TOPICS IN REVIEW

# Atrial remodeling and atrial fibrillation in acquired forms of cardiovascular disease

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Atrial fibrillation (AF) is prevalent in common conditions and acquired forms of heart disease, including diabetes mellitus (DM), hypertension, cardiac hypertrophy, and heart failure. AF is also prevalent in aging. Although acquired heart disease is common in aging individuals, age is also an independent risk factor for AF. Importantly, not all individuals age at the same rate. Rather, individuals of the same chronological age can vary in health status from fit to frail. Frailty can be quantified using a frailty index, which can be used to assess heterogeneity in individuals of the same chronological age. AF is thought to occur in association with electrical remodeling due to changes in ion channel expression or function as well as structural remodeling due to fibrosis, myocyte hypertrophy, or adiposity. These forms of remodeling can lead to triggered activity and electrical re-entry, which are fundamental mechanisms of AF initiation and maintenance. Nevertheless, the underlying determinants of electrical and structural remodeling are distinct in different conditions and disease states. In this focused review, we consider the factors leading to atrial electrical and structural remodeling in human patients and animal models of acquired cardiovascular disease or associated risk factors. Our goal is to identify similarities and differences in the cellular and molecular bases for atrial electrical and structural remodeling in conditions including DM, hypertension, hypertrophy, heart failure, aging, and frailty.

**KEYWORDS** Aging; Diabetes mellitus; Electrical remodeling; Fibrosis; Frailty; Heart failure; Hypertension; Hypertrophy; Obesity

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## Introduction

Atrial fibrillation (AF) is well recognized as the most common sustained arrhythmia. In North America and Europe, the overall prevalence of AF is ~1%–2%, and this is projected to double over the next 2 decades.[1,2] AF is associated with substantial morbidity and mortality. This includes an increased risk of ischemic stroke, heart failure (HF), and significant impairment in quality of life.[3,4] Major risk factors for AF include aging, obesity, hypertension, cardiac hypertrophy, HF, and diabetes mellitus (DM).[1,5] Current therapeutic approaches for AF are limited by a lack of efficacy and numerous undesirable side effects. This is likely due to an incomplete understanding of the mechanistic basis for AF development and progression in different conditions or disease states. Atrial remodeling, including electrical and structural remodeling, is thought to be important in the development of a substrate for AF (Figure 1). In this focused review, we consider the bases for atrial electrical and structural remodeling in different conditions and commonly acquired forms of disease, including DM, obesity, hypertension, hypertrophy, HF, aging, and frailty. Our goal is to address the concept that the cellular and molecular mechanisms that underlie atrial remodeling may be distinct among these different conditions. Improving our understanding of these phenomena in these distinct conditions could lead to better and more effective therapeutic options for AF prevention and treatment.

We note that there is also a genetic component to AF.[6–8] Heritable genetic variants can underlie AF independently but can also occur in combination with age and acquired risk factors, including the common forms of heart disease addressed in this review. Although the genetics of AF is an important developing area of research, it will not be considered in detail in this review. We also note that there

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## KEY FINDINGS

- Atrial fibrillation is prevalent in hypertension, heart failure, diabetes mellitus, and aging.
- Atrial fibrillation can occur in association with electrical remodeling and structural remodeling in the atria.
- Studies in humans and animal models show that the basis for atrial remodeling is distinct in different forms of acquired cardiovascular disease.
- Determining the mechanistic basis for atrial remodeling in different conditions and diseases could lead to better therapeutic approaches for atrial fibrillation in these conditions.

are well-known differences in cellular electrophysiology between males and females[9,10] and that the overall incidence of AF is lower in females.[9,11] The role of sex differences may be more pronounced in some conditions compared to others. For example, the associations between hypertension and AF may be similar between the sexes.[12,13] Conversely, some studies have found that AF occurs more prevalently in females in DM.[14] Sex differences in AF and atrial remodeling remain poorly understood. Accordingly, detailed mechanistic investigations of sex differences in atrial remodeling in common conditions and acquired forms of heart disease, including in humans and animal models, are needed.

## Atrial physiology

In the normal heart, electrical conduction in the atria is highly organized due to the functional properties of cardiomyocytes and the connectivity of these myocytes via gap junctions. Spontaneous action potentials (APs) generated in the sinoatrial node lead to the generation of atrial APs that are propagated through the right and left atria before being conducted to the ventricular myocardium via the atrioventricular node and the ventricular conduction system.[15,16]

Atrial myocytes are characterized by the presence of a stable resting membrane potential due to the activity of the inward rectifier $K^+$ channel ($I_{K1}$, carried by $K_{ir}2.1$ channels). The AP upstroke is produced by the sodium current $I_{Na}$ (carried by $Na_V1.5$ channels). Subsequently, activation of the L-type $Ca^{2+}$ channel ($I_{Ca,L}$; carried by $Ca_V1.2$ and $Ca_V1.3$ channels) and the transient outward $K^+$ channel ($I_{to}$; carried by $K_V4.2/4.3$ channels) leads to the development of a plateau phase in the AP, which can be relatively short in atrial myocytes. In addition to $I_{to}$, repolarization of the atrial AP is facilitated by the activity of several more $K^+$ currents, including the ultrarapid delayed rectifier $K^+$ current ($I_{Kur}$; an atrial-specific $K^+$ current carried by $K_V1.5$ channels), the steady-state $K^+$ current ($I_{Kss}$; carried by $K_V2.1$ channels), the delayed rectifier $K^+$ currents $I_{Kr}$ and $I_{Ks}$ (carried by $K_V11.1$ and $K_V7.1$, respectively), and $I_{K1}$. It is important to note that the expression and functional role of these different repolarizing $K^+$ channels vary in different species. The ability of atrial myocytes to fire subsequent APs is importantly affected by the refractory period, which is determined by

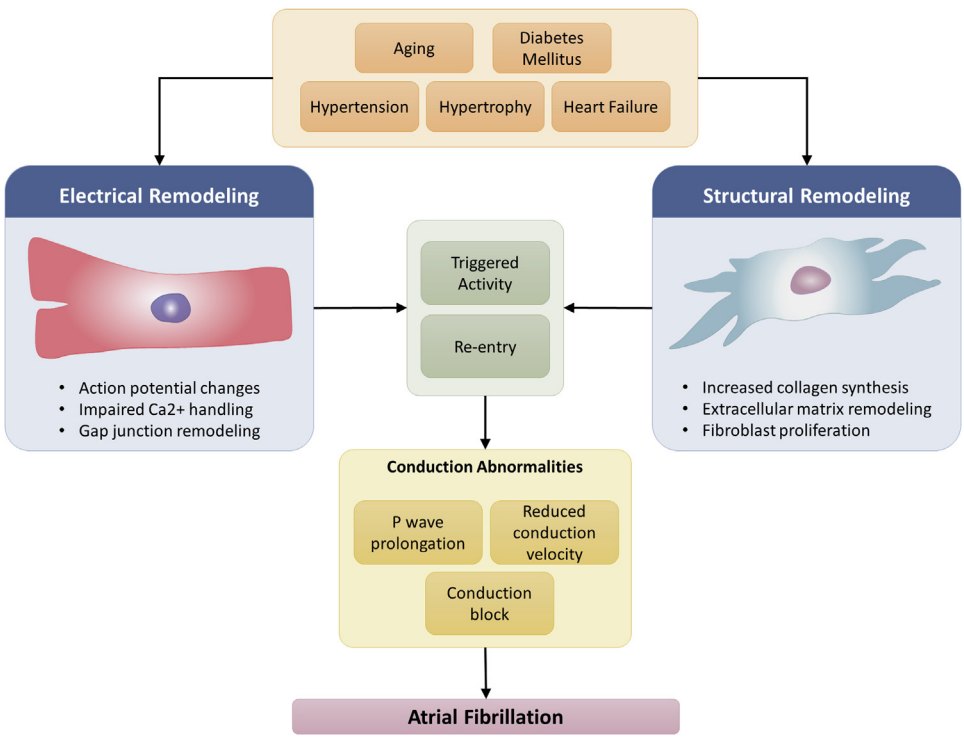


**Figure 1** Schematic illustration of the links between common conditions and diseases that lead to electrical and structural remodeling of the atria. These remodeling events can create a substrate for arrhythmia via triggered activity and electrical re-entry, leading to conduction abnormalities and the occurrence of atrial fibrillation.

the time course of repolarization and the recovery of $Na^+$ channels from inactivation.[17,18]

Atrial myocytes are electrically coupled to each other via gap junctions, which are formed from connexins. Connexin 40 (Cx40) and connexin 43 (Cx43) are the predominant connexins expressed in the atria.[17] Connexins ensure the rapid spread of electrical activity throughout the atria in a well-coordinated fashion. This is further facilitated by the structural organization of atrial myocytes, which is maintained by the interstitial collagens (produced and secreted by fibroblasts) in the atrial myocardium.[19] Collectively, these electrical and structural properties enable the atria to contract in a well-coordinated manner so that blood can be moved from the atria to the ventricles.

## Mechanisms of arrhythmia in AF

AF may arise when triggered activity occurs on a vulnerable substrate leading to electrical re-entry (Figure 1).[1] Forms of triggered activity thought to contribute to AF generation include early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). EADs typically occur when repolarization of the atrial myocyte is delayed or prolonged leading to an increase in action potential duration (APD). This allows $Ca^{2+}$ channels to recover from inactivation and reactivate, resulting in the generation of ectopic activity. DADs have been attributed to abnormalities in $Ca^{2+}$ handling by the sarcoplasmic reticulum (SR), leading to activation of the $Na^+$-$Ca^{2+}$ exchanger (NCX). Extrusion of $Ca^{2+}$ from the myocyte via NCX results in an inward current ($I_{NCX}$; sometimes called a transient inward current), which causes depolarizations that can lead to a triggered AP before the next sinus beat.

Re-entry can be anatomic or functional in origin.[1,20,21] In anatomic re-entry, fibrosis or other structural abnormalities can create anatomic re-entry points within the atrial myocardium. In functional re-entry, premature impulses are able to conduct around a border that was refractory in a unidirectional pattern. Re-entry allows a wave of excitation to travel a fixed pathway when an excitable gap develops (ie, the tissue behind the leading wave comes out of refractoriness to become excitable again), leading to a stable circuit that can develop into a tachyarrhythmia. The likelihood that re-entry–induced arrhythmia will ensue is determined by the wavelength of re-entry, which is the product of the conduction velocity and the effective refractory period (ERP). Reductions in either conduction velocity or ERP shorten the wavelength, creating a larger excitable gap and increasing the likelihood of re-entry. Atrial structural or electrical remodeling can develop in a number of ways in specific disease conditions, which can increase the likelihood of triggered activity (EADs or DADs) and/or electrical re-entry.

## DM

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are metabolic disorders associated with the development of hyperglycemia and changes in insulin production and signaling.[22–24] T1DM commonly manifests in childhood and is an autoimmune disorder in which the body destroys the insulin-producing β islet cells of the pancreas. Without these β cells, the pancreas is unable to produce insulin, which is responsible for stimulating glucose uptake from the bloodstream. As a result, people with T1DM fail to maintain normal blood glucose homeostasis, leading to hyperglycemia that must be managed by insulin supplementation.

T2DM usually develops in older adults and is synonymous with insulin resistance, as the pancreas is still capable of producing insulin but the tissues are less able to respond to it. It should be noted, however, that more young people (including children) are being diagnosed with T2DM in association with increasing rates of obesity.[25] As a result, the pancreas becomes chronically stimulated to secrete insulin. Eventually, organs and tissues can become resistant to insulin and hyperglycemia develops, leading to similar complications as seen in T1DM if the disease is not managed properly.[22] Over time, the demand placed on the pancreatic β cells can lead to insulin insufficiency, rendering those with T2DM insulin deficient as well as resistant. Loss of insulin production and hyperglycemia lead to a number of complications, including cardiovascular disease, which is prevalent in patients with T1DM and T2DM.

## Atrial remodeling and AF in T1DM

Whereas the proportion of people with T1DM is relatively small in comparison to those with T2DM, the incidence of T1DM continues to increase.[26,27] T1DM comes with an increased risk for AF, with women being more susceptible than men.[14,28] Consistent with this, a randomized controlled study revealed that complex fractionated atrial electrograms, which can be associated with atrial fibrosis, were higher in AF patients with T1DM than in those without T1DM,[29] suggesting that structural remodeling is more severe in those with AF and T1DM than in those with AF alone. Although direct assessment of atrial fibrosis in T1DM patients is lacking, a previous study observed interstitial fibrosis of the right ventricle in a small sample of T1DM patients without a history of coronary artery disease.[30] E/A ratios tend to be smaller (in association with larger A waves) in patients with T1DM, suggesting that the left atrium contributes more to filling of the left ventricle in T1DM.[31] This is consistent with diastolic dysfunction seen in patients with T1DM[31] and further suggests pathologic remodeling in the left atrium.

Animal studies have shown that atrial-specific remodeling occurs in T1DM. Commonly used models of T1DM include genetic models such as the Akita mouse (in which a genetic mutation in the *Ins2* gene causes proinsulin proteins to aggregate within β islet cells, leading to cell death and loss of insulin production) and nongenetic models that involve treating animals (usually rodents or rabbits) with either streptozotocin (STZ; an antibiotic that destroys the islet cells of the pancreas) or alloxan (a toxic glucose analogue that is selective for islet cells).[32,33]

Recently, it has been shown that Akita and STZ models of T1DM are characterized by substantial increases in AF

susceptibility and duration in association with electrical remodeling of the atria.[34,35] P-wave durations were prolonged in both models, and atrial conduction velocity was reduced in Akita mice. Detailed electrophysiological and molecular studies demonstrated that atrial AP upstroke velocity ($V_{max}$) was reduced, and APD was prolonged in Akita mice. These AP morphology changes occurred in association with reductions in atrial $I_{Na}$ and $I_{Kur}$. Atrial $I_{Na}$ was reduced due to reductions in expression of the *SCN5a* gene and a resultant decrease in $Na_V1.5$ protein in the atria, as well as a loss of phosphoinositide 3-kinase (PI3K) signaling via the second messenger phosphatidylinositol 3,4,5 trisphosphate ($PIP_3$). These observations are consistent with other studies showing that PI3K and $PIP_3$ have important effects on $Na^+$ channel function.[36] Importantly, it has been shown that insulin has important and selective effects on atrial $I_{Na}$ in Akita mice.[34] Specifically, chronic insulin treatment increased $Na_V1.5$ protein levels, atrial $I_{Na}$ density, and AP upstroke velocity. Insulin also could increase atrial $I_{Na}$ and AP upstroke velocity more rapidly (and to a smaller extent compared to chronic insulin) via the rapid activation of $PIP_3$ signaling. These effects of insulin on atrial $I_{Na}$ were associated with increases in atrial conduction velocity and were sufficient to reduce the susceptibility to AF in Akita mice. Collectively, these studies reveal a critical role for insulin in regulating atrial electrophysiology and AF susceptibility via effects on atrial $Na^+$ channel expression and function.

Structural remodeling due to increased interstitial fibrosis has been observed in models of T1DM.[35,37,38] This can be associated with an increase in deposition of collagens as well as the formation of advanced glycation end-products (AGEs), which are proteins and lipids that have become glycated. Interstitial collagen deposition was found to be increased in the atria of Akita mice,[35] STZ-treated rodents,[37–39] and alloxan-treated rabbits.[40] Fibrosis is also exacerbated by angiotensin II (Ang II),[41] and evidence indicates that inhibiting type 1 Ang II receptors prevented interstitial fibrosis in STZ-treated rats,[38] suggesting a role of profibrotic Ang II signaling in T1DM. Evidence also suggests that inhibiting dipeptidyl peptidase-4 (DPP4) may prevent atrial fibrosis in T1DM[40]; however, the mechanisms for this are unclear. In contrast, another study suggests that using glibenclamide (a sulfonylurea antidiabetic agent but not a DPP-4 inhibitor) is critical for preventing atrial fibrosis.[42] This study suggested that lowering blood glucose levels is more important than DPP4 for reducing fibrosis. This conclusion is also supported by the finding that improving glycemic control in Akita mice with insulin treatment for 4 weeks prevented atrial fibrosis.[35]

Prolonged hyperglycemia is associated with the formation of AGEs. Although this is a normal process, hyperglycemic conditions lead to excessive formation of AGEs, resulting in the formation of cross-links that can contribute to stiffening of myocardial tissue. AGEs also bind to receptors for AGE, which contribute to profibrotic signaling and fibroblast proliferation. AGE inhibitors have been of interest in preventing fibrosis in the context of diseases such as diabetes. AGE inhibition was shown to prevent fibrosis as well as stiffening of the atrial myocardium in STZ rats.[42] Altogether, the available evidence indicates that T1DM induces structural remodeling of the atria, which increases susceptibility to AF. The presence of fibrosis can also contribute to reduced conduction velocity and slow interatrial conduction time, which could further contribute to the substrate for re-entry and maintenance of arrhythmia.

In addition to fibrosis and atrial $I_{Na}$, conduction velocity in the atria is determined by connexins, which facilitate the spread of conduction to adjacent cardiomyocytes. Cx40 is prevalent in the atria, and reductions in its expression have been observed in AF patients.[43] In an STZ-induced rat model of T1DM, Cx40 expression in the left atrium was reduced, leading to reduced conduction velocity as well as increased conduction heterogeneity, ultimately promoting arrhythmogenesis.[39] In contrast, Akita atrial myocytes showed no changes in mRNA expression of Cx40.[34] Cx43 is also expressed in the atria but was unchanged in the atria in Akita mice.[34] More research is needed in this area to understand the role connexins play in T1DM.

Oxidative stress, which has been implicated in DM, can promote atrial remodeling through the upregulation of profibrotic signaling pathways as well as by altering cellular electrophysiology. In STZ-treated mice, small conductance $Ca^{2+}$-activated $K^+$ channels (SK2 and SK3) were reduced and atrial APD was prolonged in association with oxidative stress.[44] Additionally, treating alloxan-induced diabetic rabbits with antioxidant compounds improved $I_{Ca,L}$ and $I_{Na}$, reducing AF susceptibility.[45,46] In addition to improving cellular electrophysiology, these antioxidants shortened P-wave morphology and atrial effective refractory period (AERP).

## Atrial remodeling and AF in T2DM

Clinical research investigating atrial remodeling in T2DM is more common than in T1DM. Impaired $Ca^{2+}$ handling has been a common theme in these studies. One study showed that $Ca^{2+}$ transient rise time is prolonged in atrial myocytes of T2DM patients, whereas the decay phase was unchanged.[47] This study proposed that reduced ryanodine receptor (RyR2) expression was responsible for these changes. In contrast, a separate study found that RyR2 was unchanged in atrial myocytes of T2DM patients, whereas sarcoplasmic/endoplasmic reticulum $Ca^{2+}$ adenosine triphosphatase 2a (SERCA2a) was upregulated and phospholamban was downregulated.[48] This study suggested this may be a compensation mechanism for the impaired relaxation they observed in atrial trabeculae in T2DM. Both of these studies were conducted in nonfailing myocardium from diabetic patients. Thus, $Ca^{2+}$ handling seems to be impaired in the atria in T2DM patients; however, further studies are needed to definitively establish the underlying mechanisms involved. Increases in cytosolic $Ca^{2+}$ could trigger arrhythmia via DADs.

It has been shown that interstitial fibrosis was increased in T2DM patients.[48] Consistent with this, fibroblasts isolated from the atria of T2DM patients expressed increased levels of collagen type 1 in comparison to nondiabetic controls.[49]

Although structural remodeling in T1DM is exacerbated by hyperglycemia, its basis in T2DM could be more multifactorial as hyperglycemia is not necessarily the only determinant in this group. T2DM is commonly associated with obesity and hypertension (metabolic syndrome) as well as atherosclerosis and other cardiovascular complications. Obesity itself (ie, even without overt DM) is linked to increased amounts of epicardial adipose tissue and creates a substrate for AF.[50] These fatty deposits are unique to visceral fat as they lie directly adjacent to the myocardium, underneath the pericardial sac. This fat can infiltrate the myocardium and has been observed in obese patients.[51] Adipose tissue (similar to collagen fibers) is less conductive than cardiomyocytes, and this can create barriers that promote or sustain arrhythmogenesis.[52,53]

Experimental work in animal models has provided critical insight into atrial remodeling and arrhythmogenesis in T2DM. Two common mouse models of T2DM are db/db and ob/ob mice.[32] Both models arose as the result of spontaneous mutations in the leptin receptor and leptin, respectively. Leptin is critical for appetite control, and without a functioning leptin receptor (db/db) or circulating leptin (ob/ob), these mice become obese and hyperglycemic early in life. Zucker diabetic fatty (ZDF) rats are similar to db/db mice as they also have a mutation in the leptin receptor; however, they are not overtly hyperglycemic, and females are less affected than males.[33] These genetic models of T2DM provide relevant models for diabetes in humans.

Diet-induced diabetes is a widely used approach in rodents as well as larger mammals.[32,33] In this approach, animals are given a high-fat or "Western-style" (high-fat and high-sugar) diet for a period of time in order to gain weight. Eventually these animals become insulin resistant, similar to humans; however, these models tend to be less hyperglycemic than the genetic models. As a result, a low dose of STZ is sometimes used in conjunction with a high-fat or Western diet. This mimics late-stage T2DM in which the islet cells are unable to keep up with the demand for increased insulin production and atrophy.

Studies of atrial electrical remodeling have shown ZDF rats exhibit prolonged APDs due to reduced $I_{to}$, $I_{Kur}$, and $I_{Ca,L}$ in association with decreases in their corresponding ion channel subunits (Kv4.3, Kv1.5, and $Ca_V1.2$, respectively).[54] It is possible that the loss of insulin signaling contributes to these changes as Kv4.2 expression is also reduced in an insulin receptor knockout mouse.[55] ZDF rats also exhibit increased left atrial size as well as fibrosis.[54,56] Together, these pathologic changes resulted in enhanced AF susceptibility.

Increased $Ca^{2+}$ spark frequency and reduced conduction velocity have been described in rats with diet-induced diabetes.[57] Although no changes in AP morphology were observed, there were increases in reactive oxygen species, collagens, and transforming growth factor β (TGFβ) in atrial tissue. Optical mapping of atria being induced into AF with simultaneous voltage and $Ca^{2+}$ imaging suggests $Ca^{2+}$ handling abnormalities contribute to arrhythmogenesis in this model. This may be due to an increase in oxidized $Ca^{2+}$/calmodulin dependent kinase II (CaMKII), which is associated with arrhythmia independently of DM.[58] Consistent with this, O-GlcNAcylation of CaMKII has been shown to be proarrhythmic by augmenting RyR2 leak and subsequent $Ca^{2+}$ sparks in ventricular myocytes in diabetic rats.[59] O-GlcNAc of CaMKII was increased in hearts and brains of those with T2DM compared to heathy controls as well as when ventricular myocytes were kept in hyperglycemic conditions. Both inhibition of O-GlcNAc of CaMKII and CaMKII itself reduced spontaneous DAD activity, highlighting the significance of this modification secondary to hyperglycemia. The role of O-GlcNAc of CaMKII in the atrial myocardium in DM is yet to be investigated.

Studies of connexin function in T2DM have found that neither Cx40 or Cx43 expression is changed; however, lateralization of Cx43 has been observed in ZDF rats.[56] This lateralization of connexins could result in increased conduction heterogeneity, which could lead to the creation of a substrate for arrhythmogenesis. Thus, a number of studies have identified determinants of electrical remodeling in animal models of T2DM; however, further studies of these phenomena, the mechanisms involved, and their role in AF are still needed.

Both genetic and diet-induced models of T2DM display atrial structural remodeling, including fibrosis, inflammation, and lipidosis in association with increased susceptibility to AF.[56,57,60] Adipokines such as leptin have been implicated in the exacerbation of atrial fibrosis of diabetic mice,[61] emphasizing the complex relationship between T2DM and obesity. Increased fibrosis also may depend on several mechanisms, including increased collagen deposition as well as others. Cathepsin A, which is a proteolytic enzyme active in the extracellular space, has been shown to play a role in augmenting the levels of atrial fibrosis in ZDF rats.[56] Its expression was increased specifically in the atria, and inhibiting its enzymatic activity pharmacologically prevented fibrosis (as well as connexin remodeling).

Although increasing insulin levels can reverse some of the adverse atrial remodeling in animal models of T1DM, this may not be as effective in T2DM due to insulin resistance. Therefore, a common goal for treating patients with T2DM is to increase their sensitivity to insulin via other pathways. Incretin hormone analogues are a class of compounds that may achieve this. Incretin hormones are derived from the gut in response to the presence of glucose in the bloodstream.[62,63] They are endogenous insulin sensitizers, enhancing the ability of tissues to respond to insulin, take up glucose from the blood, and prevent hyperglycemia. Incretins include gastric inhibitory peptide and glucagon-like peptide 1 (GLP-1). GLP-1 has become an important target with respect to synthesizing pharmaceutical compounds. The GLP-1 receptor (GLP-1R) is a G-protein–coupled receptor. When activated by GLP-1, stimulatory G proteins activate adenylyl cyclase, which increase cyclic adenosine monophosphate production and protein kinase A activity. Evidence suggests that GLP-1R activation may also directly

stimulate the PI3K-Akt pathway in cultured atrial myocytes.[63]

The active form of GLP-1 (ie, GLP-1 [7-36 amide]) is a short-acting compound with a half-life of only 1–2 minutes; however, novel mimetics of this peptide, such as liraglutide, have a half-life of up to 13 hours.[64] Liraglutide is a commonly used medication injected once per day to improve glucose-dependent responses to hyperglycemia. Other strategies to harness the insulin-sensitizing effects of GLP-1 include inhibitors of DPP-4, which converts active GLP-1 (7-36 amide) into inactive GLP-1 (9-36 amide).[63] GLP-1 has also been associated with reduced ventricular fibrosis in obese, hypertensive, and aging hearts.[65] In nondiabetic tachypaced dogs, liraglutide prevented pacing-induced atrial electrical remodeling, suppressing AF susceptibility and changes in conduction velocity compared to placebo-treated controls.[66] In a study of tachypaced-induced HF in rabbits, the DPP-4 inhibitor alogliptin was found to prevent atrial fibrosis.[67] These studies in nondiabetic animals suggest that enhancing GLP-1 signaling pathways may be cardioprotective regardless of diabetic state. More studies of the effects of GLP-1 signaling on atrial electrical and structural remodeling in DM are needed.

## Atrial remodeling and AF in hypertension

Globally, chronic hypertension is a leading cause of cardiovascular disease and mortality. Hypertension involves activation of the renin-angiotensin system (RAS), which is a key regulator of blood pressure and blood volume.[68] Patients diagnosed with hypertension have enhanced RAS and increased circulating levels of Ang II, the key effector molecule of the RAS.[68] A manifestation of untreated hypertension in the clinical setting is cardiac hypertrophy, left atrial enlargement, and prolongation of P-wave duration, which is indicative of atrial remodeling.[69,70] Hypertension is an important risk factor for AF.[71]

The effects of chronic hypertension on atrial arrhythmogenesis and structural and electrical remodeling have been investigated using a variety of animal models, including spontaneously hypertensive rats (SHRs) and Ang II infusion in mice. Consistent with observations made in clinical practice, SHRs develop systolic blood pressure >150 mm Hg and have an increased susceptibility to induced AF.[72–74] This enhanced arrhythmogenesis occurs in association with an increase in atrial mass and volume and a prolongation in P-wave duration indicating atrial hypertrophy and atrial remodeling in SHRs.

Structurally, SHRs have increased levels of interstitial fibrosis.[74,75] This has been attributed to an increase in profibrotic gene expression, including collagen type I (*col1a*), collagen type III (*col3a*), *TGF*β, and connective tissue growth factor (*CTGF*).[73,75] In addition, alterations in matrix metalloproteinase 2 (MMP2) and metalloproteinase 9 (MMP9) have been identified in SHRs, indicating that extracellular matrix remodeling contributes to the enhanced levels of interstitial fibrosis.[73]

Calcium handling is altered in SHRs. SHRs exhibit a reduction in $I_{Ca,L}$ density in atrial myocytes without alterations in activation or inactivation kinetics.[75–77] Western blot analysis identified a reduction in the $Ca_V1.2$ (α1C) protein subunit in SHRs that contributes to the reduction in calcium influx. Inward and outward $I_{NCX}$ also is reduced in SHRs,[75] which indicates that calcium removal from the myocyte through NCX also is altered. Left atrial myocytes from SHRs have an increase in SR calcium load, a decrease in fractional calcium release, and a reduction in subsarcolemmal calcium transients. Mechanistically, these alterations in SR calcium handling occur in conjunction with a decrease in total RyR2 protein levels and an increase in phosphorylated RyR2 without changes in calsequestrin (CSQ), phospholamban (PLB), or SERCA2a protein levels. Lastly, the authors of that study observed an increase in spontaneous calcium release and calcium alternans that, when taken together, can serve as triggers for initiating AF.[75]

In the laboratory setting, rodents can be implanted with subcutaneous miniosmotic pumps to allow for continuous delivery of Ang II. This results in a rapid increase in systolic blood pressure to >140–150 mm Hg and diastolic blood pressure ≈100 mmHg in Ang II–infused mice.[78–80] Ang II infusion results in atrial enlargement indicating cardiac hypertrophy. The susceptibility to AF is increased in Ang II–infused mice.[78–81] This occurs in association with prolongation in P-wave duration and AERP *in vivo*. Furthermore, high-resolution optical mapping studies have identified a reduction in right and left atrial conduction velocity in isolated atrial preparations in Ang II–infused mice.[78,80] These data indicate that Ang II–induced hypertension is associated with atrial remodeling and increased AF burden.

Ang II–induced hypertension causes distinct patterns of electrical remodeling in the right and left atria, as assessed using the patch-clamp technique in isolated atrial myocytes.[78,80] AP upstroke velocity ($V_{max}$) was selectively reduced in left atrial myocytes from Ang II–infused mice but remained unchanged in the right atrium. Consistent with this finding, $I_{Na}$ was reduced by approximately 50% in association with a significant reduction in maximum conductance and a right shift in the $V_{1/2}$ of activation in left atrial myocytes. $I_{Na}$ density and activation kinetics remained unaltered in the right atrium. This indicates that Ang II infusion alters the biophysical properties of sodium channels in the left atrium. Mechanistically, the reduction in left atrial $I_{Na}$ was attributed to enhanced protein kinase Cα (PKCα) expression, as dialysis with bisindolylmaleimide 1 (BIM1; a PKC inhibitor) normalized $I_{Na}$ density and activation kinetics in left atrial myocytes isolated from Ang II–infused mice. In addition, PKCα protein expression was selectively increased in the left, but not the right, atrium of Ang II–infused mice. This indicates an important role for PKCα in the left atrium of Ang II–infused mice.[78]

AP repolarization is altered in Ang II–infused mice. APD was prolonged throughout repolarization in right and left atrial myocytes after Ang II infusion.[78,80] The prolongation in APD was greater in the left atrium compared to the right

atrium, indicating more severe impairments in left atrial repolarization. Mechanistically, the prolongation in APD occurred in conjunction with a significant reduction in outward $I_K$, which was attributed to reductions in $I_{to}$ and $I_{Kur}$ densities independent of a change in $K_v4.2$, $K_V4.3$, KChIP2, and $K_v1.5$ protein levels. Furthermore, $I_{to}$ current densities were reduced to a greater extent in left atrial myocytes and occurred in conjunction with a shift in $I_{to}$ activation kinetics in Ang II–infused mice. In contrast, $I_{Ca,L}$ density was not altered in right or left atrial myocytes from Ang II–infused mice. Collectively, these studies demonstrate distinct patterns of atrial electrical remodeling that can lead to a substrate for AF in chronic hypertension.

The effects of Ang II–induced hypertension on right and left atrial structural remodeling has been investigated. Levels of interstitial fibrosis were increased in the right and left atria of Ang II–infused mice.[78,80] In the right atrial appendage, there were no alterations in *col1a2*, *col3a1*, *TGF*β, tissue inhibitor of metalloproteinase 1 (*TIMP1*), tissue inhibitor of metalloproteinase *2* (*TIMP2*), or tissue inhibitor of metalloproteinase 4 (*TIMP4*) mRNA expression, whereas *MMP2* and *MMP9* mRNA expression was reduced in Ang II–infused mice. In contrast, there were increases in *col1a2*, *col3a1*, *MMP2*, and *TIMP1,* and reductions in *MMP9* and *TIMP3* expression in the left atrium of Ang II–infused mice. This indicates that the enhanced fibrosis in chronic hypertension results from increased collagen deposition in addition to altered extracellular matrix remodeling. Oxidative stress has also been linked to atrial fibrosis after Ang II infusion.[81,82]

## Atrial remodeling and AF in hypertrophy

Pathologic cardiac hypertrophy is characterized by an increase in heart mass that occurs as a result of increased hemodynamic stress.[83,84] Cardiac hypertrophy can be classified as either concentric or eccentric. Concentric hypertrophy occurs as a result of increased pressure overload, whereas eccentric hypertrophy results from volume overload. Initially, pathologic cardiac hypertrophy is an adaptive response to preserve cardiac function;, however, it becomes maladaptive if left untreated and can lead to HF and death.

AF affects approximately 20% of patients with hypertrophic cardiomyopathy.[85,86] A 6-year follow-up study identified a positive correlation between left atrial diameter and the probability of developing AF in patients with hypertrophic cardiomyopathy. In the study, 30% of patients with left atrial diameter >50 mm developed AF compared to <10% of patients with left atrial diameter <44 mm.[85] Furthermore, patients with hypertrophic cardiomyopathy and AF have an increased mortality rate compared to patients with hypertrophic cardiomyopathy in normal sinus rhythm.[86]

Patients with hypertrophic cardiomyopathy have an increase in both P-wave duration and left atrial size.[87] Using cardiac magnetic resonance imaging, a recent study demonstrated that atrial enlargement in patients with hypertrophic cardiomyopathy occurs in conjunction with enhanced levels of left atrial fibrosis compared healthy controls.[88] These studies indicate atrial structural remodeling in patients with cardiac hypertrophy that can lead to enhanced atrial arrhythmogenesis.

Although poorly understood, some studies in animal models have investigated the cellular and molecular alterations that occur in the setting of cardiac hypertrophy. A chronic left atrial overload model in goats induced via a left thoracotomy procedure, in which a vascular shunt is implanted between the aorta and left atrium for 4 weeks,[89] leads to an increase in left atrial pressure and left atrial enlargement as well as an increase in the overall incidence and severity of AF compared to sham controls. Persistent AF that lasted >1 week was induced in 50% of goats after vascular shunt surgery and was correlated with the extent of left atrial dilation. The increase in arrhythmogenesis occurred in association with an increase in AERP measurements, indicating electrical remodeling of the atrial myocardium. In a separate study, left atrial diameter was greater in a rabbit model of chronic volume overload (CVO) induced by arterial venous shunts.[90] Optical mapping studies revealed a reduction in right and left atrial conduction velocity in CVO rabbits compared to sham controls. Atrial tachyarrhythmias were induced in the majority of CVO hearts and observed with both focal atrial tachycardia and re-entrant pathways in Langendorff-perfused hearts, further indicating atrial remodeling in animal models of cardiac hypertrophy.

The underlying mechanisms responsible for the enhanced atrial arrhythmogenesis in cardiac hypertrophy have been explored in more detail using the transverse aortic constriction (TAC) mouse model. TAC mice display an enhanced susceptibility and severity to AF in association with increased atrial volume, increased atrial cardiomyocyte area, increased levels of interstitial fibrosis, and increased collagen content compared to sham controls.[91–95] The enhanced fibrosis is attributed to an increase in TGFβ expression, which activates the pSMAD pathway to enhance *col1a* and *col3a* gene transcription.[91] An increase in *MMP2* and a trend toward increased *TIMP1* expression also has been reported,[93] suggesting that extracellular remodeling is altered in cardiac hypertrophy in addition to enhanced collagen synthesis.

Evidence suggests altered atrial electrophysiology in cardiac hypertrophy. Optical mapping studies have revealed a prolongation in APD to a greater extent in the left atrium compared to the right atrium in TAC mice, with a corresponding reduction in $I_{to}$ density.[91] In addition, a significant prolongation in $APD_{90}$ has been observed in isolated right and left atrial myocytes from a rabbit model of left ventricular hypertrophy.[96] The authors of the study demonstrated that the impairments in late repolarization occur as a result of increased late $I_{Na}$ in left atrial myocytes from hypertrophic hearts. Spontaneous EADs and increased automaticity also was observed, which can serve as triggers for AF. The effects of hypertrophy on other ionic currents and the mechanisms underlying atrial electrical remodeling in hypertrophy remain incompletely understood.

## Atrial remodeling and AF in HF

HF is characterized as a chronic functional impairment that occurs secondary to etiologies such as DM, hypertrophy, hypertension, and advanced age. HF affects approximately 2% of the adult population and can be classified as heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF).[97,98] AF is the most common cardiac arrhythmia in patients with HF.[99] A recent study indicated that 53% of patients with HFrEF and 63% of patients with HFpEF were also diagnosed with AF.[100] AF in these patients is associated with progression of HF.

Although limited, some studies have investigated the effects of HF on atrial function and remodeling in humans. Morphologically, echocardiographic studies have identified an increase in both left atrial volume and pressure as well as left atrial wall stiffness in patients with either HFpEF or HFrEF.[98,101] In addition, atrial conduction times were prolonged and ERP measurements were increased in patients with HFrEF.[102] Bipolar voltage mapping has identified areas of low voltage and patchy electrical silence in the right atria of patients with HFrEF, which further indicates the presence of conduction impairments in these patients.[102] Enhanced left atrial interstitial fibrosis and right atrial fibrotic scars have been observed in patients with HF.[98,102] Taken together, these studies demonstrate that HF is associated with both structural and electrical remodeling.

The effects of HF on atrial remodeling have been studied using animal models of HF, including rapid pacing in dogs and coronary artery ligation in rodents. There is an increase in the incidence of AF in association with an increase in ERP measurements in dogs[103–105] and rodents[106,107] with HF. The enhanced arrhythmogenesis occurs in association with left atrial enlargement and fibrosis,[103,105,107–109] indicating structural remodeling in HF. Furthermore, there is a positive correlation between left atrial area and AF severity. This is consistent with clinical studies demonstrating that left atrial volume is a predictor of increased arrhythmogenesis and mortality in patients with HF.[110,111]

The effects of HF on atrial electrophysiology have been investigated in a number of studies in order to identify the underlying currents responsible for the increase in ERP. Patch-clamp experiments have revealed a significant prolongation in atrial APD in animals with HF.[103,112] This occurs in association with a reduction in $I_{Ca,L}$ density that occurs independently of changes in $I_{Ca,L}$ activation or inactivation kinetics or $Ca_V1.2$ protein expression.[104,106,108,112] In addition, $I_{to}$ and $I_{Ks}$ densities are reduced in atrial myocytes isolated from animals with HF which would be expected to further prolong AP.[104,112] Combined, these alterations in cellular electrophysiology could lead to DADs and create a substrate for AF.

## Atrial remodeling and AF in aging and frailty

The prevalence of AF rises with increasing age, and an estimated 13% of individuals aged >80 years have AF.[1,113] Epidemiologic studies have demonstrated that the progression from paroxysmal to persistent AF is associated with increased chronological age.[113] Although the prevalence of cardiovascular disease increases with chronological age, there is emerging evidence that advanced age, independent of other comorbidities, is an independent risk factor for developing AF.[114]

The structure and function of the atria are altered as a function of chronological age, independent of underlying disease. In the human heart, several studies have identified alterations in the gross morphology of the senescent atria. This includes an age-related reduction in the number of atrial cardiomyocytes, increases in atrial size, cardiomyocyte hypertrophy, increased abundance of cardiac fibroblasts, and increased presence of epicardial adipose tissue deposits.[53,115–119] Furthermore, there is a positive correlation between chronological age and the level of interstitial fibrosis in the human right atrial appendage.[120,121] This indicates progressive and continual structural remodeling of the atrial myocardium with aging.

Electrophysiological studies have identified age-dependent alterations in the human heart. There is an age-dependent increase in P-wave duration,[122] increased ERP,[120,122] and negative correlation between age and atrial conduction velocity in the right and left atria in otherwise healthy humans.[119,122,123] Electrophysiological mapping of the human right atrium identified an increase in fractionated electrograms in adults older than 60 years compared to adults younger than 30 years.[122,123] Combined, these patterns of nonuniform conduction across the atria of aged individuals may contribute to a substrate for AF. Although the underlying mechanisms and changes in ionic currents require further investigation, these studies demonstrate age-related changes to the structure and function of the human heart.

Evidence suggests that calcium handling is altered in the aged human heart. One study characterized calcium homeostasis in the human right atrium using tissue biopsies from patients aged <55 years, 55–74 years, and >75 years without a history of AF and with normal left atrial dimensions.[124] Using confocal microscopy, the authors identified a stepwise reduction in calcium transient amplitude with increased chronological age that occurred in association with an increase in the calcium transient duration. Furthermore, propagation of calcium transients toward the center of the cell was slower in patients >75 years of age. In addition, $I_{Ca,L}$ density was significantly reduced in right atrial myocytes from patients >75 years of age compared to those <55 years of age. This occurred in conjunction with an increase in the fast and slow steady-state $I_{Ca,L}$ inactivation times in patients >75 years of age. The reduction in $I_{Ca,L}$ and altered inactivation kinetics were attributed to an age-dependent reduction in $Ca_V1.2$ protein expression. Therefore, there is an age-dependent reduction in calcium entry into the cell. Mechanistically, the alterations in calcium homeostasis were also attributed to an age-dependent alteration in SR calcium content. Total calcium load released after the application of calcium was reduced in patients >55 years of age compared to those <55 years of age. The reduction in SR content occurred

in association with reductions in SERCA2 and CSQ2 protein levels in the aged population. Collectively, these findings demonstrate several age-dependent alterations in calcium homeostasis in the human right atrium.

Studies in animal models have further enhanced our understanding of the effects of aging on atrial structure and electrophysiology. Consistent with clinical studies, *in vivo* studies have demonstrated that advanced chronological age is associated with an increase in the susceptibility to AF in conjunction with an increase in P-wave duration, prolongation in AERP, and reductions in conduction velocity across the right and left atria in aged mice,[115,125,126] rats,[116,127] and dogs.[128–130] These alterations in atrial function have been attributed to structural and electrical remodeling of the atria.

Consistent with histologic studies of human atrial biopsy samples, levels of right and left atrial interstitial fibrosis are increased in animal models of aging, including mice,[115,125] rats,[116,127] dogs,[129] and sheep.[53,118] Mechanistically, enhanced fibrosis is attributed to an increase in total collagen content that occurs independently of an increase in collagen type I and collagen type III or expression of profibrotic genes such as TGFβ or CTGF.[125] Rather, enhanced fibrosis has been attributed to altered extracellular matrix remodeling that is driven by a shift in the balance between MMPs and TIMPs in the atria. MMPs function to degrade extracellular proteins, whereas TIMPs inhibit MMPs. The balance in expression and function of these enzymes regulates maintenance and remodeling of the extracellular matrix.[131] In aged mice, TIMP1/MMP2 and TIMP2/MMP2 expression ratios were increased, whereas TIMP3/MMP9 ratio was reduced in the left atrium of aged mice. TIMP3/MMP9 ratio was reduced in the right atrium of aged mice, and TIMP4/MMP2 ratio was increased in both the right and left atria of aged mice.[125] These findings suggest that remodeling of the extracellular matrix by MMPs and TIMPs is a critical determinant of atrial fibrosis in aging.

Although incompletely understood, some studies have investigated electrical remodeling of the atria in animal models of aging. Previous studies have identified alterations in AP morphology using high-resolution optical mapping or the patch-clamp technique in isolated atrial myocytes, although there is considerable variability in the results. For example, a study in aged dogs observed no change in AP $V_{max}$[129] or a reduction in $V_{max}$[128] using microelectrode recordings in atrial preparations isolated from old dogs. Similarly, previous studies have reported no change in $V_{max}$[132] in right atrial preparations or an age-dependent reduction in $V_{max}$ in left atrial appendage preparations in rabbits.[133]

Several studies have identified changes in atrial APD in aged animals. Using high-resolution optical mapping of atrial preparations isolated from adult and aged mice, no changes were seen in $APD_{50}$, but $APD_{90}$ was shortened.[125] One study in aged rats reported no change in $APD_{50}$ or $APD_{95}$ in atrial preparations,[134] whereas another study observed an increase in $APD_{90}$ in isolated left atrial myocytes from aged rats.[127] Studies in aged dogs have shown no change in $APD_{50}$, whereas $APD_{90}$ was increased in atrial preparations[128,129] and in isolated atrial myocytes.[130,135] Increases in $APD_{50}$ and $APD_{90}$[133] or a reduction in $APD_{90}$[132] have been observed in aged rabbits. Although few studies have investigated the effects of aging on ionic currents, an age-dependent reduction in $I_{Ca,L}$ density has been observed with a corresponding reduction in $Ca_V1.2$ protein in aged dogs[130,135] and sheep.[117] An increase in $I_{to}$ current density has been observed in aged dogs[136] and mice.[115] Collectively, these studies indicate that, although poorly understood, there are age-dependent alterations in atrial AP morphology and ionic currents. These studies demonstrate that although age is an independent risk factor for the development of AF, further studies are needed to determine the cellular and molecular bases and to address inconsistencies reported in the literature.

Calcium homeostasis is altered in animal models of aging, which could contribute to a substrate for AF. In aged mice, an approximately 3-fold increase in $Ca^{2+}$ spark frequency and spontaneous $Ca^{2+}$ transient occurrence has been observed without any alterations in $Ca^{2+}$ spark or transient amplitude.[137] Western blot analysis determined that although there was no difference in total RyR2 protein expression, there was a substantial increase in the level of oxidized RyR2 and phosphorylated RyR2 at serine 2814, indicating that RyR2 activity is altered in aged mice. Mechanistically, the increase in RyR2 activity was attributed to enhanced reactive oxygen species and CaMKII activity in the aged atria, as exposure of aged atrial myocytes to dithiothreitol (DTT; an antioxidant) or KN93 (CaMKII inhibitor) reduced both $Ca^{2+}$ spark frequency and spontaneous $Ca^{2+}$ transients compared to controls. These alterations in calcium handling could lead to DADs, which can serve as a trigger for AF.

## Frailty as a determinant of atrial remodeling in aging

Frailty is a measure of biological age and is defined as an increased vulnerability to adverse health outcomes, including death.[138–140] As individuals age, they accumulate health deficits that are health-related signs, symptoms, diseases, disabilities, and laboratory abnormalities.[141] Importantly, there is heterogeneity in the rate with which these deficits accumulate, such that 2 individuals of the same chronological age can vary in overall health status from very fit to frail. In addition, the rate at which deficits accumulate increases exponentially with age and in individuals with poor health status. Epidemiologic studies have demonstrated that the prevalence of AF is higher in frail patients compared to less frail patients of the same chronological age and that frailty can be used as a predictor of mortality in patients with AF.[142–144] Frailty can be quantified in both the clinical and laboratory setting using a frailty index (FI).[141,145] Accordingly, frailty can be used as a powerful tool to investigate heterogeneity in the effects of age on cardiovascular function and arrhythmogenesis.

The effects of age and frailty on atrial arrhythmogenesis, function, and remodeling have been investigated in

mice.[125,146] These studies demonstrated that AF duration was longer in aged mice and mice with higher FI scores. Not only was P-wave duration prolonged in aged mice, but there was a positive correlation between P-wave duration and FI score such that a higher FI score corresponded with a longer P-wave duration. High-resolution optical mapping studies demonstrate that conduction velocity in the right and left atrial appendages was reduced in aged mice and that there was a negative correlation between atrial conduction velocity and FI score.

The effects of age and frailty on structural and electrical remodeling in the right and left atria were studied to determine how these processes contribute to the alterations in conduction velocity and *in vivo* function.[125] There was an increase in interstitial collagen levels and total collagen content in aged mice. In addition, there was a positive correlation between interstitial fibrosis and total collagen content in the right and left atrial appendages and FI score. Mechanistically, the increase in fibrosis levels was attributed to altered MMP/TIMP ratios rather than alterations in collagen type I and collagen type III expression. The effects of age and frailty on electrical remodeling also were characterized using high-resolution optical mapping. $APD_{90}$ was reduced in the right and left atria of aged mice, whereas $APD_{50}$ remained unchanged. Importantly, when assessed as a function of frailty there was a negative correlation between right atrial $APD_{50}$, right atrial $APD_{90}$, and left atrial $APD_{90}$ and FI score. Thus, this novel approach to quantifying frailty in animal models showed that frailty is a powerful predictor of atrial structure and function, including at the cellular and molecular levels. Furthermore, the data demonstrate that, in some cases, frailty can better identify alterations in atrial remodeling than chronological age. Ongoing studies are necessary to further understand the impacts of age and frailty on atrial remodeling and how frailty could be modified in these contexts.

## Conclusion

AF is prevalent in common conditions and acquired disease states. Electrical and structural remodeling of the atria is a common theme in the creation of a substrate for AF to develop and progress; however, the cellular and molecular bases for atrial remodeling are distinct in different conditions and diseases. Although significant progress has been made, these phenomena remain incompletely or poorly understood, which likely contributes to the limited effectiveness of therapeutic approaches for AF. Improved understanding of the mechanistic basis for AF in different conditions may facilitate the development of novel antiarrhythmic approaches that target the specific components of atrial remodeling that are altered in different disease states or conditions. This represents both a challenge and an opportunity. Thus, ongoing research in human patients and animal models is essential and should lead to improved therapeutic approaches that could be tailored based on the specific conditions in which AF is present.

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