

Ion Channel Dysfunction and Electrical Instability in Atrial Fibrillation

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Abstract: Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia that considerably impacts the health of the world's population. Atrial fibrillation is closely related to an elevated risk of stroke, heart failure, cognitive decline, and mortality. This disorder is frequent among the aging population, and it is still challenging to treat efficiently. This review discusses the role of cardiac ion channels and calcium release in AF initiation and maintenance. The normal electrocardiographic features of the heart are explained, including the action potential shape, pacemaker activity, refractoriness, and conduction properties. The role of various ionic channels in the pathophysiology of AF is described in detail. Particular attention is paid to the contribution of calcium mishandling, rotors, alternans, and wavefront breakup to AF sustaining. The basic principles of cardiac signal conduction are discussed, including such concepts as wavefront curvature, source-sink interactions, and anisotropic conduction. Finally, the available pharmacological and catheter treatments of AF are reviewed, and some new approaches to its prevention and personalized management are discussed. In particular, the concepts of substrate-trigger-modulator AF maintenance are linked to the mechanisms of drug action, and the role of cellular Ca²⁺ mishandling in AF is highlighted. New approaches to AF control include ion channel-specific pharmacological agents, genetic screening tests, and noninvasive detection methods such as smart-watch technology.

Keywords: Atrial fibrillation, Ion channel dysfunction, Cardiac electrophysiology, Electrical remodelling, Calcium handling; Atrial fibrosis, Catheter ablation

1. Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia that has become a global public health hazard affecting 33 million people around the world and is expected to affect more people as the world ages, especially in emerging countries such as China, India, Brazil, Indonesia, and many others. Additionally, AF afflicts more than 13% of those over eighty years old and is connected to advancing age, which is a core risk factor, although the condition affects persons of all ages. AF's prevalence is projected to rise sharply as the world's population ages. AF is a major contributor to morbidity and mortality since it raises the risk of stroke, heart failure, myocardial infarction, chronic kidney disease, dementia, and mortality while also presenting a significant socioeconomic burden to populations and healthcare systems. Despite being a significant clinical problem, AF therapy options are currently insufficient, and catheter ablation, an effective therapy, is linked to high recurrence rates because the arrhythmia's mechanisms are not fully understood. Additionally, there is a lack of knowledge about AF's causes and epidemiology, making it challenging to develop screening, prevention, and treatment policies, particularly in developing nations. A better understanding of AF's underlying mechanisms would result in more effective individualized therapy and better management of this complex condition. Ion channel remodeling such as IK1 and IKACH dysfunction, atrial fibrosis, and novel biomarkers such as anti M2 receptor antibodies and RDW have all been implicated in AF's development. Additionally, the clinical relevance of AF was emphasized, and its prevalence and incidence in emerging and developed nations were investigated, although much data on AF's epidemiology in Africa, South America, and Asia, in general, and the risk factors and mechanisms in these areas in particular, are lacking. Finally, this review analyzes ion channel dysfunction in atrial fibrillation, covering cardiac electrophysiology basics, electrical remodeling, and changes in sodium,

calcium, and potassium channels. It evaluates existing therapies and highlights emerging approaches to enhance diagnosis and treatment.

Cardiac Electrophysiology

Normal heart rhythm is controlled by the sinoatrial (SA) node, a group of specialized cells that generate electrical impulses automatically. This automatic behavior relies on two key mechanisms: the voltage clock and the calcium clock. The voltage clock involves the pacemaker current, known as I_f which flows through hyperpolarization activated cyclic nucleotide gated (HCN) channels. The calcium clock, on the other hand, depends on the release of calcium from the sarcoplasmic reticulum via ryanodine receptors (RyR2), along with the actions of the SERCA2a calcium pump and the sodium calcium exchanger (NCX). Together, these two systems drive the slow phase 4 depolarization seen in pacemaker cells, setting the stage for an action potential. Along with other ion channels, they help regulate the heart's electrical signaling.

Once generated, the electrical impulse travels through the heart's conduction system, which includes the SA node, AV node, bundle of His, bundle branches, and Purkinje fibers. The SA node starts the signal, while the AV node briefly delays it, allowing the atria to contract before the ventricles. This coordination is essential for efficient pumping. If any part of this system fails, it can result in rhythm disorders like atrial fibrillation.

Heart cells produce two types of action potentials: slow response and fast response. Slow response action potentials occur in the SA and AV nodes and are responsible for the heart's natural rhythm. Fast response action potentials happen in the atrial and ventricular muscle cells and in the Purkinje fibers. These fast responses have five distinct phases. Phase 0 begins with a rapid influx of sodium ions (Na⁺) through voltage gated channels (INa) and inward rectifier potassium

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channels (IK1), causing the cell to depolarize. Phase 1 follows, marked by a brief outward flow of potassium (Ito), leading to a small degree of repolarization.

Phase 2, the plateau phase, occurs when L type calcium channels (ICa,L) open, allowing calcium (Ca²⁺) to enter the cell while potassium (K⁺) exits. This balance keeps the membrane potential relatively stable. In phase 3, delayed rectifier potassium currents (IKr and IKs) and IK1 dominate, driving full repolarization. Phase 4 is the resting state, maintained primarily by IK1. During the effective refractory period (ERP) which spans most of the action potential heart cells cannot respond to new stimuli. This pause ensures the chambers have time to empty and prevents premature reactivation, reducing the risk of abnormal rhythms. The relationship between conduction speed and ERP determines the action potential wavelength. A longer wavelength helps prevent arrhythmias by discouraging re entry circuits, while a shorter one increases the risk.

At the cellular level, membrane voltage and calcium levels work together to control heart activity. They influence each other closely, so disruptions in either system can lead to irregular heartbeats. For example, a small influx of calcium through L type channels triggers a much larger release from the sarcoplasmic reticulum via RyR2, initiating contraction. Relaxation occurs when SERCA2a and NCX remove calcium from the cytoplasm. Because changes in calcium affect the membrane potential and vice versa any malfunction in these regulatory systems can alter the shape of the action potential. When such issues affect many cells at once, they may disrupt normal electrical conduction.

At the tissue level, electrical signals spread from cell to cell through transmembrane currents, creating a wave of excitation that moves uniformly across the atria and ventricles. However, under certain conditions like uneven recovery of excitability, slower conduction, shortened ERP, or mismatched current flow this organized wavefront can break into smaller, chaotic wavelets. This shift from orderly impulses to disorganized filaments leads to sustained irregular activity, such as the rapid, uncoordinated beating seen in atrial fibrillation.

Clinically, the surface electrocardiogram (ECG) reflects these electrical events. Electrodes placed on the skin detect the heart's electrical activity, producing a trace with distinct features: the P wave, QRS complex, and T wave. The P wave shows atrial depolarization, the QRS complex represents ventricular depolarization, and the T wave corresponds to ventricular repolarization. Important intervals include the PR interval, which measures the time from the start of atrial activation to the beginning of ventricular activation; the QT interval, indicating total ventricular activity time; and the ST segment, reflecting the period between depolarization and repolarization. These components directly mirror the cellular electrical processes discussed. Any disturbance in the heart's electrical function typically appears on the ECG as changes in these waves, segments, or intervals, making the ECG a vital tool for diagnosing heart rhythm problems.

Ion Channels & Electrochemistry

The normal electrical activity of the heart, as seen on an electrocardiogram, depends on a precise sequence of ionic movements across the membranes of heart muscle cells. Sodium, calcium, and potassium ions flow through specific channels, shaping the cardiac action potential its form, length, and speed of conduction allowing electrical signals to spread efficiently through heart tissue. Any disruption to these ion flows, whether from genetic mutations, faulty regulation, or structural changes in the heart, can lead to abnormal heart rhythms, particularly in the atria.

Sodium channels are key in initiating the rapid upstroke of the action potential. The primary cardiac sodium channel, Nav1.5, encoded by the SCN5A gene, generates the main inward current (INa) that depolarizes working heart muscle cells, except in the SA and AV nodes. Mutations in SCN5A are linked to several arrhythmia disorders: loss of function variants cause Brugada syndrome, while gain of function ones lead to long QT syndrome type 3. Additionally, Nav1.5's function is fine tuned by auxiliary subunits Navβ1–β4, which influence how the channel moves to the cell membrane, inactivates, and clusters. Nav1.5 also interacts with structural proteins like N cadherin, connexin 43, and plakophilin 2 at intercellular junctions called intercalated discs. Mutations in these proteins can trigger arrhythmias even without directly affecting ion flow. More recently, Nav1.8 a sodium channel once thought to exist only in sensory nerves has been found in heart cells and cardiac ganglia. Blocking Nav1.8 shortens the action potential and reduces late sodium current (INaL), a current that helps shape the plateau phase and can promote abnormal electrical triggers. This makes Nav1.8 a potential target for antiarrhythmic drugs, though conflicting evidence about its role in promoting arrhythmias has limited its clinical use.

L type calcium channels (ICaL) sustain the plateau phase of the action potential and initiate muscle contraction by triggering calcium release from the sarcoplasmic reticulum via the ryanodine receptor (RyR2). In ventricular muscle, Cav1.2 is the dominant L type channel, while Cav1.3 is mainly found in the SA and AV nodes, where it helps regulate pacemaker activity and nodal conduction. Mutations in Cav1.3 can result in a syndrome combining slow heart rate and hearing loss. Other calcium channels also contribute: T type channels (Cav3.1/3.2) influence pacemaker potentials and blood vessel tone, while N type channels (Cav2.2) control norepinephrine release from sympathetic nerves. Gain of function mutations in CACNA1C, the gene for Cav1.2, are tied to long QT syndrome and Timothy syndrome, whereas reduced function in Cav1.2 or other L type channels is associated with Brugada syndrome. Calcium balance is tightly regulated. RyR2 releases calcium from storage, SERCA2a pumps it back, and the sodium calcium exchanger (NCX) removes it from the cell in exchange for sodium. Because NCX brings in three sodium ions for every calcium ion exported, it can slightly depolarize the cell, especially if RyR2 malfunctions and fails to close properly. This shows how closely calcium handling and electrical stability are connected disruptions in either system can set the stage for arrhythmias.

Potassium channels are essential for maintaining the resting membrane potential and driving the repolarization phase of

the action potential. Four major potassium currents shape this process in heart cells. The transient outward current (I_{to}), formed mainly by Kv4.3 and Kv1.4, initiates early repolarization. The delayed rectifier currents I_{Kr} (from Kv11.1/hERG) and I_{Ks} (from Kv7.1/KvLQT1) are crucial for later repolarization. I_{K1}, carried by Kir2.1 in ventricles and Kir2.3 in atria, helps stabilize the resting state. Another important channel, Kv1.5, carries the ultra rapid delayed rectifier (I_{Kur}), which is active mainly in atrial cells. Meanwhile, I_{KACH}, made of Kir3.1 and Kir3.4 subunits, responds to acetylcholine and mediates vagal slowing of the heart rate, primarily in the atria and SA nodes. Because I_{KACH} is largely absent in ventricles, blocking it could prolong the atrial refractory period without affecting ventricular function making it an attractive target for new antiarrhythmic drugs. Genetic defects also play a role: mutations in KCNQ1 (Kv7.1) cause long QT syndrome, while those in KCNJ2 (Kir2.1) lead to Andersen Tawil syndrome. Interestingly, gain of function changes in KCNJ2 are linked to short QT syndrome and atrial fibrillation, and the gene's expression is influenced by microRNA 26. ATP sensitive potassium channels (I_{KATP}), composed of Kir6.2 and SUR subunits, remain closed under normal conditions but open during ischemia, shortening the action potential. This dual role means they can be both protective (by reducing calcium overload) and dangerous (by promoting electrical instability). Recently, calcium activated potassium channels (I_{KCa2.3} and I_{KCa3.1}) have been found to increase in atrial fibrillation, suggesting they contribute to the disease's progression.

Beyond ion channels, cellular connections and signaling systems also influence heart rhythm. Connexin43 and connexin40 form low resistance gap junctions at intercalated discs, allowing electrical current to flow smoothly between cells often alongside Nav1.5. When gap junction function declines due to ischemia, atrial fibrillation, or genetic defects electrical conduction slows, increasing the risk of re entrant circuits. Some scientists also propose alternative, non gap junction pathways for cell to cell communication. The SA node's pacemaker activity relies on a distinct set of currents: the "funny" current (I_f), activated by hyperpolarization and carried by HCN channels, drives slow diastolic depolarization. This process is supported by T type (I_{CaT}) and L type (I_{CaL}) calcium currents, as well as reverse mode NCX. Together, these create the gradual voltage rise that triggers each heartbeat. Finally, most ion channels are regulated by protein kinases like CaMKII, PKA, and PKC, and by hormonal systems such as the β adrenergic and renin angiotensin aldosterone pathways. When these regulatory systems go awry, even structurally normal channels can behave abnormally highlighting how improper control, not just broken parts, can lead to arrhythmias.

Electrical instability

When ion channels malfunction, a critical question arises: how do these small scale changes result in the widespread, chaotic electrical activity seen in atrial fibrillation? The answer lies in three interconnected mechanisms abnormal automaticity, triggered activity, and disrupted impulse conduction each capable of influencing the others in complex ways. Abnormal automaticity occurs when heart cells fire too easily or too often, often due to a steeper rise in phase 4 of the action potential, a lower threshold for activation, or a less

negative resting membrane potential. Normally, the sinoatrial (SA) node sets the heart's rhythm, but if it fails, backup pacemakers like those in the AV node or Purkinje fibers can take over, though at a slower rate. This redundancy shows how damage to any part of the heart's natural pacing system can lead to arrhythmias.

Another source of irregular rhythms is triggered activity, caused by abnormal electrical shifts known as afterdepolarizations. These come in two types: early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). While both generate extra electrical impulses, they arise through different processes. EADs happen during phases 2 or 3 of the action potential and are linked to prolonged inward currents especially increased activity in L type calcium channels or reduced potassium outflow. DADs, on the other hand, occur only after full repolarization, at the end of phase 4. They are typically triggered by excess calcium inside the cell, often due to excessive release from the sarcoplasmic reticulum via ryanodine receptors. This calcium overload can activate the sodium calcium exchanger, allowing more sodium into the cell and potentially sparking another action potential.

Calcium buildup also weakens communication between neighboring heart cells by reducing the number of connexin proteins, which form the channels that allow electrical signals to pass. This uncoupling is made worse by acidosis and low ATP levels, both of which can result from cellular swelling. Poor cell to cell connection leads to uneven action potential shapes, varying recovery times, and differing susceptibility to EADs all of which slow down electrical conduction and may cause blockages. Additionally, DADs can inactivate sodium channels, lowering tissue excitability and creating conditions favorable for re entry, where electrical impulses loop abnormally.

Re entry is the third major cause of arrhythmias in atrial fibrillation. It happens when an electrical signal travels in a continuous circle, often around a physical barrier. However, this isn't always necessary functional re entry can occur without a fixed obstacle. One model, the "leading circle" or spiral wave, depends on the balance between conduction speed and refractory period. The core of this rotating wave acts like an abnormal pacemaker: a stable rotor produces a regular rhythm like ventricular tachycardia, while an unstable, wandering rotor leads to the disorganized patterns of fibrillation. Another variation, the figure of eight re entry, involves two opposing rotors circling around a shared obstacle. A special case called phase 2 re entry occurs when a single abnormal action potential both triggers and sustains reentry. In this scenario, one area of heart tissue maintains a normal spike and dome shape but fails to fully depolarize, while a neighboring region has a dome shaped potential that can reactivate the first. This mechanism is thought to explain dangerous rhythms like torsades de pointes in Brugada syndrome.

The uneven recovery times needed for reentry aren't usually present in a healthy heart but can develop through dynamic instabilities. Most arrhythmias stem from disturbances in the cardiac action potential, including alternans a beat to beat fluctuation in either action potential duration or calcium

release. Alternans can be driven by voltage changes or calcium imbalances. Voltage driven alternans often results from a steep restitution curve, caused by increased transient outward potassium current (Ito) during fast heart rates, or by dysfunction in the L type calcium window current combined with impaired IKs current in failing hearts. Calcium driven alternans arises when the relationship between calcium stored in the sarcoplasmic reticulum and its release becomes unstable either because of erratic release or because ryanodine receptors need time to recover between activations. When adjacent cells alternate out of sync a condition called spatially discordant alternans it creates significant differences in recovery times, forming a powerful foundation for arrhythmias.

This variability in recovery directly affects rotor stability rotating waves of electrical activity that can sustain themselves. Steeper restitution curves make rotors more unstable, causing them to drift or split into multiple wavelets, supporting the idea that fibrillation involves many shifting circuits. Alternatively, fibrillation can be driven by highly stable mother rotors that don't break apart but instead disrupt surrounding tissue by shortening its refractory period. These two models aren't mutually exclusive; in fact, the mother rotor concept fits within the broader multiple wavelet theory, and both likely contribute to human atrial fibrillation. Some experts also differentiate true rotor fragmentation where long lasting rotors exist from electrical turbulence which involves rapidly changing, irregular patterns in refractoriness that require a broader analysis than single wave models. This distinction matters clinically, as rotor based arrhythmias may respond better to targeted ablation therapies than those driven by widespread electrical chaos.

Overall, growing evidence suggests that atrial fibrillation is a multi level disorder. It begins with tiny disruptions such as faulty ion channels or transporters but ultimately leads to large scale disorganization of electrical activity across the atria. These abnormalities may already be unevenly distributed even during normal sinus rhythm, setting the stage for future episodes.

Physics of signal propagation

Cardiac conduction is dictated by the properties of the myocardium itself, but also the geometry of a wavefront as it propagates. For small curvatures, conduction velocity can be approximated as $u = u_0 + D\rho$, where u_0 is the velocity of a flat wavefront, D is tissue properties, and ρ is the curvature of the wavefront. Convex wavefronts conduct slowly due to a larger distribution of depolarizing current to downstream tissue while concave wavefronts concentrate their current, allowing them to propagate faster. Conduction velocity thus becomes a property of the wave, and not the underlying tissue. As curvature is increased, conduction velocity will decrease up to a critical curvature at which point conduction fails. The critical radius depends on tissue properties and the base conduction velocity of the tissue, with faster waves being less able to tolerate large curvatures. This provides a biophysical mechanism for relating rapid atrial activation to conduction failure. Similar concepts apply to the tip of a rotor, where the extreme bending of a wavefront reduces its ability to activate tissue in the center, allowing it to instead rotate around a central phase singularity. The capacity for a wavefront to

propagate also depends on the ratio of the source provided by the depolarized tissue and the sink of tissue that must be depolarized to sustain the wave. When a wavefront propagates from a relatively narrow strand or isthmus into a broader expanse of tissue, the wavefront will widen and become more convex, requiring more current to depolarize the next region. If the available source from the parent tissue is insufficient to depolarize the child, conduction will fail. The concept of a source-sink mismatch provides a biophysical basis for conduction failure at anatomical discontinuities and regions of heterogeneous tissue. When a wavefront encounters an unexcitable obstacle, increasing curvature eventually causes the portion of the wavefront adjacent to the obstacle to detach and propagate back toward it. The detached wavefront can then curl around the center of a region of unexcitable tissue to form a spiral or rotor. Reduced excitability of tissue, such as from reduced sodium-channel availability, can increase the likelihood of such an uncoupling. The dynamics of rotors are governed by a complex interplay between the curvature of the wavefront, the wavelength of excitation, and tissue recovery. Depending on the interplay between these effects, rotor tips can rotate in a relatively circular trajectory or meander. Differences in conduction velocity and refractoriness between locations can lead to drifts in a rotor's position, while localized discontinuities can pin a rotor, causing it to transition from meandering motion to stable rotation around a central region. The environment surrounding a rotor is thus heterogeneous, as the availability of sodium channels dictates the excitability of tissue on either side of the rotor, creating gaps of different excitation properties for the wavefront to travel through. Regions of tissue close to the center of the rotor, which may be following high-frequency activations, will have different properties to tissue further away, which may have a longer refractory period. These differences in excitability and refractoriness can lead to intermittent conduction failures and wavebreaks, allowing a relatively simple reentrant source to generate increasingly complex patterns of fibrillatory conduction throughout the atria. Cardiac propagation also has an anisotropic component, as the directional arrangement of muscle fibers and interstitial junctions causes fibers to conduct more rapidly in the longitudinal direction compared to perpendicular. Consequently, a wavefront can have different conduction velocities in different directions. This property becomes particularly important when considering heterogeneities in conduction velocity between regions, in terms of both refractory properties and tissue structure, as this has the capacity to cause additional wavefront deformations and conduction failures. The biophysics of cardiac activation underlie a wide range of concepts that are analogous to fluid turbulence, ranging from the scale of individual wavefronts to the overall properties of reentry. However, such comparisons are necessarily superficial in nature, as turbulent flows are governed by entirely different dynamics to cardiac electrical activation. Turbulence is a manifestation of fluid flow and transport, whereas cardiac conduction is primarily a reaction-diffusion process. Cardiac tissue consists of a medium of cells that are regenerated through specific ionic mechanisms, whereas fluid turbulence is a phenomenon of transport of conserved fluid quantities. The analogy breaks down most strongly when considering the concept of energy dissipation and the range of scales over which it occurs. While fluid turbulent flows display a self-similar dissipation of energy

over a broad range of scales (i.e., a Kolmogorov spectrum), the equivalent concept of energy dissipation for cardiac waves becomes the fragmentation of wave fronts and conduction failure. The multi-scale nature of AF can therefore be considered to arise from the interaction between wave fronts and the complex heterogeneous tissue they propagate through. Finally, the dynamic nature of refractory periods create a spatially varying non-linear barrier to wavefront propagation. Refractory regions can lead to conduction failure while wavefront curvature and source-sink properties dictate whether a wavefront fragments or is able to persist. Repeated wavefront fragmentations can cause relatively simple conduction patterns to evolve into more complex daughter wavefronts and fibrillatory conduction. This provides a biophysical mechanism for the change from large-scale coherent electrical activity to the more complex patterns characteristic of AF.

AF Mechanisms

Atrial fibrillation (AF) has a well-documented positive feedback cycle that favors its own perpetuation: “AF begets AF,” a phrase that encapsulates how rapid atrial activation leads to electrophysiological changes that facilitate the initiation and/or maintenance of AF. These changes, driven by rapid atrial rate rather than fibrillation itself, are often referred to as atrial tachycardia remodeling (ATR). AF is best conceptualized as a combination of triggers, substrate, and modulators — with the former initiating AF episodes, the latter being the vulnerable tissue state that supports re-entry, and the middle acting as modifiers like autonomic tone and calcium handling. At the most basic level, this framework encompasses diverse electrical, structural, autonomic, and calcium-related abnormalities rather than viewing them as competing processes. One essential link between remodeling and re-entry is the shortening of the atrial wavelength, which is determined by the product of conduction velocity and refractory period. ATR primarily shortens wavelength by reducing the atrial refractory period and action-potential duration. Shorter wavelengths allow for more simultaneous reentrant circuits and thus render AF increasingly refractory to termination, explaining how self-terminating AF can transform into persistent AF. On the trigger side, abnormal diastolic Ca^{2+} release associated with hyperphosphorylated and calstabin-uncoupled ryanodine receptors can generate ectopic activity that can engage the vulnerable substrate. Therefore, AF initiation and maintenance are related but mechanistically distinct: eliminating a trigger cannot guarantee elimination of the substrate that permits AF to perpetuate. The distinction between trigger and substrate is critical because a given set of electrical circumstances can include both an initiating event and a perpetuating mechanism. For example, a premature ectopic beat can encounter tissue with spatially varying refractoriness that allows unidirectional conduction and subsequent re-entry. Once reentry is initiated, rapid activation of the atria favors further remodeling in turn, resulting in a positive feedback loop in which the arrhythmia induces substrate that favors its own perpetuation. Calcium Handling and AF

Calcium handling can contribute to AF in three distinct ways: triggered activity, conduction abnormalities and re-entry, and Ca^{2+} -dependent alternans with abnormal buffering. In the DAD pathway, altered CaMKII and RyR2 activity, coupled

with enhanced SERCA activity, can promote spontaneous SR Ca^{2+} release as sparks and waves that activate the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, resulting in an inward depolarizing current that can lead to delayed afterdepolarizations (DADs) and thus trigger an action potential if threshold is reached. A second mechanism involves late-phase-3 early afterdepolarizations (EADs). Classical EADs are typically associated with prolonged action potentials, whereas AF commonly provokes action-potential shortening. However, during rapid atrial activity, elevated intracellular and SR Ca^{2+} loading can lead to abnormal depolarization late in repolarization despite shortening of the overall action potential. Therefore, Ca^{2+} dysregulation can contribute to triggering via mechanisms in addition to the classical EAD pathway. Reduced L-type Ca^{2+} current (ICaL) contributes to electrical remodeling. Enhanced Ca^{2+} /calmodulin signaling has been hypothesized to activate calcineurin, which regulates NFAT-mediated transcription, and can lead to decreased expression of the channel α -subunit, thereby reducing ICaL and contributing to action-potential shortening and increased susceptibility to re-entry. Calcium cycling can undergo beat-to-beat instability resulting in Ca^{2+} alternans and spatial differences in repolarization and refractoriness that favor re-entry. Critically, Ca^{2+} remodeling is not universally pro-arrhythmic. A contrasting “ Ca^{2+} signaling silencing” phenotype that includes impaired Ca^{2+} propagation, decreased systolic Ca^{2+} transients, RyR complex remodeling, and decreased Na^+ -dependent Ca^{2+} loading may represent an adaptive anti-arrhythmic process. The balance between Ca^{2+} -induced destabilizing and protective remodeling may depend on the context of associated disease (e.g., heart failure). Overall, Ca^{2+} handling can influence both sides of AF pathophysiology: abnormal SR release provides triggers, whereas altered ICaL and Ca^{2+} -dependent heterogeneity contribute to the substrate. At the cellular level, calcium and voltage are tightly coupled. Altered Ca^{2+} release can dictate membrane potential via NCX and changes in membrane currents can affect Ca^{2+} entry/loading. Consequently, a disturbance that begins as abnormal intracellular Ca^{2+} cycling can spread into action-potential abnormalities and conduction disturbances. This coupling may explain why Ca^{2+} -handling defects can simultaneously generate ectopic triggers and modify the reentry substrate rather than being an isolated pathway.

Ion-Channel Remodeling

Ion-channel remodeling further contributes to the atrial action potential. Three major contributors to AF-associated action-potential shortening are decreased ICaL, increased IK1, and constitutively active IKACH. Although action-potential shortening may initially limit Ca^{2+} loading during rapid atrial activity, excessive shortening reduces the effective refractory period and facilitates reentry and wavefront fractionation. ICaL dysfunction can occur at several regulatory levels. Increased PP1/PP2A phosphatase activity may reduce Cav1.2 channel open probability, whereas Src-family kinase dysregulation, altered S-nitrosylation, and changes in accessory subunits can also impair channel function. Sodium-channel remodeling is less firmly established — while INa density and Nav1.5 expression are reduced in some experimental models, human AF studies have yielded mixed results. Therefore, reduced INa should be

considered a potential contributor to conduction slowing rather than a definitive feature of AF. Potassium-channel remodeling is similarly heterogeneous. Reduced Ito is associated with decreased Kv4.3 expression and may involve calpain-mediated proteolysis, CaMKII activity, and calcineurin/NFAT signaling. Findings for IKur/Kv1.5 are inconsistent, while the roles of IKr and IKs in human AF remain unclear due to technical limitations in measuring these channels in human atrial myocytes. Remodeling therefore does not represent a simple global increase or decrease in potassium current. Structural coupling is also affected: connexin remodeling, including reduced connexin-43 and heterogeneous connexin-40 changes, can slow conduction and increase spatial heterogeneity. Additional Ca(2+)-dependent pathways may contribute to AF, including IP3R2-mediated SR release and SK-channel remodeling. Enhanced RyR2 phosphorylation and increased SR leak can promote triggered activity even without an increase in total SR Ca(2+) content, emphasizing the importance of abnormal Ca(2+) release regulation over simple Ca(2+) overload. Structural Remodeling and Fibrosis Atrial fibrosis transforms electrical vulnerability into a structural substrate. Excess extracellular matrix disrupts myocardial fiber continuity and creates regions of heterogeneous conduction, while fibroblasts can electrically couple to cardiomyocytes through gap junctions and influence myocyte electrophysiology. Perivascular fibrosis may also impair oxygen and nutrient delivery. The relationship between fibrosis and AF is bidirectional: preexisting fibrosis provides a substrate for AF, but AF also promotes further fibrosis. This extends "AF begets AF" from an electrical remodeling concept to a structural positive-feedback loop, explaining why long-standing AF becomes progressively harder to control. Paroxysmal AF is often more trigger-dependent (e.g., based on pulmonary-vein sources), whereas persistent AF is associated with greater substrate remodeling and multiple reentrant waves capable of sustaining AF. Patient-specific three-dimensional models further illustrate how fibrotic substrates can harbor reentrant drivers such as rotors, linking fibrosis remodeling to AF maintenance. However, this does not prove that rotors specifically localize to fibrotic boundary zones, a finding that would need separate evidence. AF mechanisms may therefore exist along a continuous, substrate-dependent spectrum, with the dominant mechanism varying between patients and changing as structural remodeling progresses. Inflammation and Fibrosis Inflammation provides another entrée into this remodeling process. NLRP3 inflammasome activation is increased in paroxysmal and long-standing persistent AF and has been associated with postoperative AF and AF risk factors. Experimental activation of NLRP3 in atrial cardiomyocytes promotes atrial hypertrophy, premature atrial contractions, and inducible AF. NLRP3 signaling can also promote fibroblast-to-myofibroblast differentiation and IL-1 β /IL-18 signaling, connecting inflammation to fibrosis. Critically, calcium-handling abnormalities and NLRP3/CaMKII activation can coincide, suggesting convergence between inflammatory and calcium-dependent electrical remodeling. The presence of calcium-permeable channels in fibroblasts provides an additional link: TRPM7 is upregulated in AF-associated atrial fibroblasts in a TGF- β 1-dependent manner, while TRPC3 is also increased. Decreasing these channels reduces fibroblast differentiation or proliferation, suggesting that Ca(2+) dysregulation can

contribute to structural remodeling as well as cardiomyocyte electrical instability. Microstructural Organization and AF Persistence Finally, computational modeling provides a complementary explanation for why AF can become persistent. A conduction-block/percolation (CMP) framework proposes that persistent AF can emerge when complex reentrant circuits are more likely to activate than terminate. Self-contained circuits may require fewer conduction-block failures to initiate than to extinguish because secondary pathways allow waves to bypass individual blocks. Coupled circuits can also perpetuate activity when termination of one circuit immediately activates a neighboring dormant circuit, resulting in a relay of reentrant activity. Importantly, with identical global model parameters, sinus rhythm, paroxysmal AF, or persistent AF can arise depending on the microscopic distribution of conduction-block-susceptible regions. This suggests that the local organization of structural and electrical discontinuities may be as critical as their overall quantity. Therefore, two atria with similar overall tissue uncoupling could theoretically exhibit different AF behaviors if their microstructural organization differs. However, the CMP model is a hypothesis-generating framework because it does not incorporate detailed ion-channel dynamics, APD/conduction-velocity restitution, alternans, realistic three-dimensional fiber architecture, or full electrical and structural remodeling. Altogether, these mechanisms show that AF persistence emerges from the interaction between triggers, ion-channel and calcium-handling abnormalities, heterogeneous conduction, fibrosis, inflammation, and complex reentrant organization

2. Treatment

AF management has progressed from ventricular-rate control alone toward an integrated approach targeting stroke prevention, symptomatic relief, risk-factor modification, and sinus rhythm maintenance. The 2020 ESC guidelines used an ABC pathway for AF management, which was modified in the 2024 ESC guidelines to create the AF-CARE pathway (comorbidity & risk-factor management; avoidance of stroke, thromboembolism; reduction of symptoms by rate/rhythm control; evaluation/reassessment). This highlights the importance of addressing both arrhythmia and the pathogenic diseases involved in AF perpetuation.

Historically, rate control was favored over rhythm control since classic trials, including PIAF, AFFIRM, RACE, STAF, AF-CHF, and J-RHYTHM found little difference in outcome between the two strategies but the latter was often associated with greater hospital admissions. However, these studies were mostly performed in patients who had already developed AF, using older antiarrhythmic agents, less intensive monitoring and varied approaches to cardiovascular risk-factor modification. Hence, this evidence has since been re-evaluated and contributed to a contemporary focus on earlier rhythm control, supported by subsequent trials such as EAST-AFNET 4.

Pharmacological rhythm control continues to play an important role but should be considered in the context of the patient's cardiac substrate. Flecainide and propafenone can be used for cardioversion in appropriately selected patients

without structural heart disease, including a 'pill-in-the-pocket' strategy for suitable patients with infrequent symptomatic paroxysmal AF after appropriate safety assessment. Amiodarone, which works on multiple electrophysiologic pathways, is still a valuable agent for selected patients with AF and coexistent heart failure or left-ventricular dysfunction, but is limited by its extracardiac toxicity and drug-drug interactions. Dronedarone offers a less effective but relatively safe alternative in appropriately selected patients, although it is contraindicated in certain forms of heart failure and high-risk permanent AF. Such limitations highlight the general challenge of pharmacological therapy in AF: suppression of the AF substrate without excessive systemic or proarrhythmic effects.

Catheter ablation has gradually moved from a rescue therapy to a treatment for earlier rhythm control. Pulmonary-vein isolation (PVI) remains the cornerstone since it electrically isolates pulmonary-vein activity from the atrium. Randomized trials including RAAFT, RAAFT-2, MANTRA-PAF, and CABANA have shown that ablation confers reduced AF recurrence or AF burden compared to pharmacological therapy, although there are still risks associated with the procedure and the possibility of recurrence. A similar conclusion was reached by the FIRE AND ICE trial, which compared cryoballoon versus radiofrequency ablation for paroxysmal AF and found the former to be non-inferior. However, acute PVI does not guarantee long-term durability of the procedure since reconnecting pathways can develop.

The limitations of PVI have led to attempts to target additional sources of AF that are located outside the pulmonary veins. Finding such a driver is challenging since complex fractionated atrial electrograms (CFAEs) are widely distributed and do not reliably reflect AF-maintaining substrate. Similarly, Focal Impulse and Rotor Modulation (FIRM) mapping identified a rotor as the driver of AF, which initially appeared to be a promising treatment, but the randomized REAFFIRM trial found that adding FIRM to PVI did not improve outcomes over PVI alone. This shows the difference between a theoretically attractive intervention and one supported by solid evidence. Noninvasive body-surface mapping and charge-density mapping with AcQMap represent further innovations which could potentially identify AF drivers but their clinical superiority is yet to be proven.

An important consideration is whether ablation beyond PVI should directly target individual AF drivers or instead use anatomical lesions to compartmentalize the atrium, thereby preventing propagation regardless of the specific driver. Neither approach has been clearly superior to date. A further consideration is that response to ablation might depend on the underlying structural substrate: late gadolinium-enhancement MRI can characterize atrial fibrosis, and extensive fibrosis is associated with worse sinus rhythm maintenance after conventional ablation. Therefore, structural characterization might eventually allow identification of patients who are likely to benefit from different ablative strategies.

Ablation in patients with heart failure with reduced ejection fraction (HFrEF) might improve outcomes beyond simple

rhythm control. Studies such as AATAC and CASTLE-AF found that ablation improved AF control and ventricular function, with the former also reporting reduced cardiovascular hospitalization and mortality. This suggests a bidirectional interaction between AF and ventricular dysfunction, but such benefits should not be extrapolated to all patients with HFrEF.

The limitations of conventional therapies have led to the development of mechanism-based and atrial-selective drugs which are relevant to an ion-channel-focused review. SK-channel blockade has shown encouraging early results for cardioversion but remains uncertain due to concerns about QT effects and the role of SK channels in the arrhythmogenesis of AF. TASK-1 is another promising target: it is an atrial-enriched potassium channel that contributes to pathological shortening of the action potential in AF, and preclinical inhibition can restore atrial electrophysiology with limited ventricular effects. There is ongoing clinical investigation of TASK-1 inhibitors, and combination therapy such as low-dose ranolazine with dronedarone in the HARMONY trial also demonstrates the potential for synergistic effects between different electrophysiologic mechanisms to improve rhythm control while limiting individual drug exposure.

A number of novel approaches aim to modify the AF substrate rather than target individual ion channels. Pulsed-field ablation uses irreversible electroporation to cause tissue injury by applying electrical fields, and might offer greater tissue specificity than conventional thermal approaches, although early clinical experience is limited. Anti-inflammatory and antifibrotic approaches, including targeting IL-1 β and metabolic pathways, are also under investigation. These developments demonstrate the shift from general electrical suppression toward earlier, more substrate-specific, and increasingly mechanism-specific treatment of AF.

3. Future Direction

The review discusses future strategies for managing atrial fibrillation (AF). A significant proportion of AF is determined by genetics that can be both structural, such as MYL4, MYH7, LMNA, and TTN genes promoting atrial dilatation and remodeling, and ion-channel related, including SCN5A, KCNQ1, and KCNA5 genes responsible for altered excitability and conductivity. For instance, SCN5A loss-of-function can cause conduction velocity reduction whereas both gain- and loss-of-function KCNQ1 variants trigger early-onset AF. However, the role of many monogenic AF genes is still debated because small family studies and candidate-gene approaches failed to validate the initial results.

Polygenic AF risk is determined by common variants in genes involved in cardiac development or pulmonary-vein formation such as PITX2, and NKX2-5 contributing to familial AF cases, genome-wide association studies (GWAS) have reported an increased risk in loci 4q25/PITX2, 16q22, and 1q21.1. This genetic predisposition can contribute to AF pathophysiology by mechanisms independent of rare variants, usually affecting gene regulation, structure, or function, thereby only moderately contributing to the overall disease risk. Altogether, these findings may impact the clinical

management of AF patients since the polygenic risk score and the genetic testing for monogenic AF are promising tools to guide the choice of therapy.

Genetic testing may impact the early-onset AF management since the 2023 ACC/AHA/ACCP/HRS guideline classified such a test as reasonable for young patients with unexplained AF. Indeed, pathogenic rare variants were found in 4-11% of early-onset AF cases. AF genetic variants can also overlap with cardiomyopathy and arrhythmia susceptibility genes. Therefore, integrating genetic testing into the clinical workflow may help to sort out patients benefiting from more extensive cardiovascular screening. The individualized approach based on genetic risk factors can guide the treatment selection depending on the genetic background and improve the clinical outcomes in AF patients.

Earlier rhythm control is another key strategy for managing AF. EAST-AFNET 4 randomized trial enrolling 2,789 patients with AF diagnosed within the prior 12 months tested the clinical benefits of early rhythm control. Early intervention was associated with a reduced risk of cardiovascular death, stroke, hospitalization for worsening heart failure, or acute coronary syndrome (HR 0.79; $P = 0.005$). The mechanism explaining this benefit can be related to the substrate hypothesis described earlier in this review. AF triggers electrical and structural remodeling leading to AF-promoting substrate strengthening the self-sustaining spiral waves of electrical activity during AF. Therefore, early intervention can prevent such maladaptive remodeling and AF progression. The concept of early rhythm control fits into the broader context of substrate modification as a part of the trigger-substrate-modulator theory of AF. The modulation of specific molecular targets such as SK channels, TASK-1, inhibition of the slow inward sodium current, and multi-channel approaches are also under investigation. Moreover, the use of novel techniques for pulmonary vein isolation such as pulsed-field ablation can be considered to minimize the pro-arrhythmic effects on the ventricles. These methods are mainly relevant to AF patients with ion-channel rare variants since they are mostly linked to specific electrophysiological mechanisms. However, the proarrhythmic risks still need to be validated in clinical trials, and the evidence for the benefits of substrate modification seems limited at this stage.

Earlier detection of AF may also be a critical link in AF management since early intervention can be too late to affect remodeling and AF progression. AF screening using wearable devices and specific algorithms can be used for early AF detection before developing overt symptoms at an early stage. The systematic review mentioned in the source estimated that single-time-point screening in adults aged ≥ 65 years would identify 1 treatable AF case for every 83 adults screened. The individual risk profile stratification combined with the clinical and genetic risk factors and the use of artificial intelligence might be helpful in selecting patients for early AF screening. This approach would benefit from the individual patient risk profile, selecting those who might benefit from rhythm control or early intervention and AF substrate modification. Therefore, the future of AF management will be focused on these three themes: early detection, personalized risk assessment, and individualized treatment.