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Disruptions in Cardiac Conduction and the Biology of Arrhythmias: Insights from Physiology, Ion Channels, and Translational Research

Steve Jerome

CPS Global School, AS Levels
Email: *stevejerome72[at]gmail.com*

Abstract: ***Every year, millions of people die because their hearts stop beating in the right rhythm. Arrhythmias , disruptions in the heart's electrical conduction system , are behind a significant portion of those deaths, from sudden cardiac arrests that strike without warning to the quieter, chronic toll of conditions like atrial fibrillation. What makes this particularly striking is that the underlying machinery of the heart is extraordinarily precise. Under normal conditions, it truly coordinates every single beat with millisecond accuracy, billions of times over a lifetime. When something goes wrong at the molecular level, the consequences can be catastrophic. This review examines what that machinery looks like when it works, what goes wrong when it fails, and where medicine currently stands in its efforts to fix it at the source. The focus is on ion channels, gap junctions, and the specific molecular mechanisms re-entry circuits, channelopathies, calcium handling disorders that turn a healthy electrical system into an arrhythmogenic one. It also honestly examines the barriers between what science can currently do in the laboratory and what can realistically be offered to a patient. Gene therapy, CRISPR-based editing, and RNA therapeutics all feature — not as science fiction, but as real and rapidly advancing approaches with genuine obstacles still to overcome.***

Keywords: cardiac conduction, arrhythmias, ion channels, action potential, re-entry, channelopathy, gene therapy

1. Introduction

Consider what the heart actually does. It beats around 100,000 times a day, every day, for decades and each beat requires the precise, coordinated electrical activation of hundreds of millions of cells in a specific sequence, within a window of milliseconds. No other organ in the body does anything remotely like it. The fact that this works as reliably as it does, for as long as it does, is genuinely remarkable.

But the same precision that makes the system extraordinary also makes it vulnerable. Sudden cardiac death the majority of which is arrhythmia-driven claims an estimated 3.7 million lives annually worldwide (Hayashi et al., 2015). Atrial fibrillation affects over 37 million people globally, a number that has more than doubled since 1990 (Lippi et al., 2021). These are not rare conditions affecting a small subset of the population. They are among the most common causes of death and disability on the planet, and they are increasing.

What connects all arrhythmias, despite their enormous clinical variety, is a breakdown in the electrical system that coordinates the heartbeat. Sometimes this comes from a genetic mutation in an ion channel that has been present since birth. Sometimes it comes from scar tissue left by a heart attack. Sometimes it develops gradually over years of structural remodelling in heart failure or atrial fibrillation. The biology differs. The outcome of disorganised electrical activity that impairs the heart's ability to pump is the same.

This review traces that biology from its foundations. It begins with the normal physiology of the cardiac conduction system, moves through the specific molecular mechanisms by which arrhythmias arise, examines what animal models have taught us and where their limits lie, and ends with an assessment of the translational and ethical landscape. The aim throughout is not just to describe what is known, but to understand it well enough to see where it might be changed.

2. Methods

This narrative literature review was conducted by searching PubMed, ScienceDirect, and Google Scholar using terms including "cardiac conduction system," "ion channels arrhythmias," "cardiac action potential," "re-entry arrhythmia," "connexin gap junction," and "gene therapy arrhythmias." The search was restricted to peer-reviewed English-language articles published between 2010 and 2026.

Around 50 articles were screened initially by title and abstract. Eleven were selected for detailed analysis based on their depth of coverage across normal conduction physiology, arrhythmogenic mechanisms, animal model comparisons, and translational challenges. Given the narrative structure of the review, findings are synthesised thematically rather than quantitatively the goal being conceptual clarity rather than statistical aggregation.

3. The Cardiac Conduction System

To understand what goes wrong in an arrhythmia, you first need a clear picture of what normal looks like. The heart's conduction system is essentially a biological relay a precisely timed cascade of electrical signals that begins in one small cluster of cells and ends with the entire muscular mass of both ventricles contracting in unison. It is a system that evolved over

hundreds of millions of years, and it shows.

It begins in the sinoatrial (SA) node, a cluster of around 10,000 specialised pacemaker cells tucked into the right atrium near the superior vena cava. These cells fire spontaneously and rhythmically 60 to 100 times per minute under normal autonomic tone making the SA node the heart's natural pacemaker (Park & Fishman, 2011). The electrical impulse they generate spreads across both atria, reaching the left atrium via Bachmann's bundle, before arriving at the atrioventricular (AV) node. Here, the signal is deliberately slowed a pause of 120 to 200 milliseconds to ensure the ventricles have finished filling before they contract. From the AV node, the signal travels down the bundle of His, splits into left and right bundle branches, and fans out through the Purkinje fibre network to activate the ventricles from the apex upward, squeezing blood out with every beat.

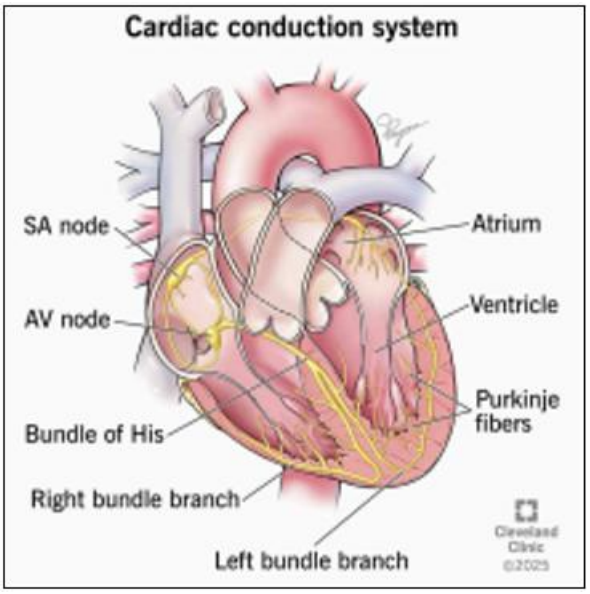

Figure 1: The cardiac conduction system. Impulses originate in the SA node, delay at the AV node, and distribute via the bundle of His, bundle branches, and Purkinje fibres to coordinate ventricular contraction. Adapted from Cleveland Clinic (2025).

All of this depends on voltage-gated ion channels proteins that open and close in response to changes in membrane voltage, controlling the flow of charged ions across the cell membrane. In SA nodal cells, the process that drives spontaneous firing is the "funny current" (If): a slow inward flow of sodium and potassium ions through HCN4 channels during diastole that gradually depolarises the membrane until it reaches the threshold for firing. It is called the funny current because it behaves in the opposite direction to most channels opening when the membrane is hyperpolarised rather than depolarised. This quirk is precisely what makes it useful as a pacemaker mechanism.

In working cardiomyocytes, the action potential that follows has five distinct phases. Phase 0 is the initial rapid depolarisation, driven by sodium rushing into the cell through Nav1.5 channels a fast, all-or-nothing event. Phase 1 is a brief early repolarisation from transient potassium outflow. Phase 2 is the plateau the longest phase, lasting around 200 ms sustained by calcium entering through L-type channels (Cav1.2), balanced against potassium leaving through IKr and IKs channels. This plateau is what drives contraction; it is the electrical correlate of the mechanical squeeze. Phase 3 is repolarisation, predominantly driven by IKr and IK1 pushing the membrane back toward its resting potential. Phase 4 is the resting state, held stable by IK1.

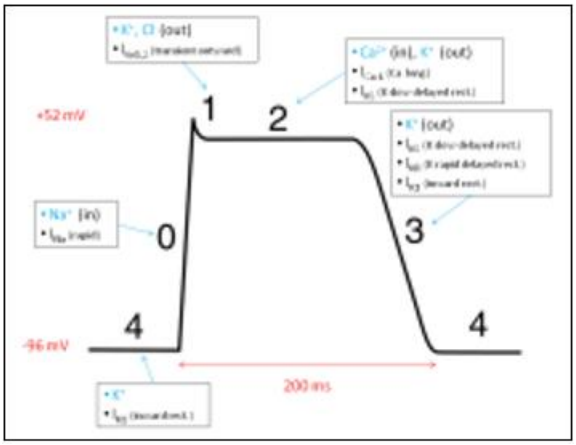

Figure 2: The five phases of the ventricular action potential. Phase 0 (Na+ influx via INa) initiates depolarisation. The plateau (Phase 2) is maintained by ICa-L against IKs ef lux. Repolarisation (Phase 3) is driven by IKr, IKs, and IK1. Total duration approximately 200 ms.

The long refractory period this creates is not a side effect it is an essential safety feature. Because the cell cannot be re-excited immediately after firing, the heart is protected from the kind of sustained tetanic contraction that would be fatal. The system is designed with this protection built in.

Between cells, electrical coupling happens through gap junctions intercellular channels formed by connexin proteins, primarily connexin-43 (Cx43) in ventricular muscle and connexin-40 (Cx40) in the His-Purkinje system. These allow ions to flow directly from one cell to the next, enabling the rapid, synchronised spread of excitation at conduction velocities of around 2 to 4 metres per second in the Purkinje network. The health of these gap junctions matters just as much as the ion channels themselves something that becomes very apparent when we look at what happens after a heart attack.

4. Disruptions in Cardiac Conduction and the Biology of Arrhythmias

Arrhythmias, in almost every case, come down to one of three problems: an electrical impulse circulates where it should not, a cell fires when it should not, or a cell is nudged into firing by an abnormal voltage fluctuation. These three mechanisms re-entry, abnormal automaticity, and triggered activity account for the vast majority of clinically significant arrhythmias (Clauss et al., 2019). They are distinct in their biology, and

understanding that distinction matters for treatment.

4.1 Re-entry Circuits

Re-entry is the most common mechanism behind serious arrhythmias atrial flutter, atrioventricular nodal re-entrant tachycardia (AVNRT), and post-infarction ventricular tachycardia among them. The basic idea is not complicated: instead of an electrical wavefront dying out after activating tissue, it finds a circular pathway and keeps going, re-exciting tissue it has already passed through in a self-sustaining loop. What is required for this to happen is a specific combination of three conditions: two anatomically or functionally distinct conduction pathways, unidirectional block in one of them, and sufficiently slow conduction through the other to allow the blocked pathway time to recover before the wavefront arrives (Blackwell et al., 2022). Remove any one of those three conditions, and re-entry terminates.

In real hearts, this substrate is most commonly created by structural damage. After myocardial infarction, the peri-infarct zone the border region between dead and surviving tissue becomes a patchwork of viable myocyte strands separated by collagen deposits. Electrical impulses can no longer spread smoothly; they are forced through narrow, tortuous channels, slowing dramatically. Connexin-43 simultaneously relocates from its normal position at the intercalated disc to the lateral cell membrane a process called gap junction lateralisation further fragmenting the orderly, directional spread of excitation. The result is a tissue architecture that almost seems designed to sustain re-entry, even though it is simply the consequence of healing.

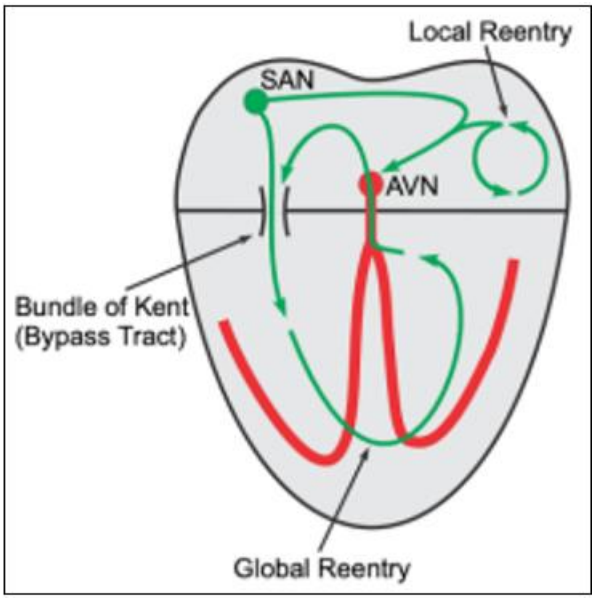

Figure 3: Re-entry circuit types. Local re-entry (top right) involves a small anatomical or functional loop. Global re-entry involves large-scale circus movement, sometimes facilitated by an accessory pathway such as the Bundle of Kent (as in Wolf -Parkinson-White syndrome). SAN = sinoatrial node; AVN = atrioventricular node.

4.2 Ion Channel Dysfunction

Not every arrhythmia requires structural damage. Some of the most dangerous are rooted entirely in the channels themselves inherited mutations that alter how a single protein behaves, with consequences that ripple through the entire action potential. SCN5A, the gene encoding Nav1.5, is probably the most instructive example. Lose-of-function mutations in SCN5A reduce peak sodium current, slowing conduction across the right ventricle and producing the characteristic ST-elevation pattern of Brugada syndrome- a condition that can cause ventricular fibrillation during sleep or fever, in people who may have had no warning signs whatsoever. Gain-of-function mutations in the very same gene do the opposite: they keep sodium channels open too long, sustaining a pathological late current that prolongs the action potential plateau and creates long QT syndrome type 3. In LQT3, the extended repolarisation phase opens a window during which L-type calcium channels can reactivate, generating early afterdepolarisations (EADs) that trigger torsades de pointes a dangerous polymorphic ventricular tachycardia (Lei et al., 2024). One gene. Two mutations. Two completely different arrhythmias, each potentially fatal.

Calcium handling disorders tell a similar story. In catecholaminergic polymorphic ventricular tachycardia (CPVT), mutations in either RyR2 (the ryanodine receptor) or CASQ2 (calsequestrin 2) cause the sarcoplasmic reticulum to leak calcium during diastole at the precise moment when the cell is supposed to be resting. This rogue calcium activates the sodium-calcium exchanger (NCX), generating a small depolarising current (Iti) that produces a delayed afterdepolarisation (DAD). If the DAD is large enough to reach threshold, it fires an ectopic beat. Under adrenergic stress a sprint, a shock, an argument — these ectopic beats can multiply and degenerate into polymorphic ventricular tachycardia. Children with CPVT can collapse on a playground. The mutation has been present since conception.

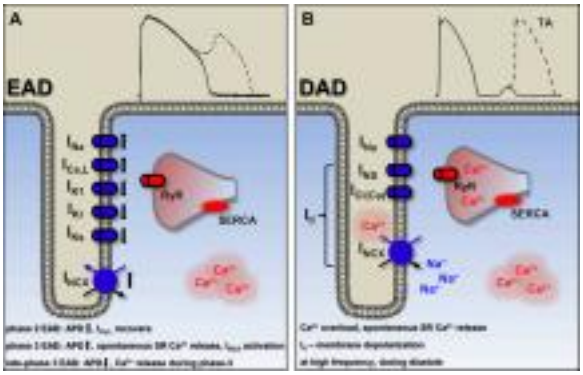

Figure 4: Cellular mechanisms of triggered activity. Panel A: Early afterdepolarisations (EADs) arise from prolonged action potential duration with reactivation of ICa-L during phases 2–3. Panel B: Delayed afterdepolarisations (DADs) arise from spontaneous sarcoplasmic reticulum calcium leak via RyR, activating NCX (INCX) to produce a depolarising Iti current during diastole- the mechanism underlying CPVT. Adapted from Lei et al. (2024).

4.3 Cellular and Tissue-Level Remodelling

Beyond inherited channelopathies, acquired remodelling builds arrhythmogenic substrates gradually often over years. In chronic heart failure, progressive downregulation of Kv4.3 (Ito) and IKr channels prolongs action potential duration and creates spatial heterogeneity in repolarisation across the ventricle. This dispersion of refractoriness- the fact that neighbouring regions of myocardium are at different stages of recovery at the same moment is one of the most reliable predictors of ventricular arrhythmia risk.

Atrial fibrillation illustrates a particularly vicious form of this remodelling. Sustained rapid atrial activation progressively downregulates L-type calcium channels, shortening the atrial action potential and refractory period. At the same time, the mechanical stress and inflammation that accompany AF promote atrial fibrosis, fragmenting conduction pathways. The shortened refractory period means more re-entrant circuits can be sustained simultaneously; the fibrosis provides the structural substrate to sustain them. The result is a positive feedback loop- AF remodels the atria in ways that make AF easier to maintain and harder to terminate. This is what clinicians mean when they say that "AF begets AF," and it is why treating AF early, before remodelling becomes established, matters so much.

5. Animal Models vs. Human Arrhythmias

A great deal of what we understand about arrhythmia mechanisms came first from animals, not humans. That is both a strength and a limitation and understanding the limitation is as important as appreciating the insight.

Mice are by far the most widely used model. They are cheap, genetically tractable, and can be engineered to carry virtually any human ion channel mutation within months. The insights they have provided into molecular pathways are substantial. But mice have a resting heart rate of 400 to 600 beats per minute up to ten times that of a human and a much shorter action potential dominated by Ito rather than IKr for repolarisation (Joukar, 2021). These are not trivial differences. When researchers introduce long QT syndrome mutations into mice, the animals frequently fail to develop arrhythmias, because the short murine action potential simply does not last long enough for EADs to develop. The model is studying the right gene in the wrong heart.

Larger animals close this gap considerably. Pigs and dogs share much of human cardiac anatomy, coronary circulation, and electrophysiology. Porcine infarction models in particular replicate the peri-infarct zone remodelling the fibrosis, the connexin redistribution, the slow conduction channels that underlies post-infarction ventricular tachycardia in humans with high fidelity. These are the models used to test ablation strategies and antiarrhythmic drugs before human trials. Zebrafish offer something different: rapid generation times, transparent embryos, and high genomic homology with human cardiac genes make them invaluable for large-scale screening of mutations and compounds, even if their single-ventricle anatomy limits direct comparison with human ventricular arrhythmias (Clauss et al., 2019).

There is also something more fundamental that animal models have revealed, almost as a side observation. Zebrafish and neonatal mice can regenerate cardiac muscle after injury. Adult mammals including humans largely cannot. The regenerative programme is suppressed in adult mammalian hearts through mechanisms including Hippo pathway activation and cardiomyocyte cell cycle arrest. Understanding this suppression, and potentially reversing it pharmacologically, could offer a way to prevent arrhythmogenic scar from forming in the first place a far more elegant solution than trying to correct it after the fact.

6. Translational Barriers and Ethical Concerns

There is a wide gap between a finding that works in a dish and a treatment that reaches a patient. In cardiac gene therapy, that gap is particularly challenging, and it is worth being honest about why.

The most clinically advanced gene delivery vehicles are adeno-associated virus (AAV) vectors. They are efficient, relatively well-tolerated, and have already been approved for use in several non-cardiac conditions. But they have a packaging limit of approximately 4.7 kilobases and SCN5A, the gene most relevant to several major channelopathies, is around 6 kilobases. The vector simply cannot carry it. This is not a solvable problem through better engineering at the margin; it is a fundamental size constraint. Add to this that a substantial proportion of the general population already carries neutralising antibodies to common AAV serotypes meaning the immune system would destroy the vector before it reached the heart and the delivery challenge alone is formidable (Bains et al., 2026).

Cell-based therapies bring their own complications. Stem cell-derived cardiomyocytes, when transplanted into damaged myocardium, often retain immature electrophysiological properties. They are spontaneously active when they should be quiescent, and they couple poorly with the surrounding tissue. Rather than restoring normal rhythm, they can introduce new ectopic foci. This is not a reason to abandon cell therapy, but it is a reason to take the preclinical evidence seriously before moving to human trials.

CRISPR-Cas9 base editing and prime editing have produced genuinely exciting results in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), correcting gain-of-function long QT mutations at the level of the genome (Grisorio et al., 2026). The principle is compelling: instead of managing the downstream consequences of a mutation, fix the mutation itself. The concerns are real but not necessarily insurmountable off-target editing events, incomplete correction across the billions of cardiomyocytes in a human heart, and the practical difficulty of confirming safety before a therapy is administered. RNA-based approaches, including antisense oligonucleotides

and siRNA targeting specific arrhythmogenic transcripts, offer a more cautious alternative reversible, modifiable, with a better-established safety profile.

On the pharmacological side, the central problem has not fundamentally changed in decades: most ion channel blocking agents are not selective enough. Drugs that suppress IKr to treat ventricular tachycardia risk prolonging the QT interval and causing the very arrhythmia they were designed to prevent. Late sodium current inhibitors like ranolazine represent a more targeted approach reducing the pathological persistent INa seen in LQT3 and heart failure without meaningfully affecting peak sodium current and normal conduction. This kind of mechanistic precision, matching a specific molecular target to a specific drug action, is where pharmacology needs to go.

Then there are the ethical questions, which deserve more than a passing mention. The prospect of correcting inherited channelopathies through germline editing fixing the mutation in a pre-implantation embryo so that neither that individual nor any of their descendants carries it is scientifically plausible and medically appealing. It is also a step into genuinely uncertain territory. Heritable genomic changes made in an embryo cannot be reversed. Off-target edits would be passed on. The individuals most affected the descendants cannot consent. These are not hypothetical concerns; they are the reason the scientific community responded with alarm to the first reported cases of germline editing in humans. Getting this right requires bioethicists, patient advocates, and regulatory bodies at the table alongside the scientists. Equally pressing, though less often discussed, is access. Gene therapies currently approved for other conditions carry price tags of several hundred thousand dollars per patient. Without serious structural engagement with health systems, insurance coverage, and international equity, the most transformative treatments in cardiac medicine will remain available only to those born in wealthy countries, a morally indefensible outcome that the field cannot afford to ignore.

7. Conclusion

What this review has tried to show is that the heart's electrical system is both extraordinarily capable and specifically fragile. A single mutation in SCN5A can produce two completely different fatal arrhythmia syndromes depending on whether it gains or loses function. Calcium leaking from the sarcoplasmic reticulum during diastole can kill a child on a playground. Scar tissue from a heart attack can sustain a ventricular tachycardia circuit for decades. These are not mysterious failures. They are consequences of specific molecular events that we now understand well enough to name, to trace, and increasingly to target.

That understanding has matured enormously in a short time. Twenty years ago, CRISPR did not exist. hiPSC-derived cardiomyocytes did not exist. The detailed ion channel pharmacology that now allows us to distinguish between peak and late sodium current as therapeutic targets did not exist. The science is moving fast, and the direction is the right one: toward correcting arrhythmogenic substrates at their source rather than suppressing their symptoms indefinitely.

What would be a mistake is treating the remaining barriers as purely technical problems. The AAV packaging limit, the immune response, the off-target editing risk — these are hard scientific challenges and they will be solved by hard scientific work. But the ethical questions around germline editing, and the equity questions around who gets access to these therapies when they arrive, will not be solved by science alone. They require the same seriousness of attention. A treatment that works but reaches only a fraction of the people who need it is not a success. Getting the biology right is necessary. It is not sufficient.

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