Atrial Remodeling and Atrial Fibrillation
Mechanisms and Implications

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It can occur at any age but is very rare in children and becomes extremely common in the elderly, with a prevalence approaching 20% in patients >85 years of age.1 AF is associated with a wide range of potential complications and contributes significantly to population morbidity and mortality. Present therapeutic approaches to AF have major limitations, including limited efficacy and significant adverse effect liability. These limitations have inspired substantial efforts to improve our understanding of the mechanisms underlying AF, with the premise that improved mechanistic insights will lead to innovative and improved therapeutic approaches.2

Our understanding of AF pathophysiology has advanced significantly over the past 10 to 15 years through an increased awareness of the role of “atrial remodeling.” Any persistent change in atrial structure or function constitutes atrial remodeling. Many forms of atrial remodeling promote the occurrence or maintenance of AF by acting on the fundamental arrhythmia mechanisms illustrated in Figure 1. Both rapid ectopic firing and reentry can maintain AF. Reentry requires a suitable vulnerable substrate, as well as a trigger that acts on the substrate to initiate reentry. Ectopic firing contributes to reentry by providing triggers for reentry induction. Atrial remodeling has the potential to increase the likelihood of ectopic or reentrant activity through a multitude of potential mechanisms. This article reviews the types of atrial remodeling, their underlying pathophysiology, the molecular basis of their occurrence, and finally, their potential therapeutic significance.

Physiological Mechanisms by Which Remodeling Promotes AF

The mechanisms underlying AF are portrayed schematically in Figure 2. AF can be maintained by rapid focal firing, which may itself be regular but result in fibrillatory activity because of wave breakup in portions of the atrium that fail to follow 1:1 conduction (Figure 2A).3 In addition to their potential role as an AF driver, ectopic foci can contribute to AF by acting on vulnerable reentrant substrates to initiate AF. One form of reentrant AF involves a single, rapidly firing reentrant circuit, which (like rapid focal firing) produces fibrillatory activity by virtue of an irregular, fractionated atrial response (Figure 2B). Fibrillatory activity can also be an intrinsic consequence of the AF-maintaining mechanism, when AF is maintained by multiple simultaneous functional reentry circuits (Figure 2C).

Atrial Remodeling and Reentry

Figure 3 illustrates the fundamental determinants of reentry and the effects of atrial remodeling. Figure 3A shows the initiation of reentry in a schematic circuit. An ectopic beat encounters refractory tissue when propagating in one direction, while able to conduct in faster-recovering tissue in the other direction (“unidirectional block”). For reentry to be maintained (Figure 3B), the impulse must traverse the entire circuit slowly enough for all points to regain excitability, i.e., the conduction time has to be greater than the longest refractory period in the circuit. Conduction time is determined by circuit path length and conduction velocity: Long path lengths and slow conduction increase circuit time, which makes it more likely that all points will have recovered excitability early enough to be reactivated by the reentering impulse. The recovery of excitability is governed by the refractory period: Short refractory periods increase the likelihood that tissue will be available for reactivation when the reentering impulse passes through. The “wavelength,” or distance traveled by an impulse in 1 refractory period (given as the product of refractory period and conduction speed), is a useful concept to relate the determinants of reentry. The wavelength approximates the shortest path length for reentry and determines the size of functional reentry circuits. Factors that reduce the atrial wavelength decrease reentry-circuit dimensions, which increases the potential number of simultaneous circuits and augments the probability of AF maintenance.

The ways in which atrial remodeling can promote reentry are illustrated at the bottom of Figure 3 (for a detailed description of the underlying physiology, see reference 4). Atrial refractoriness depends on cardiac action potential duration (APD), because the Na+ channels that govern cardiomyocyte excitability inactivate when cells are depolarized and require repolarization to ≈−60 mV for channel
availability to return (Figure 3C). APD is determined by the balance between inward currents (primarily Ca\(^{2+}\), which tends to keep the cell depolarized) and outward currents (primarily K\(^{+}\), which tends to repolarize) during the action potential plateau. Atrial remodeling can abbreviate APDs and refractory periods in either way: Sustained rapid atrial activation, as occurs during AF, reduces inward L-type Ca\(^{2+}\) current (\(I_{Ca,L}\)) and also enhances outward K\(^{+}\) currents.\(^4\) These actions are major contributors to clinically relevant AF promotion.\(^5,6\)

Atrial conduction slowing can result from changes in sarcolemmal (cell membrane) Na\(^{+}\) channels, gap junction channels (connexins), or tissue structure (Figure 3D). Normal impulse conduction depends on the balance between the energy for conduction provided by tissue firing (the current “source”) and the dissipation of this energy by the downstream tissue that has to be fired (the current “sink”). The energy source for conduction derives from the large phase 0 Na\(^{+}\) current (\(I_{Na}\)). Energy dissipation is minimized by having good electrical coupling between cardiac cells (provided by low-resistance gap junction channels that connect cell ends in a longitudinal fashion) and a high resistance to lateral current leakage (ensured by a continuous cable-like organization of cardiomyocyte bundles). Atrial tachycardia appears to suppress expression of the atrial-selective connexin-40.\(^7\) There is also evidence that atrial tachycardia remodeling (ATR) reduces \(I_{Na}\).\(^8\) Congestive heart failure (CHF), a strong promoter of atrial remodeling that facilitates fibrillation, causes atrial tissue fibrosis that interferes with local atrial conduction by disturbing the continuous cable-like arrangement of cardiomyocytes.\(^9,10\)

Atrial dilation increases the amount of atrial tissue that can accommodate reentry circuits (Figure 3E). Larger atrial size means that more circuits can be accommodated and that long-wavelength circuits that are too large for a normal atrium can be supported. Atrial dimensions are a particularly important determinant of the occurrence of multiple-circuit reentry.\(^11\) Atrial enlargement can occur with both atrial tachycardia– and CHF-related remodeling;\(^12\) and is an important clinical predictor of AF maintenance.\(^13\) However, atrial dilation is not essential for the maintenance of CHF-related AF: After full hemodynamic recovery from CHF, fibrosis remains, and sustained AF is still inducible, despite the absence of atrial dilation.\(^10\)

Atrial Remodeling and Ectopic Activity

Figure 4 illustrates the principal mechanisms that generate ectopic activity. The spontaneous firing rate of potentially automatic atrial foci is determined by the slope of phase 4 depolarization, which establishes the time required to reach threshold potential and generate a spontaneous action potential. If the atrial cell firing rate is slower than the sinus node rate, no ectopic activity occurs. When the slope of phase 4 is accelerated, the spontaneous rate increases, and ectopic beats or sustained tachycardias may occur. Increased atrial expression of ion channel subunits that underlie a potentially important contributor to phase 4 depolarization, the “funny current” (\(I_{f}\)),\(^4\) has been observed in both atrial tachycardia–related\(^14\) and CHF-related\(^15\) remodeling; however, there has been no direct demonstration of enhanced automaticity due to accelerated phase 4 depolarization in AF.

Abnormalities in cellular Ca\(^{2+}\) handling, particularly Ca\(^{2+}\) overload, can cause delayed afterdepolarizations (DADs; Figure 4B), which are spontaneous hump-shaped depolarizations after full cellular repolarization. DADs differ from...
spontaneous phase 4 depolarization in both shape and mechanism. When DADs become large enough to reach threshold potential, they cause cell firing, either as the single ectopic beat illustrated in Figure 4B or as a sustained tachycardia. Ca²⁺ enters cells through L-type Ca²⁺ channels with each action potential, so rapid firing rates increase Ca²⁺ entry and can induce DAD-related tachyarrhythmias (so-called triggered activity). CHF promotes atrial DADs by enhancing cellular Ca²⁺ loading. Pulmonary veins may be particularly prone to triggered activity, although the evidence for this is controversial.

Early afterdepolarizations (EADs; Figure 4C) occur when action potentials become abnormally prolonged, which allows ICa,L to recover from inactivation and to generate abnormal depolarizations at plateau potentials. Although EADs are most characteristic of Purkinje fiber tissue and long-QT syndrome ventricular tachyarrhythmias, EAD-related arrhythmias can also occur at the atrial level. Investigators have yet to demonstrate a clear role for EAD-related mechanisms in atrial remodeling.

**Components of Atrial Remodeling**

Although many processes can alter atrial properties and promote AF, animal models and clinical studies have provided insights into 2 major forms of atrial remodeling: ATR, which occurs with rapid atrial tachyarrhythmias such as AF and atrial flutter, and atrial structural remodeling (ASR), which is associated with CHF and other fibrosis-promoting conditions.

**Molecular Basis of Atrial Remodeling**

**Atrial Repolarization Abnormalities**

The recognition that AF alters atrial electrophysiological properties, promoting AF induction and maintenance, was an important advance in AF pathophysiology. AF induces electrical remodeling primarily by virtue of a very rapid atrial rate and associated ATR. Whether AF can produce additional forms of remodeling, particularly when the arrhythmia...
remains sustained for prolonged periods, remains uncertain. \(^24\) Figure 5 summarizes the molecular mechanisms that underlie ATR promotion of reentrant AF. ATR abbreviates atrial refractoriness by decreasing APD, primarily by \(I_{\text{CaL}}\) down-regulation\(^2\) but also via increased inward-rectifier \(K^+\) currents such as the background current \(I_{\text{K1}}\) and a constitutively active form of acetylcholine-dependent \(K^+\) current \(I_{\text{KACh,c}}\).\(^6,25,26\) In addition, ATR impairs atrial contractility, principally by causing \(Ca^{2+}\)-handling abnormalities,\(^27\) which causes atrial dilation\(^12\) that further promotes reentry.

**L-Type \(Ca^{2+}\) Current**

The abrupt \(9\)-fold increase in atrial rate with the onset of AF substantially increases \(Ca^{2+}\) loading. Atrial cardiomyocytes respond by reducing \(Ca^{2+}\) influx via \(I_{\text{CaL}}\) to prevent potentially cytotoxic \(Ca^{2+}\) overload, but reduced \(I_{\text{CaL}}\) decreases APD and wavelength, which favors AF perpetuation (Figure 5). Initially, rapid APD shortening occurs because of functional \(I_{\text{CaL}}\) inactivation. Sustained AF causes more persistent \(I_{\text{CaL}}\) decreases, predominantly via downregulation of \(I_{\text{CaL}}\) pore-forming \(\alpha\)-subunit mRNA\(^28\) but possibly also via posttranscriptional mechanisms such as protein dephosphorylation and breakdown.\(^29,30\) In addition, intracellular \(Ca^{2+}\) handling is altered, which contributes to loss of APD rate dependence and favors reentry-facilitating alternans behavior.\(^31\) Some studies at the protein level have confirmed ATR-induced reductions in Cav1.2 \(\alpha\)-subunit abundance,\(^28,32\) whereas others suggest unchanged \(\alpha\)-subunit protein.\(^29,33,34\) Investigators have also detected reduced expression of \(\beta_1, \beta_2, \beta_3, \beta_4\), and \(\alpha_{2,3}\) accessory \(I_{\text{CaL}}\) subunits.\(^29,33,35,36\) Decreased expression of the endogenous antioxidant glutathione, the major cellular reducing agent, accompanies enhanced \(S\)-nitrosylation.\(^37\) Cav1.2 \(S\)-nitrosylation is increased in AF, and exogenously applied glutathione partially restores AF-related \(I_{\text{CaL}}\) reductions.\(^37\) Thus, oxidative stress could play an important role in \(I_{\text{CaL}}\) changes. Recent findings also suggest increased atrial expression of \(ZnT-1\), a protein originally associated with zinc homeostasis, in ATR.\(^38,39\) \(ZnT-1\) suppresses \(I_{\text{CaL}}\) via presently unknown mechanisms.\(^38\) Protein kinases attach phosphate groups to proteins, which causes phosphorylation that controls protein function. Altered regulation of \(I_{\text{CaL}}\) by src-type tyrosine kinases may also cause \(I_{\text{CaL}}\) dysregulation.\(^34\)

**Inward-Rectifier \(K^+\) Currents**

The cardiomyocyte resting membrane potential is set by background \(K^+\) conductances, primarily inward rectifiers, and becomes more negative in AF.\(^25,26,40\) The main background conductance that controls atrial resting potential is designated \(I_{\text{K1}}\) and is formed by Kir2.1-family subunits, especially Kir2.1. AF increases expression levels of Kir2.1 mRNA\(^25,35\) and protein,\(^35\) which enlarge \(I_{\text{K1}}\).

The inward-rectifier \(K^+\) current \(I_{\text{KACh}}\) mediates cardiac vagal effects: Acetylcholine released from vagal nerve endings activates \(I_{\text{KACh}}\), which causes APD abbreviation and cell-membrane hyperpolarization. Increased vagal activity strongly promotes AF by stabilizing atrial reentrant rotors, and clinical AF often begins under vagotonic conditions.\(^42\) ATR alters the \(I_{\text{KACh}}\) system such that agonist-stimulated \(I_{\text{KACh}}\) (as occurs with vagal activation) is reduced, but agonist-independent ("constitutive") \(I_{\text{KACh}}\) \((I_{\text{KACh,c}})\) is enhanced.\(^5,26,43,44\) Increased \(I_{\text{KACh,c}}\) enhancement is due to increased single-channel open probability caused by slowed channel closure.\(^44\) mRNA and protein expression of Kir3 subunits underlying \(I_{\text{KACh}}\) are unchanged in experimental ATR,\(^43,44\) whereas in AF patients, they are decreased,\(^26\) so increased \(I_{\text{KACh,c}}\) is not due to increased expression of the underlying ion channel subunits. Inhibition of protein kinase C (PKC) reduces \(I_{\text{KACh,c}}\) activity, and PKC\(\varepsilon\) protein is upregulated in AF,\(^45\) which suggests that increased protein kinase C–mediated phosphorylation is important for AF-induced \(I_{\text{KACh,c}}\) augmentation. \(I_{\text{KACh,c}}\) blockade suppresses ATR-induced APD abbreviation and AF promotion,\(^6\) which indicates that \(I_{\text{KACh,c}}\) plays an important role in arrhythmogenesis.

The ATP-sensitive inward-rectifier \(K^+\) current \((I_{\text{KATP}})\) is an important contributor to ischemia-induced electrophysiological abnormalities, and relative ischemia is a potential con-

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**Figure 5.** Mechanisms underlying ATR. Rapid atrial rates increase potentially cytotoxic \(Ca^{2+}\) loading. Autoprotective \(I_{\text{CaL}}\) reductions occur via rapidly developing functional changes (\(I_{\text{CaL}}\) inactivation) and more slowly developing changes in gene and protein expression. Decreased \(I_{\text{CaL}}\) reduces \(Ca^{2+}\) loading but decreases APD. Diminished APD shortens refractoriness and reduces the wavelength (WL), which allows for smaller and more atrial reentry circuits, thus making AF unlikely to terminate. Atrial tachycardia also increases inward-rectifier currents such as \(I_{\text{K1}}\) and \(I_{\text{KACh,c}}\), which further reduces APD and promotes AF. RP indicates refractory period; WL, wavelength.
Atrial Conduction Abnormalities

Structural Remodeling and Fibrosis

Extensive evidence indicates that structural remodeling, particularly interstitial fibrosis, is an important contributor to the AF substrate. The regulatory mechanisms that underlie atrial extracellular matrix remodeling are incompletely understood, and the precise signaling pathways that lead to structural changes may vary in different heart disease paradigms. Several secreted factors are known to be profibrotic. In addition to their individual effects, they often act synergistically. Angiotensin II and transforming growth factor-β1 (TGF-β1) are well-established profibrotic molecules, and recent evidence points to significant roles for platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF). Figure 6 depicts the interplay of various signaling systems.

Angiotensin II

Angiotensin II mediates cardiac fibrosis in a variety of cardiac pathologies, including hypertensive heart disease, CHF, myocardial infarction, and cardiomyopathy. Transgenic mice with cardiac-restricted ACE overexpression show marked atrial dilation with focal fibrosis and AF. Angiotensin II acts by binding to 2 discrete receptor subtypes, angiotensin type I (AT1R) and type II (AT2R) receptors. The signaling cascades coupled to AT1Rs and AT2Rs are distinct and often have opposing actions. AT1Rs mediate the profibrotic effects of angiotensin II by stimulating fibroblast proliferation, cardiomyocyte hypertrophy, and apoptosis. Angiotensin II signaling through the Shc/Grb2/SOS adapter-protein complex activates the small GTPase protein Ras, which initiates mitogen-activated protein kinase phosphorylation cascades that are centrally involved in remodeling. The mitogen-activated protein kinases ERK (extracellular signal-related kinase)-1 and -2, p38, and JNK (c-Jun N-terminal kinase)-1 and -2, protein kinase C; PDGFR, PDGF receptor; PIP2, phosphatidylinositol bisphosphate; PLC, phospholipase C; PPIA, protein serine/threonine phosphatase 2A; PTP, phosphotyrosine phosphatase; Shc, src homologous and collagen protein; SMAD, SMA- and MAD-related proteins; SOS, son of sevenless protein; STAT, signal transducers and activators of transcription; TAK1, TGF-β₁-activated kinase 1; TF, transcription factor; TGF-β; TIMP, tissue inhibitor of matrix metalloproteinase.

Figure 6. Major profibrotic signaling pathways involved in atrial fibrosis. Interaction between pathways produces positive feedback that is important in fibrosis development. αβ indicates integrin receptor α- and β-subunits; Ang II, angiotensin II; AP-1, activator protein-1; DAG, diacetyl glycerol; ERK 1/2, extracellular signal-related kinase 1/2; Grb2, growth factor receptor binding protein 2; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK 1/2, mitogen-activated/ERK kinase 1/2; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PKC, protein kinase C; PDGFR, PDGF receptor; PIP2, phosphatidylinositol bisphosphate; PLC, phospholipase C; PPIA, protein serine/threonine phosphatase 2A; PTP, phosphotyrosine phosphatase; Shc, src homologous and collagen protein; SMAD, SMA- and MAD-related proteins; SOS, son of sevenless protein; STAT, signal transducers and activators of transcription; TAK1, TGF-β₁-activated kinase 1; TF, transcription factor; TGF-β; TIMP, tissue inhibitor of matrix metalloproteinase.
kinase) activate transcription factors (Elk-1, c-jun, and c-fos) that modulate gene expression. In addition, AT1R activation stimulates phospholipase C. Phospholipase C breaks down membrane phosphoinositide bisphosphate (PIP2) into diacylglycerol and inositol 1,4,5-trisphosphate (IP3). Diacylglycerol activates protein kinase C, and IP3 causes intracellular Ca2+ release, both of which promote remodeling. Signal transduction also occurs through the JAK/STAT pathway, activating transcription factors such as activator protein-1 and nuclear factor-kB. AT2R activation inhibits mitogen-activated protein kinasesthrough dephosphorylating actions of phosphatase and protein phosphatase 2A and produces antiproliferative and survival-promoting effects that oppose AT1R-mediated changes. The balance between the 2 counterregulatory angiotensin II receptor subtypes (AT1R and AT2R) may have important therapeutic implications.

**Transforming Growth Factor β1**

TGF-β1 is secreted by both cardiomyocytes and fibroblasts and acts as a primary downstream mediator of angiotensin II effects in both autocrine (influencing the cell that produces angiotensin II/TGF-β1) and paracrine (influencing adjacent cells) manners. Angiotensin II induces TGF-β1 synthesis, which potently stimulates fibroblast activity. In turn, TGF-β1 reciprocally enhances the production of angiotensin II and additional profibrotic factors to create positive feedback. TGF-β1 acts primarily through the SMAD protein (homolog of the Drosophila protein “mothers against decapentaplegic,” or MAD, and the Caenorhabditis elegans protein, SMA) pathway to stimulate fibroblast activation and collagen deposition. Cardiac overexpression of constitutively active TGF-β1 causes selective atrial fibrosis, atrial conduction heterogeneity, and AF promotion.

**Platelet-Derived Growth Factor**

PDGF, a PDGF/vascular endothelial growth factor family member, stimulates fibroblast proliferation and differentiation. Occupation of PDGF receptors causes them to dimerize, which activates a tyrosine kinase that forms part of the PDGF receptor molecule. This tyrosine kinase phosphorylates intracellular domains of the PDGF receptor (autophosphorylation). Autophosphorylation activates PDGF receptors, initiating signaling via mitogen-activated protein kinase, JAK/STAT, and phospholipase C pathways shared with TGF-β1 and angiotensin II. PDGF appears to underlie atrium-selective fibroblast hyperresponsiveness, which may explain why atria are much more susceptible to fibrotic remodeling than ventricles.

**Connective Tissue Growth Factor**

CTGF is a member of the CCN (cyr61, ctgf, nov) protein family and a major downstream effector of TGF-β1 fibrosis promotion. Areas with active myocardial remodeling show coordinate CTGF expression with TGF-β1. CTGF is upregulated by both angiotensin II and TGF-β1, and it directly activates fibroblasts.

**Profibrotic Signaling in AF Paradigms**

Atrial angiotensin II expression increases rapidly in tachycardia-induced CHF. Renin-angiotensin-aldosterone inhibition by ACE inhibitors, AT1R blockers, or aldosterone antagonists prevents atrial fibrosis and associated AF promotion. Atrial TGF-β1 is activated rapidly during tachypacing-induced CHF and TGF-β1 inhibition by pirfenidone attenuates remodeling and AF. Pathway analysis has implicated CTGF as a potentially important atrial fibrotic mediator. There is a delicate balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases in extracellular matrix degradation, and important changes in the tissue inhibitor of metalloproteinases/matrix metalloproteinase system are seen in AF.

Leukocyte infiltration and increased cell death occur in CHF-induced ASR. Oxidant stress is enhanced in AF, which promotes fibrosis through both cell death and proinflammatory pathways. Rac1 GTPase, a small G-protein NADPH oxidase regulator that increases oxidant stress, is upregulated in AF and produces atrial fibrosis–related AF in mice. Statins, which inhibit Rac1 GTPase, prevent ASR, possibly by antioxidant mechanisms.

**Ion Channels Involved in Atrial Conduction**

**Gap Junction Remodeling**

Relatively little is certain about atrial gap junction remodeling; results reported in the literature vary widely. Some of the discrepancies may relate to differences in the duration of AF and the nature of the underlying cardiac pathology. Spatially heterogeneous connexin-40 remodeling occurs in the well-established goat AF-remodeling system, consistent with clinical evidence for genetically controlled variability in connexin-40 as a determinant of AF predisposition.

**Sodium Channel Remodeling**

I Na is reduced in canine ATR, with corresponding decreases in mRNA and protein expression. However, studies in AF patients have not confirmed I Na downregulation.

**Ectopic Impulse Formation**

Ca2+-related triggered activity caused by abnormal Ca2+ handling is a strong candidate mechanism to underlie AF-generating ectopic foci. The main determinants of cellular Ca2+ handling are illustrated in Figure 7. Ca2+ enters cells principally via Ca2+ influx through L-type Ca2+ channels. Ca2+ entry triggers opening of SR Ca2+-release channels (commonly called ryanodine receptors, or RyRs), which causes substantial Ca2+-induced Ca2+ release. The Ca2+ that has entered the cytoplasm during systole is removed in diastole by 2 primary mechanisms: (1) active pumping back into the sarcoplasmic reticulum (SR) via SR Ca2+-ATPase (or SERCA), and (2) extrusion across the cell membrane through the Na+-Ca2+ exchanger (NCX). NCX transfers 3 Na+ ions into the cell for every Ca2+ ion exported, which yields a net inward (depolarizing) current. SERCA is regulated by the associated protein phospholamban, which inhibits SERCA function. Phospholamban phosphorylation reduces its SERCA-inhibitory capacity and enhances SR Ca2+ uptake. The accessory protein FKBP12.6 binds to and stabilizes RyR function, which prevents diastolic RyR reopening. Hyperphosphorylated RyRs lose FKBP12.6 binding, which causes arrhythmogenic diastolic SR Ca2+ leak. Any cause of diastol-
ic Ca\textsuperscript{2+} leak, including cell Ca\textsuperscript{2+} overload and RyR dysfunction due to FKBP12.6 unbinding, increases diastolic [Ca\textsuperscript{2+}], and enhances Ca\textsuperscript{2+} extrusion via NCX-mediated exchange. Enhanced diastolic NCX activity produces a depolarizing current that causes DADs. Calsequestrin is the main SR Ca\textsuperscript{2+}-binding protein. Ca\textsuperscript{2+} binding by calsequestrin allows the SR to maintain large Ca\textsuperscript{2+} stores without excessive free Ca\textsuperscript{2+} concentration. Calsequestrin deficiency impairs SR Ca\textsuperscript{2+} binding and function, which promotes Ca\textsuperscript{2+}-release events and DADs.

Relatively little is known about the molecular basis for abnormal Ca\textsuperscript{2+} handling in AF. The expression levels of calsequestrin, RyRs, and phospholamban are preserved in AF.\textsuperscript{29,35,82} NCX expression may be upregulated,\textsuperscript{35,83} which accelerates Ca\textsuperscript{2+} extrusion from the cytoplasm at the expense of larger DAD-generating inward currents produced by electrogenic Ca\textsuperscript{2+} removal. The phosphorylation states of several key Ca\textsuperscript{2+}-handling proteins are altered in AF. Protein kinase A (PKA) and Ca\textsuperscript{2+} calmodulin kinase II (CaMKII) hyperphosphorylation of phospholamban,\textsuperscript{84} along with decreased sarcolipin\textsuperscript{85} (another SERCA inhibitor), enhances SR Ca\textsuperscript{2+} uptake, which reduces diastolic [Ca\textsuperscript{2+}], load at the expense of promoting SR Ca\textsuperscript{2+} overload. Protein kinase A–overexpressing mice have hyperphosphorylated phospholamban and RyRs and develop AF.\textsuperscript{86} Besides enhanced phosphorylation by kinases, phospholamban and RyR2 hyperphosphorylation may also result from reduced dephosphorylation. Protein phosphatase 1 (PP1) is a key dephosphorylating enzyme. PP1 function is inhibited in AF by increased activity of an endogenous inhibitor, phosphatase inhibitor protein-1 (I-1).\textsuperscript{87} I-1 is activated by protein kinase A phosphorylation. I-1 protein kinase A phosphorylation is increased 10-fold in AF, to a level that completely inhibits SR-bound PP1 activity.\textsuperscript{84} IP\textsubscript{3} receptor (IP\textsubscript{3}R2)-mediated SR Ca\textsuperscript{2+} release may amplify Ca\textsuperscript{2+} leak via RyRs to promote atrial arrhythmogenesis,\textsuperscript{88} and IP\textsubscript{3}R2 protein expression is increased by ATR.\textsuperscript{89} IP\textsubscript{3}R2-coupled atrial SR Ca\textsuperscript{2+}-release enhancement and related arrhythmogenesis\textsuperscript{90} may thus be an important contributor to AF-related ectopic activity.

Figure 8 summarizes the interplay between various Ca\textsuperscript{2+} homeostasis–related factors in AF. We have already discussed the role of Ca\textsuperscript{2+} loading and associated ionic changes in ATR-induced reentry promotion. Protein hyperphosphorylation due to enhanced I-1, CaMKII, or protein kinase A function,\textsuperscript{82,84,86} along with decreased SR-bound PP1 activity,\textsuperscript{84} causes arrhythmogenic dysfunction of RyR/FKBP12.6 and SERCA/phospholamban complexes. Calmodulin and calcineurin are Ca\textsuperscript{2+}-regulated proteins that play key roles in remodeling, and nitric oxide and NADPH oxidase control oxidation-state changes that regulate remodeling and Ca\textsuperscript{2+} handling. Both reentry and focal driver mechanisms related to triggered activity contribute to CHF-induced AF.\textsuperscript{5,16,17} CaMKII-mediated phospholamban hyperphosphorylation contributes to SR Ca\textsuperscript{2+} overload in CHF, causing spontaneous Ca\textsuperscript{2+}-release events and DAD-related triggered activity.\textsuperscript{17}
Potential Therapeutic Implications

Extensive evidence implicates atrial remodeling as an important player in the pathophysiology of AF. Therefore, atrial remodeling may have significant therapeutic implications.

Therapeutic Consequences of ATR

Implications for Traditional Therapeutic Approaches

The changes in ion channel function caused by ATR alter the response to antiarrhythmic drugs, which in general makes AF more drug-resistant. A poorer response of more prolonged AF has been shown for both Na\(^+\) and K\(^+\) channel blockers. Early detection and termination of AF increases the clinical effectiveness of pharmacological cardioversion. However, electrical cardioversion is highly effective in restoring sinus rhythm irrespective of AF duration, and the value of an early termination strategy for electrical cardioversion is unclear. Implantable atrial defibrillators permit rapid detection and termination of AF. A strategy of early cardioversion reduces atrial remodeling, prevents atrial dysfunction, reduces atrial size, and may prolong sinus rhythm maintenance after cardioversion. However, there is little clinical evidence for the practical value of an early cardioversion strategy.

ATR Suppression as an Antiarrhythmic Principle

ATR is a potentially interesting antiarrhythmic drug target. Both the T-type Ca\(^{2+}\) channel blocker mibefradil and amiodarone suppress ATR, whereas I\(_{\text{Ca-L}}\), K\(^{+}\), and Na\(^{+}\) channel blockers are ineffective, and it has been suggested that ATR suppression may contribute to the superior efficacy of amiodarone in AF. Bepridil, an L- and T-type Ca\(^{2+}\) channel blocker, also suppresses ATR, an action that may explain its unusual ability to convert long-standing AF. Inflammation and tissue oxidation are believed to be important mediators in atrial remodeling. Drugs with antiinflammatory and antioxidant properties, such as glucocorticoids and statins, suppress ATR and have shown some clinical value in preventing AF recurrence. ATR suppression may thus prove to be a useful principle as either a primary or adjunct property of new antiarrhythmic drugs. In addition, understanding the ionic basis of ATR may allow for the development of novel ionic targets for antiarrhythmic drug development, such as I\(_{\text{KCa}}\).

Therapeutic Consequences of ASR

Initial experiments suggested the potential value of angiotensin-production inhibition in the prevention of ASR-related

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HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; PUFAs, polyunsaturated fatty acids; and HSP, heat shock protein.

Conclusions
Considerable progress has been made in understanding the mechanisms underlying atrial remodeling. These insights have potentially important implications for our understanding of the pathophysiology of AF and for the development of new therapeutic approaches.

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Disclosures
Dr Nattel is listed as an inventor on intellectual property belonging to the Montreal Heart Institute: “Statin drugs to treat atrial fibrillation” and “Acetylcholine-dependent current as a novel ionic target for AF.” Dr Dobrev and B. Burstein report no conflicts.

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