Circulation Research Compendium on Atrial Fibrillation:

Stanley Nattel, Guest Editor

Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance, and Progression

Jordi Heijman,* Niels Voigt,* Stanley Nattel, Dobromir Dobrev

Abstract: **Atrial fibrillation (AF) is the most common clinically relevant arrhythmia and is associated with increased morbidity and mortality. The incidence of AF is expected to continue to rise with the aging of the population. AF is generally considered to be a progressive condition, occurring first in a paroxysmal form, then in persistent, and then long-standing persistent (chronic or permanent) forms. However, not all patients go through every phase, and the time spent in each can vary widely. Research over the past decades has identified a multitude of pathophysiological processes contributing to the initiation, maintenance, and progression of AF. However, many aspects of AF pathophysiology remain incompletely understood. In this review, we discuss the cellular and molecular electrophysiology of AF initiation, maintenance, and progression, predominantly based on recent data obtained in human tissue and animal models. The central role of Ca^{2+}-handling abnormalities in both focal ectopic activity and AF substrate progression is discussed, along with the underlying molecular basis. We also deal with the ionic determinants that govern AF initiation and maintenance, as well as the structural remodeling that stabilizes AF-maintaining re-entrant mechanisms and finally makes the arrhythmia refractory to therapy. In addition, we highlight important gaps in our current understanding, particularly with respect to the translation of these concepts to the clinical setting. Ultimately, a comprehensive understanding of AF pathophysiology is expected to foster the development of improved pharmacological and nonpharmacological therapeutic approaches and to greatly improve clinical management. (*Circ Res*. 2014;114:1483-1499.)**

Key Words: atrial fibrillation ■ atrial remodeling ■ calcium ■ electrophysiology

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in the developed world, affecting ≈6 million people in the United States alone, an incidence that is expected to double by 2030 because of the aging of the population.[1,2] Largely as a major risk factor for embolic stroke and worsening heart failure (HF), AF is associated with significant morbidity and mortality.[3] AF is classified as paroxysmal AF (pAF) when episodes last <7 days and spontaneously convert to normal sinus rhythm, persistent AF when lasting ≥7 days, or permanent AF when no further attempts to achieve normal sinus rhythm are made.[4] Patients with more advanced stages (long-standing persistent) of AF are generally older and have more comorbidities.[5] The progression from paroxysmal to persistent and permanent forms of AF has pronounced

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From the Institute of Pharmacology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany (J.H., N.V., D.D.); Department of Medicine, Montreal Heart Institute and Université de Montréal, Montreal, Quebec, Canada (S.N.); and Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada (S.N.).
*These authors contributed equally.
Correspondence to Dobromir Dobrev, MD, Hufelandstrasse 55, 45122 Essen, Germany. E-mail Dobromir.Dobrev@uk-essen.de

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Nonstandard Abbreviations and Acronyms	
AF	atrial fibrillation
AP	action potential
APD	action potential duration
cAF	chronic atrial fibrillation
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CREM	cAMP-response element modulator
DAD	delayed afterdepolarization
EAD	early afterdepolarization
HF	heart failure
$I_{Ca,L}$	L-type Ca^{2+} current
I_{K1}	basal inward-rectifier K^+ current
$I_{K,ACh}$	acetylcholine-dependent inward-rectifier K^+ current
I_{Ks}	slow delayed-rectifier K^+ current
I_{Kur}	ultrarapid delayed-rectifier K^+ current
I_{Na}	Na^+ current
I_{to}	transient-outward K^+ current
LA	left atrium
NCX	Na^+/Ca^{2+} exchanger
pAF	paroxysmal atrial fibrillation
PKA	protein kinase A
PP1	protein phosphatase type 1
PV	pulmonary vein
RA	right atrium
RyR2	ryanodine receptor channel type 2
SCaE	spontaneous sarcoplasmic reticulum Ca^{2+} release event
SERCA2a	sarcoplasmic reticulum Ca^{2+}-ATPase type 2a
SK	small-conductance Ca^{2+}-activated K^+
SR	sarcoplasmic reticulum
TGFβ1	transforming growth factor β1
TRP	transient receptor potential
TRPC3	transient receptor potential canonical-3

therapeutic implications, with pAF being more amenable to rhythm control therapy.[6]

Current pharmacological options have imperfect efficacy and substantial adverse side effects, including drug-induced proarrhythmia and both cardiac and noncardiac toxicity.[7–9] The limited efficacy of current pharmacological treatment options likely results from an incomplete understanding of the pathophysiology of this complex heart rhythm disorder. Here, we provide a conceptual overview of the factors involved in the initiation, maintenance, and progression of AF. Subsequently, we review the molecular mechanisms identified for each of these components. Finally, we highlight important gaps in the current understanding of AF pathophysiology, particularly with respect to the translation of these findings to the clinical setting.

Conceptual Framework

AF as a Progressive Disease

The pathophysiology of AF contains 3 major components: initiation of the arrhythmia, arrhythmia maintenance, and progression toward longer-lasting AF forms (ie, from paroxysmal to persistent/permanent AF).[10,11] Each AF episode requires initiation by a trigger acting on a vulnerable substrate. This vulnerable substrate is at least partly determined by genetic factors.[12–14] Several mutations and gene variants have been identified that allow AF initiation in the absence of traditional risk factors (Figure 1A). Although they are rare, and generally limited to isolated families, AF-causing mutations have provided important insights into the ionic mechanisms underlying AF.[12] In addition, recent genome-wide association studies have discovered several genetic variants associated with an increased risk of AF, identifying novel potential factors contributing to AF.[13] However, the exact mechanisms linking genetic loci identified with genome-wide association studies to AF are incompletely understood, because (1) causative genes are often uncertain, and (2) the likely candidates generally have poorly understood functions. Even after including genome-wide association study variants, a large portion of the heritability of AF is uncertain, with large population studies showing that a parental history of AF almost doubles the future AF risk in their offsprings.[14] Thus, other currently unknown genetic components also play a role in more common forms of AF.[13] Furthermore, genetic variants are unlikely to cause AF directly, but rather provide background vulnerability. When additional risk factors develop over time, because of physiological aging or cardiac remodeling resulting from other cardiovascular and noncardiovascular diseases, an appropriate trigger may then initiate AF (Figure 1B). Common comorbidities that promote a vulnerable substrate for the initiation and maintenance of AF include hypertension, HF, and cardiac valve disease.[5] Genetic variants that increase the risk of hypertension, valve disease, and other AF risk factors may, therefore, also augment the risk of AF, even when not directly affecting the atria. A detailed discussion of the relationships among clinical features, epidemiology, and arrhythmogenic mechanisms is provided in another article in this compendium, along with an overview of AF pathophysiology.[15]

About 5% of patients with pAF progress to persistent forms each year.[11] Further progression occurs at increasing rates, with 35% to 40% of patients with persistent AF developing permanent AF <1 year.[4] The progression rate is lowest in young patients without associated heart disease (lone AF), amounting to 1% to 3% per year.[16] However, there exists a wide variability in AF progression among patients. In some cases, AF initially presents as persistent AF (Figure 1C).[11] When AF is maintained, it causes atrial tachycardia–induced remodeling, increasing substrate vulnerability and promoting AF maintenance, progression, and stabilization. It must be recognized that Figure 1 is a schematic presentation of our present concepts of common forms of AF evolution, and that other clinical forms are possible, for example, recurrent paroxysmal AF that never becomes persistent, and initial presentation with persistent AF that is never terminated, whether because treating physicians decide that AF conversion is unnecessary or because successful conversion to sinus rhythm proves impossible.

Fundamental AF Mechanisms

Ectopic (triggered) activity and re-entry are major arrhythmogenic mechanisms in AF (Figure 2).[10,17,18] Focal ectopic/triggered activity is likely caused by early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). EADs are favored by delayed repolarization, whereas DADs depend on Ca^{2+}-handling abnormalities.[7,8,10,19] Re-entry can occur around

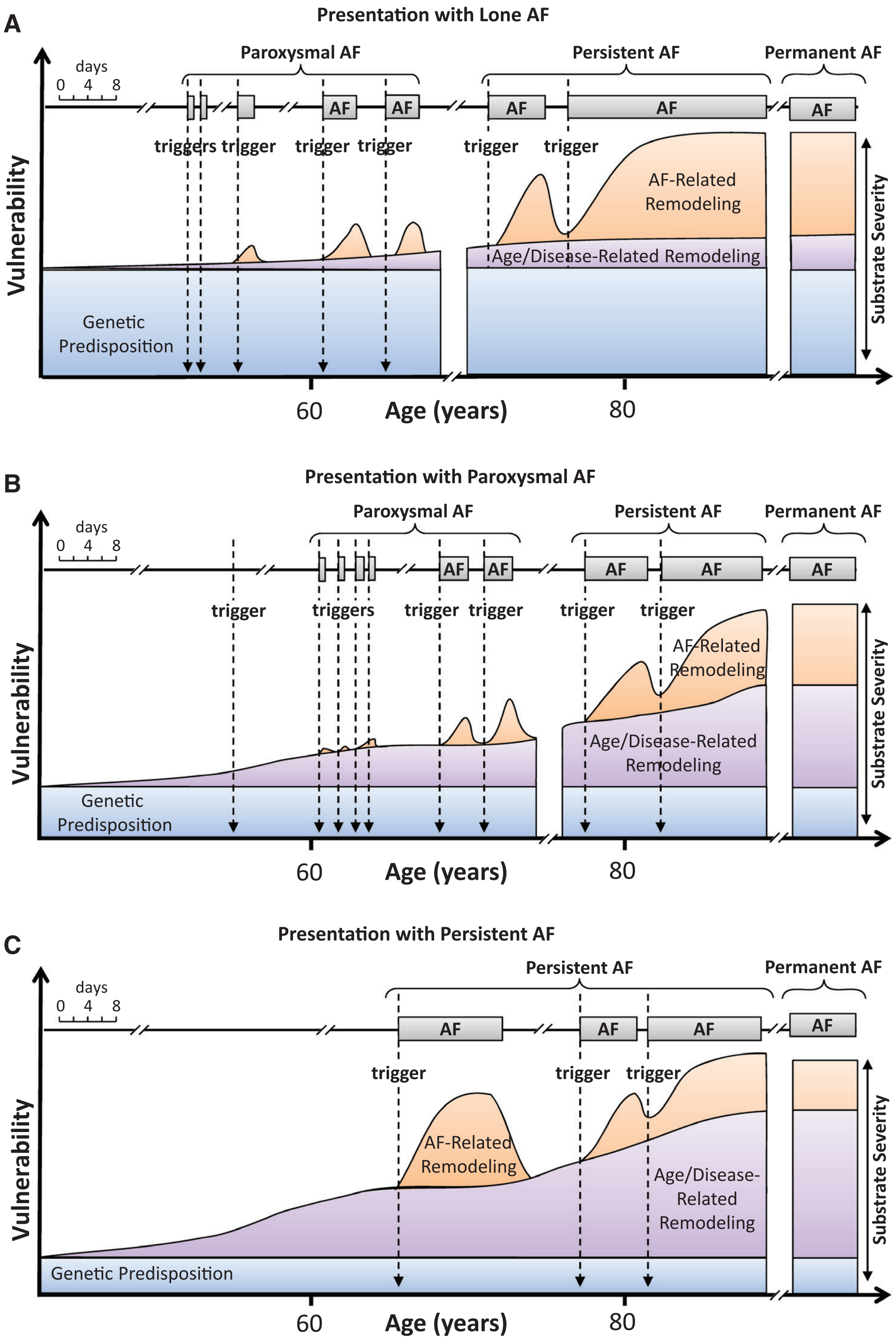

Figure 1. Conceptual framework of atrial fibrillation (AF) initiation, maintenance, and progression. A, In patients with a sufficiently large genetic predisposition, AF onset may occur at a relatively young age. AF-induced remodeling helps to maintain the arrhythmia, as well as promoting AF progression. **B**, In most patients, the genetic substrate alone does not provide sufficient susceptibility for AF. Additional disease-related remodeling may increase vulnerability and allow the initiation of paroxysmal AF episodes. Over time, some patients with paroxysmal AF may progress to longer-lasting persistent AF forms. **C**, Because of the composition of substrate and trigger, some patients have a first AF episode lasting >7 d and may progress to permanent AF due either to progression of underlying disease or to a medical decision to leave the patient in AF. (Note that for convenience the time scale for AF episodes, in gray, is expanded compared with the lower axis providing a sense of lifetime time course.)

an anatomic obstacle when each point in the pathway has sufficient time to regain excitability before the arrival of the next impulse. The likelihood of anatomic re-entry is controlled by the wavelength (conduction velocity × effective refractory period).[7] Re-entry can also be functional, when premature impulses conduct unidirectionally around an initially refractory border. Several conceptual interpretations of functional re-entry exist.[17,18] In the leading circle model, re-entry occurs in a circuit with a size equal to the wavelength with a central continuously refractory core, whereas in the spiral wave model,

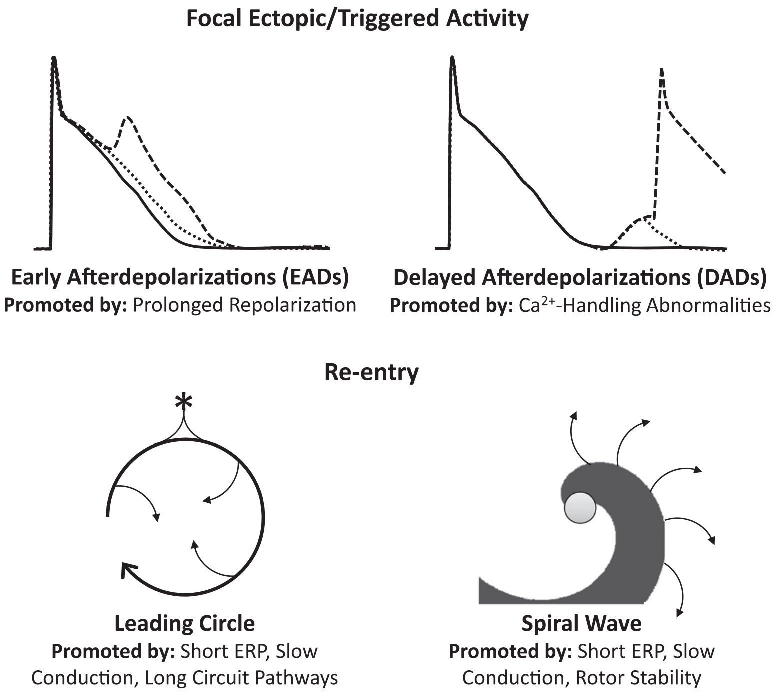

Figure 2. Major arrhythmogenic mechanisms include focal ectopic/triggered activity and re-entry. Focal ectopic/triggered activity is mediated by early and delayed afterdeplarizations, which are promoted by prolonged repolarization and Ca^{2+}-handling abnormalities, respectively. Conceptual interpretations of functional re-entry include leading circle and spiral wave. For detailed discussion of the differences between leading circle and spiral wave concepts, see Comtois et al.[17] ERP indicates effective refractory period.

excitation proceeds around a central core of excitable but unexcited tissue (Figure 2).[17] Focal ectopic firing can also arise from microre-entrant circuits that, at the macroscopic level, cannot be distinguished from EAD-/DAD-mediated triggered activity.

Focal ectopic firing is required for the initiation of AF in a vulnerable substrate. In addition, it can maintain AF when occurring repetitively at a high frequency. Multiple circuit re-entry or one or more rotors with fibrillatory conduction are the most likely mechanisms for the maintenance of long-standing AF episodes in the majority of patients.

Mechanisms of AF Initiation

Atrial Cellular Electrophysiology and Ectopic/Triggered Activity

During normal sinus rhythm, atrial action potentials (APs) are initiated through voltage-dependent activation of cardiac Na^+ channels, producing a depolarizing current (I_{Na}) responsible for the AP upstroke. The activation of L-type Ca^{2+} current ($I_{Ca,L}$) is responsible for Ca^{2+} entry that triggers a much larger release of Ca^{2+} from the sarcoplasmic reticulum (SR) stores through ryanodine receptor channel type 2 (RyR2), producing the systolic intracellular Ca^{2+} transient. Time-dependent delayed-rectifier K^+ currents (slow delayed-rectifier K^+ current [I_{Ks}], rapid delayed-rectifier K^+ current, and ultrarapid delayed-rectifier K^+ current [I_{Kur}]) and the transient-outward K^+ current (I_{to}) control AP repolarization and help to determine AP duration (APD). The basal and acetylcholine-dependent inward-rectifier K^+ currents (I_{K1} and $I_{K,ACh}$) control final AP repolarization and determine resting membrane potential. During diastole, Ca^{2+} is extruded from the cell via the electrogenic Na^+/Ca^{2+} exchanger (NCX) type 1, with 3 Na^+ entering the cell for every Ca^{2+} extruded, resulting in a depolarizing inward current. In addition, Ca^{2+} is taken back up into the SR via the SR Ca^{2+}-ATPase type 2a (SERCA2a). Together, these processes restore low resting cytosolic Ca^{2+} concentrations and allow atrial relaxation during diastole.

EADs generally occur in the setting of prolonged APD, for example, with the loss of repolarizing K^+ currents,[20] or an excessive late component of noninactivating Na^+ current (persistent/late I_{Na}).[21] During a normal AP, L-type Ca^{2+} channels undergo voltage- and Ca^{2+}-dependent inactivation, limiting the influx of Ca^{2+}. APD prolongation allows time for L-type Ca^{2+} channels to recover from inactivation, resulting in an inward current, causing an EAD (Figure 3A). DADs predominantly arise from abnormal SR Ca^{2+} leak and diastolic SR Ca^{2+} release events (SCaEs) and are promoted by increased SR Ca^{2+} load and RyR2 dysfunction (Figure 3B). Diastolic Ca^{2+} release from the SR activates NCX, producing a transient-inward current that causes membrane depolarization (Figure 3B). If the DAD reaches threshold, a triggered ectopic AP results.

Role of Ectopic/Triggered Activity for AF Initiation

Ca^{2+}-Handling Abnormalities Promote DAD-Related Ectopic Activity

Much less is known about the conditions causing clinically relevant ectopic activity than those permitting re-entry. Several mouse models have highlighted an important role for RyR2 dysfunction, increased SR Ca^{2+} leak, and SCaEs in initiating AF. Mice lacking the RyR2-stabilizing subunit FKBP12.6 show larger SR Ca^{2+} leak and more SCaEs, leading to NCX activation and DADs.[22] They also show increased susceptibility to burst pacing–induced AF, but without spontaneous AF episodes in vivo.[22] Similar results are obtained in mice with the E169K mutation in junctophilin-2, which shows reduced interaction with RyR2, suggesting an important RyR2-stabilizing role for junctophilin-2.[23] Gain-of-function mutations in RyR2 predispose patients to catecholaminergic polymorphic ventricular tachycardia and AF,[24,25] and mice with these catecholaminergic polymorphic ventricular tachycardia mutations show Ca^{2+}-handling abnormalities and burst pacing–induced AF.[26,27] Pharmacological inhibition of Ca^{2+}/calmodulin-dependent protein kinase II

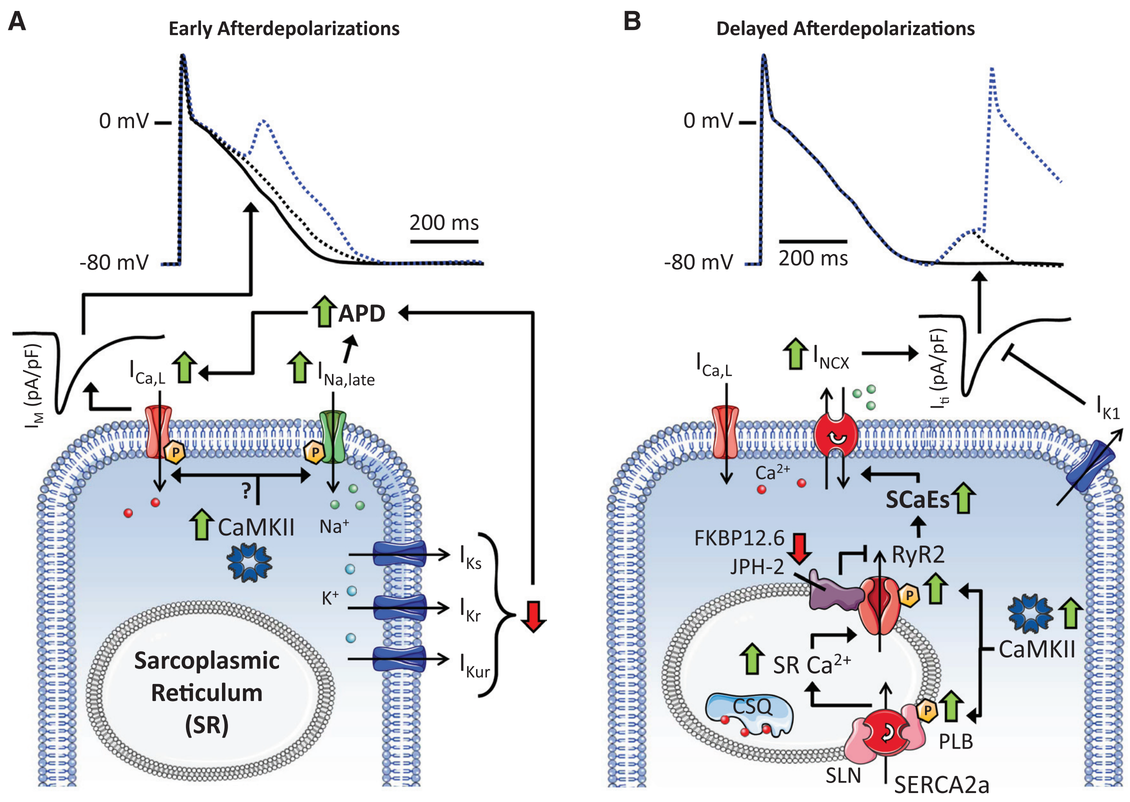

Figure 3. A, Mechanisms underlying early afterdepolarizations. Reduced repolarizing K^+ currents (slow delayed-rectifier K^+ current [I_{Ks}], rapid delayed-rectifier K^+ current [I_{Kr}], ultrarapid delayed-rectifier K^+ current [I_{Kur}]) or increased depolarizing currents (persistent/late Na^+ current [$I_{Na,late}$], L-type Ca^{2+} current [$I_{Ca,L}$]) prolong action potential duration (APD), allowing recovery from inactivation of $I_{Ca,L}$, augmenting inward currents, and causing membrane depolarization during AP phase 2 or 3. **B**, Mechanisms underlying delayed afterdepolarizations. Dysfunction of cardiac ryanodine receptor channel type 2 (RyR2) because of enhanced Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) phosphorylation or reduced stabilizing subunits (FKBP12.6, junctophilin-2 [JPH-2]), and increased sarcoplasmic reticulum (SR) Ca^{2+} load via increased SR Ca^{2+} uptake because of phospholamban (PLB) hyperphosphorylation promotes spontaneous SR Ca^{2+} release events (SCaEs), activating the Na^+/Ca^{2+} exchanger (NCX) and producing a depolarizing transient-inward current (I_{ti}), which causes delayed afterdepolarization. Inward-rectifier K^+ currents offset the resulting membrane depolarization. CSQ indicates calsequestrin; I_M, membrane current; SERCA2a, SR Ca^{2+}-ATPase type 2a; and SLN, sarcolipin.

(CaMKII), genetic inhibition of CaMKII-dependent RyR2-Ser2814 phosphorylation, and the RyR2-stabilizing compound S107 prevent AF initiation in catecholaminergic polymorphic ventricular tachycardia mice and FKBP12.6 knockout mice, supporting a critical role for RyR2 dysfunction/associated Ca^{2+}-handling abnormalities in AF vulnerability.[26,28] Ca^{2+}-handling abnormalities also contribute to AF initiation in large animal models. For example, chronic atrial ischemia/infarction creates a substrate for focal ectopic activity characterized by SCaEs and increased NCX current, particularly in the setting of β-adrenoceptor stimulation.[29] Indeed, sympathetic stimulation provides an important trigger promoting Ca^{2+}-handling abnormalities and AF initiation.[30]

Some transgenic mouse lines develop spontaneous AF episodes,[31] with the majority of these showing pronounced structural remodeling with atrial dilatation and fibrosis,[31] but the exact molecular mechanisms underlying the initiation of AF episodes remain largely unknown.

Mice with cardiac-restricted overexpression of a repressor form of the cAMP-response element modulator (CREM) develop a complex cardiac phenotype including spontaneous-onset AF.[32] CREM-transgenic mice exhibit atrial dilatation, abnormal cardiomyocyte growth, mild atrial fibrosis, reduced expression of connexin-40, and Ca^{2+}-handling abnormalities including increased incidence of SR Ca^{2+} sparks and augmented SR Ca^{2+} leak.[32] This mouse model supports an important role for Ca^{2+}-handling abnormalities in spontaneous AF, because CREM-transgenic mice treated with the SERCA2a inhibitor thapsigargin showed a reduced incidence of spontaneous AF.[32] CaMKII-dependent hyperphosphorylation of RyR2 is likely an early event in the atrial pathogenesis of CREM-transgenic mice, because when CREM-transgenic mice are crossed with RyR2-S2814A-transgenic mice resistant to CaMKII-dependent RyR2 hyperphosphorylation, spontaneous AF is eliminated.[33]

Transforming growth factor β1 (TGFβ1) plays a critical role in the development of atrial fibrosis by promoting fibroblast proliferation and differentiation into collagen-secreting myofibroblasts.[34] Mice overexpressing constitutively active TGFβ1 develop extensive atrial fibrosis.[35] Although they do not show spontaneous AF, they have inducible AF on burst pacing.[35,36] Optical mapping suggests an important role for Ca^{2+} transient–triggered depolarizations during late phase 3 of the AP in AF initiation.[36] Consistent with a Ca^{2+}-dependent initiation mechanism, reinitiation of AF episodes was prevented by the inhibition of RyR2 using ryanodine or SR Ca^{2+} uptake using thapsigargin.[36]

There is paucity of large animal models showing spontaneous AF. In dog, pig, goat, and sheep models, AF is generally initiated by burst pacing, with the duration of inducible AF being quantified as an index of the arrhythmia-maintaining substrate. One notable exception is dogs with chronic left ventricular myocardial infarction, which develop spontaneous AF episodes on sympathetic stimulation with tyramine.[37] AF was because of Ca^{2+}-dependent late phase 3 EADs around the left atrium (LA)/pulmonary vein (PV) junction.[37] Spontaneous AF initiation around the LA/PV junction also occurs in aged rats after glycolytic inhibition.[38] In this model, glycolytic inhibition interacts with the fibrotic substrate of the aged atria to amplify Ca^{2+}-handling abnormalities that facilitate EAD-mediated triggered activity.[38]

Together, these studies support the concept that focal ectopic/triggered firing resulting from Ca^{2+}-handling abnormalities, particularly in the atrial myocardium surrounding the PVs, may play an important role in the initiation of AF.

Right atrial (RA) cardiomyocytes from patients with pAF also exhibit an increased incidence of SCaEs and corresponding DADs compared with patients with sinus rhythm.[39] The underlying molecular substrate involves increased SR Ca^{2+} load and RyR2 dysregulation. The increased SR Ca^{2+} load is because of protein kinase A (PKA)–dependent hyperphosphorylation of the SERCA2a inhibitor phospholamban, relieving phospholamban inhibition of SERCA2a and thereby increasing SR Ca^{2+} uptake (Figure 4).[39] RyR2 dysregulation involves increased protein expression and larger single-channel open probability, which would result in larger probability and amplitude of SCaEs. A relative deficiency of the RyR2-stabilizing protein junctophilin-2, resulting from increased RyR2 but unaltered junctophilin-2 expression (Figure 4), might explain RyR2 dysfunction.[23]

Ectopic Activity Because of Fibroblast–Cardiomyocyte Coupling

In addition to intrinsic Ca^{2+}-dependent triggered activity in cardiomyocytes, AF could also be initiated through processes resulting from direct myofibroblast–cardiomyocyte interactions.[40] In vitro studies show gap junctional coupling through connexin-43 and connexin-45 proteins between cardiomyocytes and myofibroblasts, although big-conductance Ca^{2+}-activated K^+ channels may also play a role.[41,42] Computational analyses suggest that electrotonic myofibroblast–cardiomyocyte interactions can promote diastolic depolarization of atrial cardiomyocytes because of the relatively depolarized membrane potential of cardiac fibroblasts (≈−30 mV), thereby promoting DADs and ectopic firing.[40,43]

Ectopic Activity Because of Re-entrant Mechanisms

In line with the evidence that genetic variations in KCNE1 β-subunit of the I_{Ks} channel lead to AF in patients,[44] KCNE1-null mice have a vulnerable substrate characterized by APD

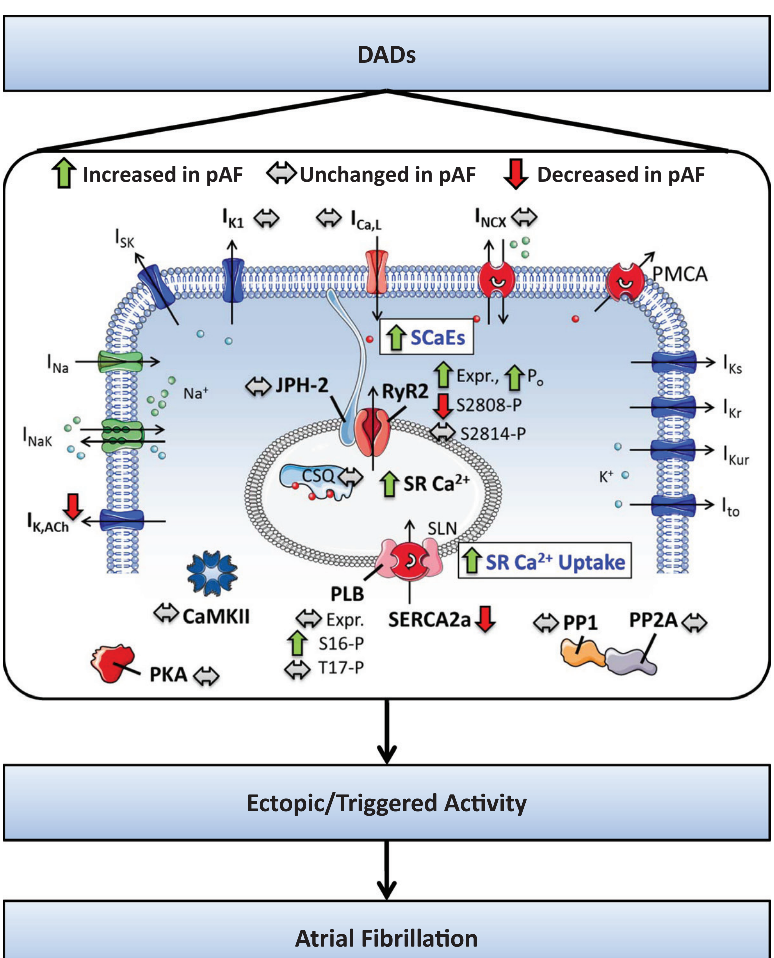

Figure 4. Molecular determinants of delayed afterdepolarization (DAD) generation, showing the changes identified to lead to DADs/triggered activity in patients with paroxysmal atrial fibrillation (pAF).[50] Green upward arrows, grey left-right arrows, and red downward arrows indicate properties that are increased, unchanged, or decreased in patients with pAF, respectively. Phospholamban (PLB) hyperphosphorylation increases sarcoplasmic reticulum (SR) Ca^{2+} uptake and SR Ca^{2+} load, despite decreased SR Ca^{2+}-ATPase type 2a (SERCA2a) expression. Ryanodine receptor channel type 2 (RyR2) dysregulation includes increased expression and single-channel open probability. Protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), protein phophatases type 1 and type 2A (PP1, PP2A), calsequestrin (CSQ) expression, and L-type Ca^{2+} current ($I_{Ca,L}$), basal inward-rectifier K^+ current (I_{K1}), and Na^+/Ca^{2+} exchanger current (I_{NCX}) are unchanged, whereas agonist-activated acetylcholine-dependent inward-rectifier K^+ current ($I_{K,ACh}$) is reduced. I_{Kr} indicates rapid delayed-rectifier K^+ current; I_{Ks}, slow delayed-rectifier K^+ current; I_{Kur}, ultrarapid delayed-rectifier K^+ current; I_{Na}, Na^+ current; I_{to}, transient-outward K^+ current; JPH-2, junctophilin-2; PMCA, plasmalemmal Ca^{2+}-ATPase; SCaEs, spontaneous SR Ca^{2+} release event; and SLN, sarcolipin.

shortening, with spontaneous AF episodes.[45] The molecular mechanisms underlying the initiation of AF were not studied, although APD prolongation with isoprenaline reduces the incidence of AF episodes.[45]

Aged spontaneously hypertensive rats have a pronounced fibrotic substrate promoting AF.[46] These rats showed spontaneous atrial tachyarrhythmias associated with an autonomic imbalance with relative vagal hyperactivity, producing repolarization shortening and heterogeneity that preceded the occurrence of arrhythmia.[47]

Role of the PVs

PV sleeves play an important role in the initiation of AF.[48] The isolation of PVs prevents AF recurrence in 75% of patients with pAF.[49] Both structural and functional properties of the PV cardiomyocyte sleeves contribute to their arrhythmogenic potential.[50] The PV sleeves have a tissue architecture consisting of discrete fibers with abrupt changes in fiber direction, resulting in reduced electrotonic load and facilitating the development of focal ectopic activity. The identification of molecular mechanisms promoting ectopic activity around the PVs in humans is difficult because of the limited availability of PV tissue from patients,[51] but recent results showed no differences in gene expression profiles of major ion channel subunits or Ca^{2+}-handling proteins between PV sleeves and LA free wall tissue samples from patients with valvular AF.[52] The transcription factor PITX2 is highly expressed around the PVs and is critical for the development of the PV sleeve myocardium.[53] PITX2 downregulates the nodal gene program, suppressing the development of focal ectopic activity around the PVs. Accordingly, reduced PITX2 expression in patients with AF and genetic variants close to the PITX2 gene have been associated with increased AF susceptibility.[54,55] Animal studies revealed reduced expression of I_{K1} in PV sleeves,[56] resulting in depolarized resting potentials that facilitate ectopic activity. The propensity for SCaEs was increased in PV regions versus LA or RA appendages in some[57] but not all studies.[58] If human PV sleeve myocytes are vulnerable to SCaEs, this could further explain their importance in AF initiation.

In addition to the re-entry-favoring fiber architecture, effective refractory periods around the PVs are shorter in patients with pAF,[59] further increasing the likelihood of a re-entrant circuit around the PVs that can initiate or maintain AF.

Mechanisms of AF Maintenance

Mechanisms of Cardiac Conduction and Re-entry

Re-entry is promoted by short effective refractory periods and slow impulse conduction. Postrepolarization refractoriness largely results from voltage-dependent inactivation of Na^+ channels.[60] Atrial Na^+ channels have been suggested to have a more negative half-inactivation voltage compared with ventricular channels, allowing for greater postrepolarization refractoriness, particularly in the presence of Na^+ channel blockers.[60]

Conduction velocity is mainly determined by excitatory Na^+ current, cardiomyocyte electric coupling through gap junctions, and muscle bundle architecture.[8,10,17] Reduced I_{Na}, decreased gap junctional coupling, and muscle bundle discontinuities resulting from fibrosis all reduce conduction velocity and promote re-entry. Ca^{2+}-handling abnormalities can also promote AF maintenance through conduction slowing.[61] Atrial conduction velocity is reduced in mice with a RyR2 catecholaminergic polymorphic ventricular tachycardia mutation causing increased SR Ca^{2+} leak and in mouse hearts with acutely elevated intracellular Ca^{2+}.[62] The underlying mechanisms seem to involve both acute Ca^{2+}-dependent inhibition of Na^+ channels and chronic downregulation of Nav1.5 expression.[63]

Experimental Models of Primary Cardiac Conditions Promoting AF Maintenance

APD Changes

In HF because of 3 to 6 weeks of ventricular tachypacing, $I_{Ca,L}$, I_{to}, and I_{Ks} are reduced; I_{K1} and T-type Ca^{2+} currents are unaltered; and NCX current is increased.[64] Atrial APD is unaltered at slow rates and slightly prolonged at faster rates.[64] Experimental HF also increases the incidence of DADs, likely because of intracellular Ca^{2+} overload.[65] In another study of long-term tachypacing-induced HF, an increase in I_{to}, largely unaltered $I_{Ca,L}$, and reduced I_{K1}, I_{Kur}, and I_{Ks} were observed, along with a shortening of atrial APD.[66] Together, these studies suggest complex time-dependent HF-induced atrial electric remodeling.[67] Other models have not been characterized as extensively. AF promotion associated with chronic volume overload in sheep is characterized by APD triangulation and $I_{Ca,L}$ reduction.[68] Endurance exercise training increases vagal tone, causing heterogeneous APD shortening via increased sensitivity to acetylcholine because of a reduction in regulators of G-protein signaling proteins.[69] Normal aging is also associated with electric remodeling, including a reduction in $I_{Ca,L}$ and increased I_{to}, although other studies have reported a seemingly contradictory APD prolongation.[70]

Ca^{2+}-Handling Abnormalities

Experimental HF increases atrial cardiomyocyte intracellular Ca^{2+} concentration, Ca^{2+} transient amplitude, and SR Ca^{2+} load, promoting SCaEs and triggered activity.[71] Underlying molecular mechanisms involve increased CaMKII and protein phosphatase type 1 (PP1) activity, CaMKII-dependent phospholamban hyperphosphorylation, reduced RyR2 expression with unaltered phosphorylation, and reduced expression of calsequestrin.[71] In addition, tachypacing-induced HF caused degeneration of the T-tubular network, responsible for synchronizing Ca^{2+}-induced Ca^{2+} release from the SR in sheep atrial cardiomyocytes.[72]

Conduction Abnormalities and Structural Remodeling

Increased atrial fibrosis and atrial dilatation are central features of atrial structural remodeling in a large number of animal AF models, including ventricular tachypacing–induced HF,[65,73–75] endurance exercise training,[69] atrial infarction,[29] chronic volume overload,[68] and aging.[70] These changes are associated with re-entry-promoting conduction abnormalities.

Angiotensin II and TGFβ1 are the major profibrotic signaling molecules, with additional roles for platelet-derived and connective tissue growth factors.[34,76] HF-induced atrial fibrosis is preceded by increased tissue angiotensin II levels and activation of mitogen-activated protein kinases, c-Jun N-terminal kinase, and extracellular signal–related kinase.[75] Although angiotensin-converting enzyme inhibition prevented these changes, atrial fibrosis was only partially reduced, highlighting the multifactorial nature of atrial fibrosis.[75]

The proliferation of fibroblasts and their differentiation into collagen-secreting myofibroblasts play a critical role in fibrosis (Figure 5), with atrial fibroblasts showing greater fibrotic responses compared with ventricular fibroblasts.[77] MicroRNA-21 plays a major role in profibrotic remodeling by reducing Sprouty-1.[78] Sprouty-1 is a negative regulator of type 1/2 extracellular signal–related kinase, thereby inhibiting fibroblast survival and density.[78,79] LA microRNA-21 knockdown suppresses atrial fibrosis and AF substrate development in rats with post-MI HF.[79] MicroRNA-29b suppresses collagen gene expression and is downregulated in canine HF, so microRNA-29 downregulation could contribute to HF-related fibrosis.[80]

Fibroblast ion channel remodeling may also promote AF. Ca^{2+} permeable transient receptor potential (TRP) canonical-3 (TRPC3) channels regulate cardiac fibroblast proliferation and differentiation, likely by mediating fibroblast Ca^{2+} entry that activates extracellular signal–related kinase signaling.[81] TRPC3 expression is increased in atria from patients with AF, goats with electrically maintained AF, and dogs with tachypacing-induced HF, because of reduced repression resulting from the downregulation of microRNA-26.[81] In contrast, TRPC3 knockdown decreases canine atrial fibroblast proliferation.[81] Kv1.5 seems to be the principal K^+ channel α-subunit in fibroblasts, and channel expression is strongly downregulated in HF dogs, thereby promoting fibroblast proliferation and suggesting a functional role in HF-induced AF-promoting fibrosis.[82] Atrial fibroblasts also express Nav1.5 α-subunits and Na^+ currents when differentiated into myofibroblasts, and the resulting Na^+ entry may contribute to their arrhythmogenic potential.[83,84]

In addition to promoting muscle bundle discontinuities, myofibroblasts can affect atrial cardiomyocytes through paracrine interactions, notably via angiotensin II and TGFβ1 (Figure 5).[85] Moreover, myofibroblasts promote re-entry via

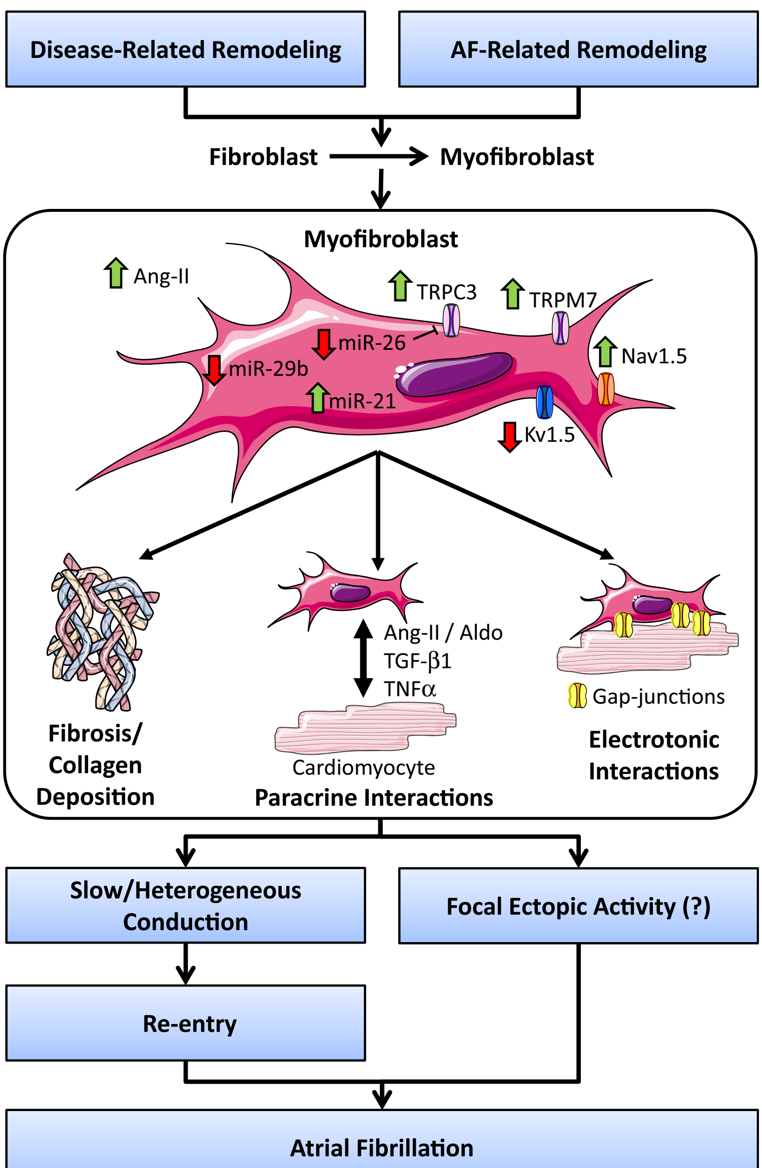

Figure 5. Arrhythmogenic changes in atrial fibroblasts. Disease- and atrial fibrillation (AF)–related remodeling promotes fibroblast differentiation into myofibroblasts, involving altered expression of several ion channel proteins and microRNAs (miRs). Myofibroblasts facilitate AF maintenance by promoting re-entry through fibrosis/collagen deposition, as well as paracrine and direct electrotonic interactions with cardiomyocytes. Ado indicates aldosterone; Ang-II, angiotensin II; TGFβ1, transforming growth factor β1; TNFα, tumor necrosis factor α; TRPC3, transient receptor potential (TRP) canonical-3; and TRPM, TRP melastatin–related 7.

direct electric interaction with cardiomyocytes (Figure 5),[40] by reducing conduction velocity through passive loading and depolarization-induced Na^+ channel inactivation.

Conduction abnormalities are also promoted by impaired cell-to-cell coupling via gap junctions. For example, acute atrial ischemia promotes AF induction by impairing cell-to-cell coupling, causing severe local conduction slowing.[86] HF causes connexin-43 dephosphorylation and associated gap junction lateralization.[73] However, because recovery from HF normalizes atrial function and connexin properties, but not fibrosis, conduction abnormalities, or AF persistence, fibrosis is probably the predominant determinant of AF maintenance in experimental HF.[73] Accordingly, the gap junction stabilizer rotigaptide suppresses AF in acute atrial ischemia but not HF.[87]

Clinical Disease–Related Atrial Remodeling Promoting AF Maintenance

Patients with valvular heart disease show substantial remodeling of cardiac ion channel gene expression, with additional remodeling because of AF.[88] Left ventricular systolic dysfunction is associated with APD shortening in the presence of unaltered $I_{Ca,L}$, I_{K1}, or sustained outward current, possibly because of increased I_{to}.[89] In contrast, mitral valve disease and low left ventricular ejection fraction are associated with reduced $I_{Ca,L}$,[90] whereas atrial dilatation involves reduced $I_{Ca,L}$ and I_{to}.[91] It is likely that such disease-related remodeling predisposes to AF, especially in combination with AF risk factors. In addition, AF can also be mediated by atrial stretch resulting from hypertension, HF, or mitral valve disease. Atrial stretch is a common paradigm in AF-related conditions and might importantly contribute to AF-promoting structural remodeling.[92] The consequences of atrial pressure and volume overload could also be directly related to these underlying diseases, independent of atrial ion channel remodeling.

AF-Induced Remodeling Promoting AF Maintenance in Animal Models

In addition to disease-related remodeling, AF-induced atrial remodeling seems to play a major role in the maintenance, progression, and stabilization of AF.[34,93–95]

APD Shortening

Atrial tachycardia pacing causes a pronounced reduction in atrial APD associated with reduced $I_{Ca,L}$ and I_{to} caused by the downregulation of the underlying Cav1.2 and Kv4.3 subunit expression, an increase in constitutively active $I_{K,ACh}$,[96] whereas I_{K1}, rapid delayed-rectifier K^+ current, I_{Ks}, I_{Kur}, and T-type Ca^{2+} currents were unaltered.[97,98] Rapid atrial cardiomyocyte firing increases intracellular Ca^{2+}, activating the Ca^{2+}-dependent phosphatase calcineurin.[99] Calcineurin dephosphorylates the nuclear factor of activated T cells, promoting its translocation to the nucleus, where it represses transcription of Cav1.2 (Figure 6).[99] MicroRNA-328 upregulation and repression of Cav1.2 may also be involved in this process,[100] and $I_{Ca,L}$ downregulation can also be because of Ca^{2+}-dependent activation of calpain, causing proteolitic breakdown of L-type Ca^{2+}-channels.[101] Overall, reduced $I_{Ca,L}$ prevents pacing-induced Ca^{2+} overload at the expense of reentry-promoting APD shortening.

The Ca^{2+}/calcineurin/nuclear factor of activated T cells–dependent pathway can reduce I_{to} in ventricular cardiomyocytes, suggesting that the rate-dependent reduction

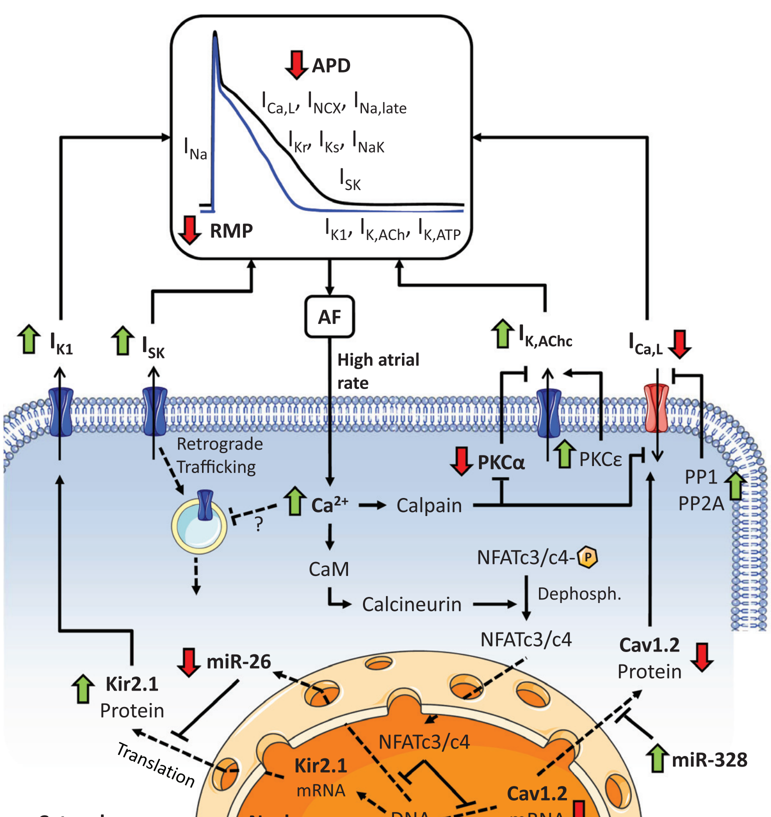

Figure 6. Mechanisms responsible for atrial fibrillation (AF)–dependent electric remodeling promoting AF maintenance and progression. Atrial tachycardia–related Ca^{2+} loading causes intracellular signaling events that increase K^+ currents and reduce L-type Ca^{2+} current ($I_{Ca,L}$). APD indicates action potential duration; CaM, calmodulin; I_{K1}, basal inward-rectifier K^+ current; $I_{K,ACh}$, acetylcholine-dependent inward-rectifier K^+ current; I_{Kr}, rapid delayed-rectifier K^+ current; I_{Ks}, slow delayed-rectifier K^+ current; $I_{K,ATP}$, ATP-dependent K^+ current; I_{Na}, Na^+ current; I_{NaK}, Na^+-K^+-ATPase current; $I_{Na,late}$, persistent/late Na^+ current; I_{NCX}, Na^+/Ca^{2+} exchanger current; I_{SK}, small-conductance Ca^{2+}-activated K^+ current; I_{to}, transient-outward K^+ current; miR, microRNA; NFAT, nuclear factor of activated T cells; PKC, protein kinase C; PP1, protein phosphatase type 1; PP2A, protein phosphatase type 2A; and RMP, resting membrane potential.

in I_{to} in AF could also be mediated via this pathway.[102,103] Interestingly, similar mechanisms are responsible for the rate-dependent upregulation of I_{K1}: nuclear factor of activated T cells reduces the expression of the inhibitory microRNA-26, removing translational inhibition of Kir2.1 by microRNA-26 (Figure 6).[104] The rate-dependent increase in constitutively active $I_{K,ACh}$ is also Ca^{2+}-dependent and is at least partly mediated via calpain, which breaks down classical protein kinase C type α-isoforms (Figure 6).[105]

Several studies have suggested a role for small-conductance Ca^{2+}-activated K^+ (SK) currents in AF. The expression of the SK1 subunit and SK channel open probability are enhanced in dogs with atrial tachycardia remodeling, promoting repolarization shortening,[106] whereas the inhibition of SK channels prolongs atrial repolarization and reduces AF duration in several animal models.[106,107]

Ca^{2+}-Handling Abnormalities

Ca^{2+} transient amplitude is reduced in dogs with atrial tachycardia remodeling, contributing to atrial contractile dysfunction.[108,109] The reduced Ca^{2+} transient amplitude feeds back on repolarization, contributing to reduced APD rate dependence in AF.[110,111] In addition, atrial tachycardia remodeling induces impaired Ca^{2+} wave propagation to the cell center and is associated with hypophosphorylation-dependent myofilament desensitization because of reduced expression of PKA and increased activity of PP1 and CaMKII.[110] In contrast, PKA-dependent phosphorylation of RyR2 is increased in dogs with atrial tachypacing, similar to patients with chronic AF (cAF), and is associated with decreased RyR2–FKBP12.6 interaction.[112] In goats with persistent AF, PKA-dependent phospholamban phosphorylation is reduced (decreasing SR Ca^{2+} uptake), whereas CaMKII-dependent RyR2 phosphorylation is increased (increasing SR Ca^{2+} leak), reducing SR Ca^{2+} load and contributing to reduced contractility associated with AF.[113] In sheep with persistent AF, the coupling efficiency between RyR and L-type Ca^{2+} channels is decreased, contributing to reduced SR Ca^{2+} release and Ca^{2+} transient amplitude despite normal SR Ca^{2+} load.[114]

Conduction Abnormalities and Structural Remodeling

Long-term atrial pacing leads to conduction slowing in several animal models. In canine atrial tachycardia remodeling, reduced conduction velocity is at least partly because of I_{Na} downregulation.[115] Heterogeneously reduced gap junction coupling because of connexin remodeling can also contribute to atrial conduction slowing. Heterogeneity in connexin-40 distribution correlated with increased AF stability in atrial cardiomyocytes from goats with AF because of repetitive burst pacing.[116] Similarly, connexin-40 expression in the PVs is decreased in the canine tachypacing model, possibly because of increased degradation by calpains activated by the Ca^{2+}-loading effects of high atrial rates.[117]

Although less pronounced than in HF, atrial tachycardia remodeling promotes atrial contractile dysfunction and causes atrial dilatation.[93] Calpain activation contributes to troponin breakdown and subsequent contractile dysfunction after high-frequency activation.[118] Atrial dilatation promotes atrial remodeling and fibrosis through increased atrial stretch.[92] Atrial tachycardia also results in atrial fibrosis and increased susceptibility to AF, even in the absence of ventricular dysfunction, indicating that a high atrial rate per se can cause fibrosis.[119] Recent work has identified components of the underlying signaling pathways. Serum from tachypaced atrial myocytes promotes fibroblast differentiation to collagen-secreting myofibroblasts, through autocrine and paracrine mechanisms.[120] Rapid atrial activation in rabbits produces fibrosis associated with increased angiotensin II and TGFβ1, activation of the Smad2/3 pathway, and inhibition of the TGFβ1/Smad-mediated fibrosis antagonist Smad7, effects that are prevented by angiotensin II type 1 receptor blockade.[121]

Tachycardia-induced nuclear factor of activated T cell–mediated decreases in fibroblast microRNA-26 may also contribute to structural remodeling. Because microRNA-26 represses TRPC3 gene expression, microRNA-26 reductions enhance TRPC3 expression, promoting fibroblast proliferation/myofibroblast differentiation.[81]

AF-Maintaining Substrates Resulting from AF-Induced Remodeling in Patients

A comparison of the electrophysiological and molecular characteristics of atrial cardiomyocytes from pAF versus patients with long-standing persistent cAF provides strong indications about the AF-promoting consequences of atrial tachycardia remodeling, because patients with pAF had been in normal sinus rhythm for days to weeks at the time of cardiac surgery, whereas patients with cAF had a persistent high atrial rate before and during surgery.

APD Shortening

In contrast to patients with pAF, atrial myocytes from patients with cAF show decreased APD. Depolarizing $I_{Ca,L}$ is consistently reduced in cAF,[122–124] likely because of an adaptive mechanism to protect atrial myocytes from toxic Ca^{2+} overload resulting from fast rates. Reduced $I_{Ca,L}$ contributes both to reduced APD, promoting re-entry, and decreased Ca^{2+} transient amplitude, reducing atrial contractility. Cav1.2 α_{1C}-subunit expression is reduced in cAF atrial cardiomyocytes in most but not all studies,[125] possibly because of an increase in microRNA-328.[100] In addition, there is evidence for altered Cav1.2 phosphorylation,[124,126] S-nitrosylation,[127] and channel subunit breakdown by calpain.[128] The complex molecular basis of reduced $I_{Ca,L}$ in cAF suggests that the precise mechanisms may differ among patients.

Increased inward-rectifier K^+ currents also contribute to APD shortening in cAF. LA I_{K1} is increased in both pAF and cAF.[129] The increase in I_{K1} is because of increased protein expression of underlying Kir2.1 subunits,[129,130] probably through a reduction of microRNAs that normally repress Kir2.1 translation[104,131] and an enhancement of single-channel open probability.[132] The increased single-channel open probability may involve stronger channel dephosphorylation by PP1 and serine/threonine protein phosphatase type 2A in cAF.[133] Agonist-activated $I_{K,ACh}$ is larger in RA than in LA from patients with sinus rhythm, but is decreased in RA of pAF and cAF because of a reduction in underlying Kir3.1 and Kir3.4 subunits.[129,130] Kir3.4, but not Kir3.1, is regulated by intracellular [Na^+],[134] resulting in an Na^+-dependent increase in agonist-activated $I_{K,ACh}$.[135] This Na^+-dependent regulation is lost in cAF, possibly because of a more pronounced reduction of the Na^+-sensitive subunit Kir3.4 than Kir3.1, and further reduces $I_{K,ACh}$ at fast rates with increased intracellular [Na^+].[135] $I_{K,ACh}$ also develops agonist-independent (constitutive) activity in cAF.[132] The constitutive activity of $I_{K,ACh}$ in cAF is promoted by abnormal channel phosphorylation by novel protein kinase C isoforms.[133] Computational studies show that increased total inward-rectifier K^+ current in cAF is the major contributor to the stabilization of re-entrant rotors by shortening APD and hyperpolarizing the resting membrane potential.[136]

There is evidence for increased I_{Ks} in patients with cAF, which might contribute to APD shortening.[137,138] The molecular mechanisms underlying increased I_{Ks} are unknown. Increased, decreased, and unaltered mRNA levels of the underlying KCNQ1 α-subunit have been reported in patients with cAF.[88,125] The expression of the KCNE1 β-subunit is reduced in patients with valvular heart disease, without differences between sinus rhythm and patients with cAF.[88]

In one study, SK current was increased in cAF atrial cardiomyocytes and augmented by high-frequency depolarizing pulses.[139] The increase in SK current was prevented by the inhibition of retrograde channel trafficking, suggesting a rate-dependent influence on membrane channel availability.[139] However, another study reported reduced SK channel expression in cAF atrial cardiomyocytes,[140] possibly because of increased microRNA-499, downregulating the SK3 subunit.[141]

Despite reduced APD at full repolarization, APD at 20% repolarization is generally prolonged.[142] This effect is partly because of smaller I_{to}[123] through reduced expression of the underlying Kv4.3 subunit. I_{to} reduction is more pronounced in LA than in RA.[137] Similarly, I_{Kur} and Kv1.5 subunits are reduced in cAF.[137,143,144] I_{Kur} reduction has indirect effects on other currents, and the overall impact on APD depends on AP morphology.[142] For example, there is evidence that reduced I_{Kur} can promote EADs in the presence of sympathetic stimulation.[145,146]

Ca^{2+}-Handling Abnormalities

Although SCaEs and DADs are more prevalent in both pAF and cAF myocytes compared with sinus rhythm, the underlying molecular mechanisms are distinct (Figure 7). Several groups have highlighted a critical role for CaMKII-dependent RyR2 phosphorylation in SR Ca^{2+} leak and SCaEs in cAF.[147–149] The oxidation of methionine 281/282 is increased in patients with cAF and contributes to increased CaMKII activity, making CaMKII a critical molecular signal coupling AF-related oxidative stress to proarrhythmic Ca^{2+}-handling abnormalities.[150] PKA-dependent RyR2 hyperphosphorylation has also been observed in patients with cAF[112,149] and might promote RyR2 dysfunction by promoting dissociation of the stabilizing FKBP12.6 subunit from the RyR2 channel,[112] although this is not unanimously accepted.[151,152] In addition, the expression

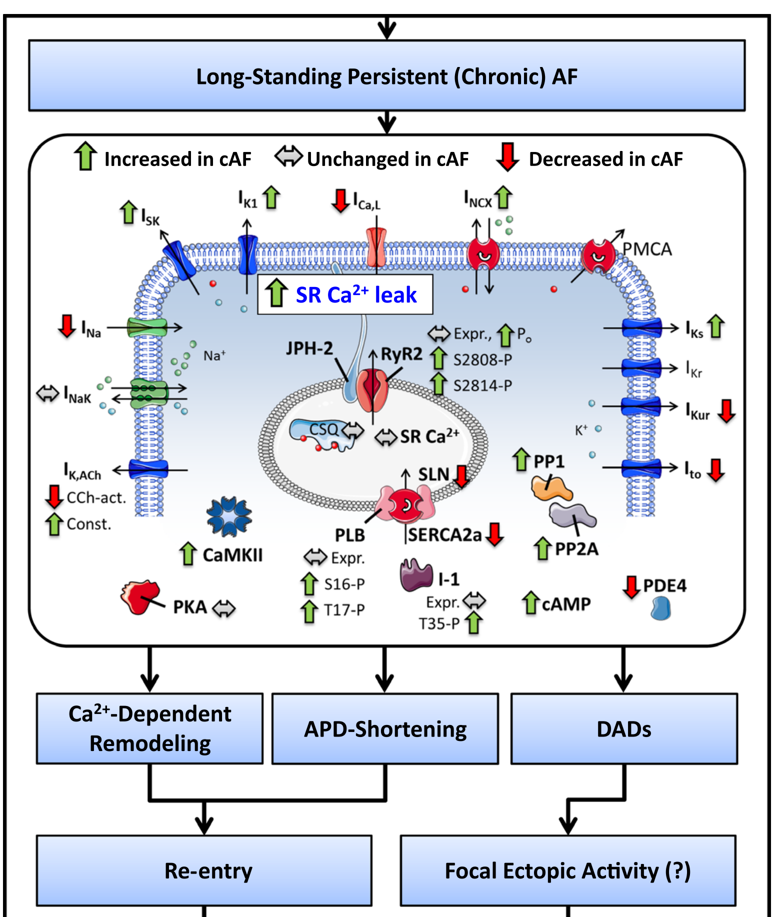

Figure 7. Ca^{2+}-handling abnormalities and alterations in ion currents in patients with long-standing persistent (chronic) atrial fibrillation (cAF) and their potential arrhythmogenic consequences. Green upward arrows, grey left-right arrows, and red downward arrows indicate properties that are increased, unchanged, or decreased in patients with cAF, respectively. Reduced L-type Ca^{2+} current ($I_{Ca,L}$) and increased basal inward-rectifier K^+ current (I_{K1}) and constitutively active acetylcholine-dependent inward-rectifier K^+ current ($I_{K,ACh}$) contribute to action potential duration (APD) shortening. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)–dependent ryanodine receptor channel type 2 (RyR2) hyperphosphorylation increases sarcoplasmic reticulum (SR) Ca^{2+} leak. Phosphodiesterase type 4 (PDE4) is reduced, increasing cyclic-AMP (cAMP) and promoting protein kinase A (PKA)–dependent phosphorylation of phospholamban (PLB) and inhibitor-1 (I-1), which together with reduced expression of sarcolipin (SLN) contributes to the unaltered SR Ca^{2+} load despite increased SR Ca^{2+} leak. CCh-act. indicates carbachol activated; Const., constitutively active; CSQ, calsequestrin; Expr., expression; I_{Kr}, rapid delayed-rectifier K^+ current; I_{Ks}, slow delayed-rectifier K^+ current; I_{Kur}, ultrarapid delayed-rectifier K^+ current; I_{Na}, Na^+ current; I_{NaK}, Na^+-K^+-ATPase current; I_{NCX}, Na^+/Ca^{2+} exchanger current; I_{SK}, small-conductance Ca^{2+}-activated K^+ current; I_{to}, transient-outward K^+ current; JPH-2, junctophilin-2; PMCA, plasmalemmal Ca^{2+}-ATPase; P_o, open probability; PP1, protein phosphatase type 1; PP2A, protein phosphatase type 2A; SERCA2a, SR Ca^{2+}-ATPase type 2a; and T35-P, Thr35-phosphorylated.

and activity of NCX are increased in cAF, so that SCaEs produce larger transient-inward currents.[149] SR Ca^{2+} load is unaltered in cAF despite the larger SR Ca^{2+} leak,[149] possibly because of increased phospholamban phosphorylation[149] or reduced expression of the SERCA2a inhibitor sarcolipin.[153,154] The increase in PP1 and protein phosphatase type 2A activity in patients with cAF would be expected to reduce phosphorylation levels[155]; however, cAMP levels are increased in cAF,[149] possibly because of reduced cAMP-hydrolyzing phosphodiesterase type 4,[156] promoting PKA activation. In addition, increased PKA-dependent activation of the PP1 inhibitory protein inhibitor-1, which controls PP1 in the SR compartment,[157] could explain phospholamban hyperphosphorylation because of local reductions in PP1 activity.[155]

Conduction Abnormalities and Structural Remodeling

Earlier studies showed no change in I_{Na} or mRNA expression of the Nav1.5 α-subunit in patients with cAF.[158,159] However, recent studies reported reduced peak I_{Na} in patients with AF that could contribute to re-entry-promoting conduction slowing.[160,161] In addition, persistent/late I_{Na} is increased in some studies.[160] Although the exact functional consequences are presently unknown, patients with early-onset lone AF also exhibit a high prevalence of Na^+ channel mutations that increase persistent/late I_{Na}.[162]

Connexin-40/connexin-43 mRNA and protein expression are altered in patients with AF, potentially contributing to re-entry-promoting conduction abnormalities.[163] Reduced connexin-40 expression has been reported in some studies,[88,164] whereas others reported increased expression at the transverse cell membrane, promoting heterogeneous conduction, which was reduced by β-adrenoceptor blockade.[165]

Fibrosis is common in patients with AF,[166] and connexin-43 remodeling correlates with atrial fibrosis in patients,[167] suggesting an interaction between these re-entry-promoting factors. High-density electroanatomic mapping in patients identified conduction abnormalities that correlated with AF progression. Because conduction abnormalities also correlated with low electrogram voltage and percentage of complex electrograms, it was suggested that conduction slowing was because of AF-related fibrosis.[168] There is evidence that fibroblast remodeling can occur as a consequence of AF, thereby promoting AF progression and stabilization. Beside the increase in TRPC3, TRP melastatin–related 7 channels are upregulated in patients with cAF and form a major Ca^{2+} permeation pathway in human atrial fibroblasts.[169] The downregulation of TRP melastatin–related 7 reduced AF fibroblast differentiation, and the atrial profibrotic effects of TGFβ1 require TRP melastatin–related 7–mediated Ca^{2+} signals.[169] Recent work suggests that fibrocytes (bone marrow–derived fibroblast-like cells) may also be involved in atrial fibrosis of patients with cAF because they display stronger proliferative capacity and higher expression of collagen-I and α-smooth muscle actin.[170]

Mechanisms of AF Progression

As depicted in Figure 1, the progression of AF substrate occurs as a result of both AF-related remodeling and remodeling because of age and heart disease. The mechanistic components of the underlying processes are discussed in detail above. The key components include changes in ion currents that promote re-entry by abbreviating APD/refractory period, alterations in connexin expression, Na^+ current decreases and fibrotic remodeling that cause conduction slowing, and changes in Ca^{2+} handling that induce focal ectopic impulse formation. AF progression can also be because of the evolution of atrial changes caused by underlying cardiac and noncardiac diseases, independent of any AF-induced remodeling. For example, AF is an established risk factor for worsening HF,[171,172] and the evolution of mixed-type atrial remodeling in patients with HF can create a vicious cycle further accelerating AF progression. In contrast, some patients show limited AF progression, remaining in paroxysmal AF for decades. The mechanisms explaining this heterogeneity in the natural history of AF are at present largely unknown.

Gaps in Current Knowledge and Translational Prospects

Despite the enormous advances in our understanding of the molecular pathophysiology of AF during the past decades, there are still numerous important gaps that need to be addressed. Structural remodeling seems a key for AF stabilization and therapy resistance. For many years, researchers focused on quantifying fibrosis as an index of structural remodeling severity. However, processes such as fat accumulation,[173] edema, amyloidosis,[174] and other still unidentified factors might have great importance for AF progression and stabilization. The dynamic nature and specific pattern of myofibroblast–cardiomyocyte interactions is just emerging, and the extent to which they contribute to the initiation and maintenance of AF is unclear.

The upstream and downstream signaling pathways leading to focal ectopic/triggered firing and AF-maintaining re-entry need precise delineation. The identification of nodal points in atrial cardiomyocyte signaling will be a key to sort out common determinants among pathophysiological contributors. This may help to identify and target key drivers of the fibrillatory process.

Cardiac genomics and proteomics require further exploration and clarification. Advanced bioinformatics and computational modeling approaches have the capacity to integrate and synthesize current insights to grapple with the complexity of AF. Computational science might play a key translational role in understanding and combating the mechanisms of AF in vivo, because sophisticated multiscale computational modeling can integrate the cellular and molecular processes in the second and third dimensions, providing key insights into the impact of molecular events for AF at the multicellular tissue level.

Although animal models have provided a wealth of information on AF pathophysiology, they have important limitations.[46] Few currently available experimental models show spontaneous AF occurrence and progression as observed in patients. Therapeutic interventions that are effective in animal models are often unsuccessful in patients, and the interpretation of genetic models may be hindered by complex compensatory phenomena.[18,46] Animal models tend to focus on specific isolated pathophysiological stressors applied for a relatively short period of time in the absence of other forms of disease (eg, AF because of experimental hypertension, HF, ischemia, diabetes mellitus, thyroid dysfunction). Clinical AF is often the result of many years of complex pathophysiology including multiple disease conditions, modified by extraneous drug therapy. Thus, the mechanisms observed in much simpler experimental models might operate in complex combinations, or even not at all, in patients with similar clinical conditions. Newer methods involving in vivo imaging of structural and functional substrate in patients may hold the key to therapeutic application of fundamental concepts,[175–178] but currently available invasive and noninvasive mapping methods that assess the dynamics of AF in patients do not adequately exploit our knowledge of the cellular and molecular pathophysiology of AF.

Importantly, the causes of AF are extremely diverse. Rather than a specific disease, AF is a final end product of a wide range of clinical conditions, as discussed in detail in another article of this compendium.[15] The exact combination of individual pathophysiological processes contributing to AF is likely distinct in specific patient subsets.[15] Improved understanding of the connection between causes of AF and cellular mechanisms is required to provide tailored therapies for select patient cohorts.

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None.

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