prevent or reverse AF, suggesting that the targeted forms of autonomic remodeling are not required for AF.

Therapeutic Approaches for Atrial Fibrillation

Current management for AF includes the use of rate and rhythm control strategies as well as surgical interventions with the goal of controlling symptoms (256). Therapeutic strategies targeted to pathophysiological processes underlying structural changes associated with AF (referred to as “upstream therapies”) are also being exploited as they have potential to prevent the occurrence or recurrence of AF by slowing (and in some cases, preventing) the

progression of atrial and left ventricular remodeling (207). Anticoagulants are also prevalently used as blood stasis can develop in the atria as a result of AF, which increases the risk of thromboembolic events such as stroke (7,49). Decisions on the strategies to use are primarily dependent on the age, degree of symptoms, and presence of underlying heart disease exhibited by the patient (256).

Rate control

Rate control strategies are thought to be useful in older AF patients (>65 years of age) in chronic settings that have limited symptoms as they control cardiac ventricular rate by targeting the atrioventricular node (AVN), a key conduction system structure of the heart that transmits electrical signals from the atria to the ventricles (91). These include β-adrenergic receptor blockers, nondihydropyridine calcium channel blockers and digitalis glycosides, which prolong AVN refractoriness (slow conduction velocity) by ultimately decreasing sympathetic tone or circumventing Ca^{2+} overload to slow ventricular rate at rest and during exercise without converting the heart to a regular rhythm (7,79,180,226,239). Digitalis is not as effective as β-adrenergic receptor blockers and calcium channel blockers as a monotherapy due to its slower onset and weaker potency (63). However, combinatorial uses with β-adrenergic receptor or calcium channel blockers have proven advantageous for rate control (63). For patients exhibiting AF in the setting of CHF, rhythm control drugs that exhibit β-adrenergic receptor blocking properties (e.g., amiodarone and dronedarone) are beneficial in slowing ventricular rate, especially when patients are intolerant to conventional rate control drugs (181). Thus, controlling ventricular rate in AF not only decreases the risk of tachycardia-related symptoms (palpitations) and cardiomyopathy associated with a rapid heart rate but can also alleviate heart failure symptoms by lengthening diastole (61). However, there remain some risks as rate control drugs can slow the heart rate too much, which can then result in complications such as sinus bradycardia and heart block (27). Patients exhibiting and prone to these symptoms, which include elderly patients, may require interventions such as permanent pacemaker implantation and AVN ablation in these cases to regain control of ventricular rate (27). Based on the principles behind rate control strategies, these drugs are also contraindicated (digitalis and calcium channel blockers) or to be used with caution (β-adrenergic receptor blockers) in AF patients exhibiting preexisting cardiac conduction abnormalities and syndromes (e.g., Wolff-Parkinson-White syndrome where an additional abnormal electrical conduction pathway distinct from AVN can cause preexcitation of the ventricle) as they can exacerbate conduction abnormalities and deleterious AF symptoms (7).

Rhythm control

Noninvasive rhythm control strategies seek to convert the heart to sinus rhythm (“cardioversion”) by using antiarrhythmic drugs (“pharmacological cardioversion”) and direct electrical currents (“electrical cardioversion”) (7) (Table 3). They are thought to be useful for patients intolerant to rate control or patients with persistent symptoms in the face of adequate rate control (276). Clinical assessments also favor younger aged patients (<65 years of age), patients with recent onset as well as patients with limited underlying heart disease since AF exacerbates atrial as well as ventricular remodeling (256, 276). The most effective rate control drugs include Class Ic and IIIc antiarrhythmic drugs (Singh and

Vaughan-Williams classification) (256). Class Ic drugs include flecainide and propafenone, which are recommended for patients with paroxysmal AF; however, their use is contraindicated for AF patients with underlying structural heart disease due to increased risk of ventricular arrhythmias and atrial flutter (7,144,256). Class IIIc drugs include ibutilide, dofetilide, amiodarone, and sotalol, which are recommended for patients with persistent AF but also found to benefit AF patients with structural heart disease; however, they harbor some proarrhythmia risk to Torsade des pointes and ventricular arrhythmias as well as greater toxicities (7,256,276). Overall, antiarrhythmic drugs work by blocking the sodium, potassium as well as calcium channels and/or adrenergic receptors (Table 3). In general, the mechanisms of action for class Ic largely differ from class IIIc based on the ion channels they target. Class Ic largely exert their effects by blocking sodium channels ("membrane-stabilizing agents"), to reduce the rate of rise of the action potential, thereby reducing excitation of the cardiac tissue (276). Class IIIc antiarrhythmic drugs largely exerted their effects by potassium channel blockade and prolonging action potential duration and refractoriness by lengthening the QT interval and thus, delaying conduction (276). Despite these categorizations, it is evident that many rhythm-control drugs impact AF by targeting ion channels and adrenergic receptors outside of their categorized class (276). For example, the most effective and commonly prescribed drug for AF is the class III drug, amiodarone, which is known to block multiple channels (276). However, caution should be taken when using amiodarone as it can potentiate the effects of anticoagulant drugs based on direct interactions with enzymes (e.g., CYP2C9) involved in drug metabolism and thus, requires surveillance for toxicity effects (66).

Direct current cardioversion is also routinely used as a method to restore sinus rhythm and is thought to be particularly useful in AF patients experiencing rapid tachycardia and hemodynamic instability or when there is a relapse in the occurrence of AF (7) (Table 3). The principles stem from disrupting the aberrant atrial electrical impulses and conduction that is associated with AF, which can result in fibrillatory conduction and multiple reentrant circuits (162). AF patients treated with anticoagulant therapies are subjected to electrical currents (monophasic or biphasic waveforms) via metal pads or patches that are synchronized with the *R* wave of the QRS complex to depolarize the atrial tissue (endocardium) that harbors the reentrant circuits (133). As a result, the circuits no longer propagate or sustain reentry because the atria essentially become refractory (133). Two randomized clinical trials have highlighted the benefits of biphasic (low-energy, current flows in both directions) versus monophasic (high-energy, current flows in one direction) waveform electrical currents in AF treatment (156,182). Predictors thought to sustain normal sinus rhythm following successful electrical cardioversion include patients (i) exhibiting early onset of AF, (ii) exhibiting minimal atrial remodeling (left atrial size of <4.5 cm in diameter and left atrial volume index of <30 mL/m^2), (iii) lacking underlying heart disease (e.g., rheumatic disease, LV dysfunction), (iv) using antiarrhythmic drugs, and (iv) harboring minimal electrophysiological defects (*P* wave durations of <135 ms) (1).

Rhythm control can also be achieved by invasive ablation techniques, which are typically used in symptomatic AF patients that are intolerant to conventional rhythm control strategies or when rhythm control drugs are ineffective or toxic (256). The AF treatment with the highest rate of success is the open-heart surgery ablation technique termed Cox-Maze

procedure, which interrupts multiple reentrant circuits and fibrillatory conduction by a series of complex biatrial surgical incisions ("cut-and-sew techniques") that create barriers at critical locations resembling a maze to prevent sustained AF (43, 45, 46). However, the complexity of the technique, need for prolonged cardiopulmonary bypass as well as lengthy operation times and increased risk for bleeding have prevented it from being widely adopted and is thus, preferentially utilized in patients already undergoing cardiac surgery (69). Modifications of the technique have been implemented to simplify the procedure, which also included exploiting alternative energy sources such as radiofrequency, cryothermal, and microwave energy as a means to create lines of scar (69). Through these efforts, radiofrequency ablation has proven to be efficacious in AF patients (74). Modifications also included the need for less invasive procedures, which gave rise to catheter ablation techniques where no incisions are needed and where catheters are inserted via the groin or neck to target the area of ablation (69). Pioneering studies by Jais and colleagues localized the triggering source of AF to the pulmonary veins (PV) (87,105), which then lead to PV antral isolation (or wide-area circumferential isolation) as the most efficacious AF ablation approach (23, 256). Radiofrequency ablation of this region not only includes the PV but also surrounding regions (left atrial roof and posterior wall and right interatrial septum), which has been shown to lead to a higher success rate and lower complication rate for AF treatment (109). Current approaches do not target the ostia (opening to PV) as their ablation have been previously associated with complications related to pulmonary stenosis (69). Modifications of these catheter ablation procedures have been adapted to include isolated or other ectopic regions in and around the PV, which include procedures such as: (i) PV segmental ostium ablation that includes less of the antrum and incomplete ablation around the vein (ii) linear ablation is used to create ablation lines of scar along the atrial roof and mitral annulus but both are associated with an increased risk of atrial flutter, (iii) complex fractionated electrogram ablation targets specific sites with an unusual electrical pattern that represents macro reentry sites surrounding the PV (iv) ganglionic plexi ablation targets nerves that control autonomic function, and (v) rotor ablation targets electrically mapped and organized reentrant circuits surrounding the PV (256).

Data from several clinical trials have revealed that there are no mortality benefits to rhythm when compared to rate control drugs (31,97,203,257). However, these findings were tempered as they were restricted to patients between the ages of 60 to 80 years (thus excluding the young and elderly populations) and included use of antiarrhythmic drugs with high toxicities as well as patients with excessive stroke risk that had been taken off of anticoagulant therapy, potentially limiting their potential for success (276). Thus, it remains to be determined whether current rhythm control strategies, which now include newer antiarrhythmic drugs and surgical interventions will tip the scale towards favoring these strategies for the treatment of AF in the future.

Upstream therapies

Intense scientific interest has focused on strategies "upstream" of the electrophysiological defects associated with AF as they are thought to target the anatomical substrate in AF, which include the structural alterations associated with atrial and ventricular remodeling (e.g., inflammation, cell death, oxidative stress, hypertrophy, and fibrosis) (207, 256). Major

pharmacotherapies that target these pathways include: (i) RAAS inhibitors [angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and aldosterone inhibitors (e.g., spironolactone)], (ii) statins, and (iii) polyunsaturated fatty acids (207, 256). RAAS inhibitors are thought to have beneficial effects on AF through pleiotropic actions that circumvent the deleterious actions of increased renin, angiotensin II, and aldosterone. Some of these effects include: prevention of left atrial dilation and fibrosis, regression of left ventricular hypertrophy, reduction of oxidative stress, and inflammation as well as modulation of sympathetic nerve activity and ion-channel function; although indirect effects on gap junction coupling and calcium handling have also been noted (69, 256). Data from clinical trials exploiting ACEI and ARBs in AF settings have been mixed especially in terms of the recurrence or secondary prevention of AF (207). However, ACEI and ARBs did exhibit potential for primary prevention of new onset of AF in hypertensive patients with left ventricular hypertrophy and symptomatic heart failure as well as MI following retrospective analyses (89, 152, 177, 186, 249). Use of the aldosterone inhibitor, spironolactone has also been associated with reduction of AF occurrence in AF patients with structural heart disease in a retrospective study; however, larger randomized controlled trials are needed to more robustly determine their effectiveness as a treatment for AF (254). Statins have also been associated with decreasing the incidence and recurrence of AF in patients (62, 225, 256). Although the precise mechanisms underlying these actions are not clear, it is thought that statins exert anti-inflammatory effects, antioxidant effects, plaque stabilizing properties (to reduce atherosclerotic disease which is a risk factor for AF), and antiarrhythmic effects by directly modulating ion channel function (69). Dietary intake of polyunsaturated fats (e.g., fish oil) can also influence the development of postoperative AF following coronary artery bypass surgery (24). It is hypothesized that they may alleviate AF by exerting antiarrhythmic effects by directly modulating ion channels as well as anti-inflammatory effects (24). A better understanding of the underlying mechanisms associated with these strategies is clearly needed. Future avenues focused on disease-specific mechanisms underlying fibrosis (via inhibition of TGF-β1), increased oxidative stress (via calcium/calmodulin-dependent protein kinase III inhibition), and decreasing gap junction uncoupling could provide for better therapeutics as they highlight more targeted approaches to circumvent the pathophysiological processes associated with the AF substrate (256).

New Areas of Investigation in Atrial Fibrillation

One of the newest areas of investigation in the area of AF includes the development of atrio-selective drugs to limit toxicities and proarrhythmia risk to the ventricle, as these are adverse effects encountered with current antiarrhythmic drugs used for rhythm control in AF. Recent studies have identified the selective expression and function of the ultrarapid delayed rectifier channel, I_{Kur}, and acetylcholine (ACh)-activated K^+(K_{ACh}) channel in the atria but not ventricular tissue (69,151). More specifically, blockers for $I_{K,Ach}$ (NTC-801) and I_{Kur} (NIP-142, RSD1235, and AVE0118) show promise as they could convert AF to normal sinus without having adverse effects on the ventricles (69,151), highlighting their potential as strong candidates for AF treatment in humans in the future. Gene therapy based approaches have also been exploited to target autonomic (acetylcholine)-based mechanisms to more specifically target autonomic substrate and AVN and provide alternative therapeutic

approaches for AF (5,16). More specifically, genetic manipulation of intracellular signals associated with muscarinic cholinergic receptor type 2 (adenoviral-mediated overexpression of constitutively active Gαi in the AV node or nonviral minigene-overexpression of Gαi and Gαo in left atrium) that is targeted by vagally released acetylcholine, were shown to decrease ventricular rate and prevent vagally induced AF, respectively (5, 16). Thus, efforts directed at targeting mechanisms that are atrial-selective and more specifically interrupt or reverse pathophysiology and substrates underlying AF clearly show promise for the future. Recent efforts have also suggested that localized applications of the antiarrhythmic drug, amiodarone, on the atrial epicardium via adhesive hydrogels can be used to reduce risk of AF postoperatively thereby minimizing risks of reported side effects (65), also highlighting the potential importance of exploiting bioengineering approaches to better tailor current therapies for AF.

New areas of research aimed at identifying sensitive ways at imaging the atria and AF are also on the horizon as they have the potential to significantly improve AF diagnosis and treatment strategies. Magnetic resonance imaging is emerging as a noninvasive tool to more precisely map and quantify structural (fibrotic) changes in the left atria as a means to explore left atrial substrate and determine the extent of low voltage tissue, which can help guide ablation therapies as well as decisions on the type of treatment strategies to be used on the patient (17,170). Three-dimensional rotation angiography is also being explored as an alternative technique to gain precise anatomy of the left atria prior to catheterization ablation and may provide advantages over CT scanning based on the low radiation exposure and ability to use contrast medium (130). Noninvasive electrocardiographic body surface imaging and computational modeling-based approaches are also being exploited as novel tools to precisely map atrial conduction and activation patterns in AF to better understand electrophysiological-based mechanisms underlying AF and improve ablation outcomes (47,161). These studies altogether highlight strategies to better diagnose and further stratify AF into subtypes based on anatomical defects to potentially allow for better therapeutic management of AF in patients.

Conclusion

AF is a complex disease that is fueled by the structural alterations (substrate) in the atria that consequently result in complex electrophysiological defects and patterns that render the atria and autonomic system dysfunctional, which then lead to a vicious cycle of exacerbated atrial and ventricular remodeling events (electrical, structural, and autonomic) that promote and maintain AF. Current therapeutic strategies are dedicated to the control of ventricular rate and conversion to sinus rhythm through pharmacotherapies as well as chemical and electrical (direct current and ablation therapy) cardioversion techniques, respectively, to circumvent AF symptoms. However, based on the limited efficiencies and toxic side effects of current strategies as well as some understanding of the substrates propagating AF, research and therapies have now also been directed to identifying and testing strategies that selectively target the atria (atrial selective agents and pathways) and substrates (upstream therapies) underlying AF. Strategies to modify current therapeutics to minimize toxicities (e.g., amiodarone adhesive hydrogels) and complexities of ablation (e.g., hybrid ablation techniques) are also important (65,256). A major focus of future directions for AF is also

dedicated to improving technologies to better stratify AF into subtypes through the use of imaging diagnostics (magnetic resonance imagine, three-dimensional rotation angiography, anatomical body surface imaging), genetics and biomarkers (256). Recent studies have also suggested that a new taxonomy may be required based on pathophysiology of the AF subtype to allow for personalized management of AF to be realized in the future (121,256).

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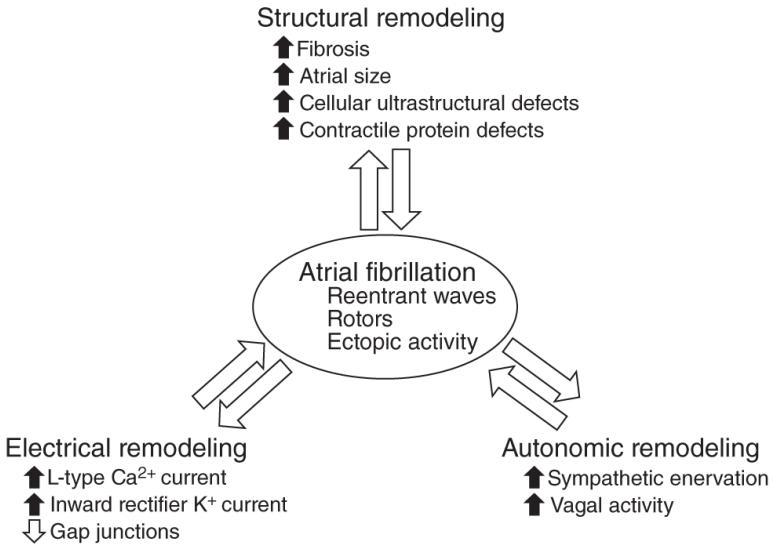

Figure 1.

Diagram representing the major types of remodeling (electrical, structural, and autonomic) that lead to AF.

Table 1

Experimental Animal Models of Atrial Fibrillation

Experimental model		Mechanisms of AF explored	Species	Reference(s)
Stimulation, disease, and injury-based strategies				
Rapid atrial pacing	Burst pacing or chronic pacing	Fibrillation-induced remodeling	Dog, goat, pig, sheep	(9, 73, 192, 252)
Cardiovascular disease-induced AF	Heart failure (rapid ventricular pacing)	Heart failure-induced remodeling	Dog, sheep, rabbit	(134, 190, 221)
	Sterile pericarditis	Postoperative AF	Dog	(179)
	Mitral regurgitation	MR-associated AF	Dog	(44)
	Volume overload	Chronic atrial stretch	Dog, goat, sheep, rabbit	(53,93,198,223)
	Hypertension	Hypertension	Sheep, rat	(37, 122)
Acute atrial insult	Aconitine	Electrical remodeling	Dog, sheep	(216)
	Direct left atrial dilatation	Acute atrial stretch	Dog rabbit	(195, 227)
	MI	MI-induced remodeling	Dog	(224)
Autonomic modulation	Autonomic stimulation	Autonomic remodeling	Dog, sheep	(75, 81, 234)

Table 2

Transgenic Mouse Models Targeting Disease Mechanisms Associated with Atrial Fibrillation

Transgenic mouse model	Mechanism	AF features observed	Reference(s)
Constitutive TGF-beta1 activation	Elevated profibrotic signaling	Atrial fibrosis, AF inducibility	(244)
ACE overexpression		Atrial enlargement, atrial fibrosis, AF	(259)
JDP2 overexpression		Atrial dilatation	(115)
Rho-A overexpression	Cardiac disease associated AF	DCM, atrial dilation, bradycardia, AV block, HF, AF	(205)
Junctin overexpression		DCM, atrial dilation, bradycardia, enlarged left ventricle, AF	(98)
MURC overexpression		Atrial dilation, AV block, AF	(171)
TNF-a overexpression		DCM, atrial fibrosis, HF, AF	(204, 208)
CREM overexpression		HCM, atrial enlargement, atrial and ventricular hypertrophy; AF	(158)
Juncate-1 overexpression		HCM, atrial enlargement, ventricular hypertrophy, bradycardia, AF	(99)
Rac1 overexpression		HCM, AF	(2)
HopX overexpression		HCM, atrial fibrosis, AF inducibility	(146)
Constitutively active Gaq		HCM, left atrial dilatation, and fibrosis; AF under anaesthesia	(94)
Connexin 40 knockout	Electrical remodeling	AF inducibility	(86)
Kir2.1 overexpression		Bradycardia, PVCs, AV block, AF	(136)
Cav1.3 knockout		Bradycardia, AV block, atrial flutter, AF	(154, 273)
KCNE1 knockout		AF	(236)
NUP155 heterozygous knockout		AF	(271)
KCNE1-KCNQ1 fusion protein overexpression		AF inducibility	(206)
FKBP12.6 knockout		AF inducibility	(228)
R176Q mutation of RYR2; RYR2-S2814A knock-in		Increased AF inducibility with R176Q mutation; decreased AF inducibility with S2814A mutation	(35)

Table 3

Mechanism of Action of Recommended Rhythm Control Strategies for Atrial Fibrillation

Rhythm control strategies	Singh and Vaughan-Williams classification	Mechanism of action	Reference(s)
Pharmacological cardioversion			
Flecainide	Class Ic	Blocks fast inward sodium channel to reduce rate of rise of AP depolarization and contractility Selectively effects cells with high rates	(194)
Propafenone	Class Ic	Blocks fast inward sodium current to reduce rate of rise of AP depolarization and contractility β-adrenergic receptor blocking properties	(69)
Ibutilide	Class IIIc	Blocks the delayed rectifier outward potassium current and enhances the slow inward sodium current which both prolong AP duration and conduction	(128, 260)
Dofetilide	Class IIIc	Selectively blocks the delayed rectifier outward potassium current to prolong AP	(202)
Sotalol	Class IIIc	Blocks the delayed rectifier outward potassium current to prolong AP β-adrenergic receptor blocking properties	(3)
Amiodarone	Class IIIc	Multi-channel blocker that effects inward sodium and calcium channels as well as repolarizing outward potassium channels, which ultimately causes prolongation of the repolarization phase of the AP and conduction α- and β-adrenergic receptor and blocking properties	(124)
Electrical cardioversion			
Direct current (monophasic or biphasic waves)	Not applicable	Block reentrant electrical circuits by depolarizing atrial tissue using high voltage (monphasic waves) or low-voltage (biphasic) electrical currents to make atria refractory	(133)
Ablation therapy	Not applicable	Block reentrant electrical circuits by making lesion/scar lines in and around the pulmonary veins	(256)