Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: June 30, 2024

Citation: Adams CD., 2024. Autoimmunity and Biological Therapies in Cardiac Arrhythmias, Medical Research Archives, [online] 12(6). https://doi.org/10.18103/mra.v12i6.5476

DOI
https://doi.org/10.18103/mra.v12i6.5476

ISSN: 2375-1924

REVIEW ARTICLE

Autoimmunity and Biological Therapies in Cardiac Arrhythmias

Christian David Adams, MD.

Center: Fundación Valle de Lili

Direction: Calle 98 # 18 - 49

Email: christian.adams@fvl.org.co

ABSTRACT:
Autoimmune (AI) diseases have a notable rise globally, affecting up to 9.4% of the global population. Cardiac involvement is not unusual in AI diseases, leading to arrhythmias through many pathophysiological mechanisms like myocardial inflammation, fibrosis, and autoantibodies targeting critical cardiac structures, leading to cardiac rhythm disorders. This review focuses on the role of autoantibodies in arrhythmias in diseases like sarcoidosis, lupus, rheumatoid arthritis, scleroderma, and others, highlighting new findings about autoantibodies against critical structural myocardial components. On the other hand, the review describes the AI association with conditions such as sinus bradycardia, atrioventricular blocks, inappropriate sinus tachycardia, atrial fibrillation, ventricular tachycardia, and sudden cardiac death, describing those processes. Emerging biomarkers indicative of inflammation, fibrosis, and autoimmunity that can predict arrhythmia risk are examined. The review also explores the field of managing cardiac arrhythmias with alternative cell therapy approaches that target gene substrate as a promising way to transfer, silence, and edit cellular disorders associated with arrhythmia generation that may help treat these conditions in the future.

Keywords: Atrial fibrillation; Autoimmune disease; Immunosuppression; Inflammation; Remodeling.

Introduction:

Over the past three decades, the prevalence of autoimmune (AI) diseases has experienced a significant rise, attributed to enhanced detection and surveillance systems; these conditions affect 7.6–9.4% of the global population[1]. In healthy individuals, basal levels of natural autoantibodies serve essential physiological functions, including early innate immune defense, clearance of apoptotic cellular debris, and immunological moderation of atherosclerosis, cancer, and autoimmune pathologies. However, when mechanisms governing physiologic tolerance fail, autoimmune diseases emerge, facilitated by autoreactive B cells that evade processes like clonal deletion, inhibition by interleukin (IL) -6 and CD40L, receptor editing, or anergy[2]. Some of these disorders could compromise the cardiovascular system, potentially culminating in cardiac rhythm disorder through various pathophysiological mechanisms; in the heart, myocardial inflammation and subsequent fibrosis emerge as primary arrhythmia drivers; other mechanisms also disrupt critical structures, leading to inflammatory abnormalities in cellular physiology and autonomic dysfunction, and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodeling [3,4]. Knowing that mechanism will enhance the comprehension of one of the pillars in the physiopathologic mechanism of arrhythmias, not only in common AI diseases but also in the role of autoantibodies in the genesis of many common arrhythmias not associated with a particular AI disease. On the other hand, cellular-based therapy offers an alternative approach, with growing evidence for the management of frequent rhythm disorders.

Rhythm Disturbances Associated with Autoimmune and Inflammatory Processes

SINUS BRADYCARDIA

Emerging evidence suggests an AI mechanism of sinus node dysfunction, particularly chronotropic incompetence. Animal studies support the hypothesis that disease-specific antibodies, anti-Ro/SSA and anti-La/SSB IgG have been shown to directly bind to the cardiac sarcolemmal α1D calcium channel protein, which is critical for pacemaker function in the sinus node [5,6]. This binding may impair calcium influx into the sinus node cells, leading to decreased automaticity and chronotropic incompetence, and may contribute to fibrosis within the sinus node. Other evidence of anti-Ro/SSA antibodies in mothers of children with congenital heart block provides further evidence for a potential role of autoimmunity in sinus node dysfunction [7]. Another mechanism of sinus node dysfunction is seen in patients with idiopathic dilated cardiomyopathy and Chagas disease, with autoantibodies targeting the muscarinic M2 receptor (see more below) [8].

CONDUCTION ABNORMALITIES

Atrioventricular (AV) blocks and bundle branch block Is the most common rhythm disorder, 5 to 35% prevalence in patients with autoimmune diseases [5]. In the 50% of AVB occurring in adults <50 years, the etiology remains unknown, and preliminary evidence from case reports suggests an AI mechanism [9]. Animal studies bring robust evidence and pathophysiological effect of the IgG anti-Ro/SSA inhibiting the L-type Ca2+ current (Cav1.2), suggesting a direct effect on the activities of cardiac ion channels by direct physical interaction between the antibodies and the pore-forming α subunit (α1C), and the chronic exposure cause Ca2+ channel internalization and intracellular Ca2+ dysregulation, followed by progressive apoptosis of the AV node cells, leading to its fibrosis and calcification [6,10], particularly anti-Ro/SSA-52kD, found in 53% of AVB-patients and their mothers, without history of autoimmune diseases [9,11]. Chronically down-regulated Cav1.2 expression shows fibrotic changes in a linear pattern, sparing the subendocardial layer in the AV node region [12]. Another described mechanism is mediated by an anti-β2 adrenergic receptor which causes the activation of the Gi protein, which regulates the potassium channels, producing membrane hyperpolarization and also inhibiting L-type calcium channels, this kind of IgG were detected in chronic Chagasic patients, the effects were blocked by atropine, suggesting the presence of autoantibodies with muscarinic agonistic function [2], antibodies against β-adrenergic receptors were found in 35.7% of patients with conduction disturbances and no other cardiac abnormalities [4].

INAPPROPRIATE SINUS TACHYCARDIA

Persistent inappropriate primary elevated resting heart rate in autoimmune disorders often stems from enhanced sinus nodal automaticity due to sympatho-vagal imbalance, in 52% of patients anti-β adrenergic receptor antibodies were detected, a phenomenon absent in healthy controls. These antibodies bind to β-adrenergic receptors, activating Gsα, and adenylyl cyclase, increasing cAMP accumulation and exerting a positive chronotropic effect [13]. In Postural Orthostatic Tachycardia Syndrome (POTS), IgG against adrenergic receptors (anti-α1, anti-β1, and anti-β2-adrenergic antibodies), acetylcholine receptor, voltage-gated potassium channel complex, cardiac lipid raft-associated proteins, and especially

angiotensin II receptor (AT2R) have been reported [14].

ATRIAL FIBRILLATION

Many factors contribute to the pathogenesis of atrial fibrillation (AF), including electrical, structural, neurohumoral, and inflammatory processes. Emerging evidence portends the involvement of autoantibodies in cardiac arrhythmias [6,15]. The first antibody detected in atrial fibrillation with a statistically significant difference was the IgG against myosin heavy chain, previously found in patients with myocarditis and dilated cardiomyopathy [6]. After that, antibodies against the α-catalytic subunit of Na/K-ATPase were more prevalent in AF patients with dilated cardiomyopathy than those with ischemic cardiomyopathy [16]. The M2 muscarinic cholinergic receptors mediate parasympathetic signaling in the heart, and derangement of vagal tone promotes the development of atrial fibrillation, the presence of autoantibodies was an independent predictor for AF [6]. Also, IgG against both the β1-adrenergic receptor was a strong predictor of atrial fibrillation in patients with Graves' disease [16]. Heat shock proteins (HSP) are stress response elements that function as intracellular chaperones for other proteins to help maintain proper protein folding, and their presence is another predictor of postoperative AF [16]. Lately, autoantibodies targeting ion channel subunit Kir3.4 of the acetylcholine-gated KACh channel (formerly GIRK1/GIRK4) that activate inwardly rectifying K+ channel with negative chronotropic effect resulting in a shortened atrial refractory period and enhanced dispersion of atrial repolarization providing an arrhythmogenic substrate for AF [15].

CHANNELOPATHIES

In cases of non-genetically arrhythmogenic mechanisms in structurally normal hearts, the amount of evidence demonstrates that autoimmunity and inflammation can promote arrhythmias by directly interfering with the expression and function of cardiac ion channels, particularly K channels [17,18]. Different types of anti-K+ channel autoantibodies were described, specific against subunits K,11.1 (hERG), K,7.1, and K,1.4, affecting the action potential of ventricular cardiomyocytes emerging in the clinical setting by changes in the QT interval (long QT or and short QT syndromes) [4]. Also, the hERG-K-channel may be disrupted by anti-Ro/SSA, detected in patients with Long QT Syndrome and connective tissue diseases such as Sjögren's syndrome (30-95%) and systemic lupus erythematosus (30-50%) [18–20]. The Inflammatory channelopathies specifically associated with TNF alpha, IL-1, and IL-6 were secondary to the modulation of the function of K+ channels with loss-of-function, leading to QT prolongation with an increased nitric oxide synthase expression and reactive oxygen species (ROS) production, as well as a decrease in the potassium-channel-interacting protein-2 (KChIP-2) ROS-induced nuclear factor kappa-B (NF-B) activation as the critical molecular step responsible for K+-channels gene expression decrease induced by Tumor necrosis factor-α (TNF-α) in cardiomyocytes [18].

VENTRICULAR TACHYCARDIA

Patients with connective tissue disease with a high burden of ventricular arrhythmias (VA) in the 24-hour Holter studies have a high incidence of IgG anti-Ro/SSA positive (50% vs. 10%) in the absence of structural cardiac abnormalities and QT interval prolongation due to IgG cross-react with KCNH2 channel, reducing channel protein expression [21]. Ventricular arrhythmias were frequent in patients with Anti-β1-adrenergic autoantibodies, detected in 35 to 80% of patients with Chagas' disease [22], idiopathic dilated cardiomyopathy, and ischemic cardiomyopathy, but not in those with valvular or hypertensive heart disease [6]. In Chagas heart disease, there is cross-reactivity between an antibody to the C-terminal region of the Trypanosoma cruzi ribosomal P2β protein and the second extracellular loop of the human β1 adrenergic receptor [22], which increased spontaneous beating frequency, increased action potential duration, enhanced L-type Ca2+ currents, and cause downregulation of Ito and IKS with a higher propensity for induction of early afterdepolarizations [6].

SUDDEN CARDIAC DEATH (SCD)

In patients with dilated cardiomyopathy who present SCD, an enzyme-linked immunoabsorbent assay recognizes antibodies to the alpha subunit of the Na/K-ATPase channel with antagonistic effects (26% versus 2% of healthy controls).In patients with complex ventricular arrhythmias, were more frequent anti-Na/k ATPase positive (81%) versus antibody-negative (32%, $p<0.001$) as was sudden cardiac death (26.9% vs. 5.4%, $p=0.0006$ with a hazard ratio of 22.5), being an independent predictor of sudden cardiac death [23]. Anti-cardiac troponin I (anti-cTnI) had a role in the disease progression in ischemic and non-ischemic cardiomyopathies, being an SCD risk marker. Anti-human heat shock protein 60 (anti-HSP60) is known to take part in the immunologically mediated promotion of atherosclerosis and can lyse the endothelial cells via antibody-dependent cellular cytotoxicity causing an arrhythmic substrate [24].

Immune Diseases Associated with Arrhythmias

SARCOIDOSIS

In sarcoidosis, ventricular tachycardia (VT) emerges as the predominant rhythm disorder, affecting up to 23% of patients, while atrial arrhythmias are less prevalent, occurring in 15–17% of cases. Among supraventricular arrhythmias, atrial fibrillation (AF) is the most common (18%), followed by atrial tachycardias (7%), and atrial flutter (5%). The arrhythmic mechanisms in sarcoidosis are associated with the granulomatous inflammation that enhances automaticity, which persists beyond the active inflammation. Corticosteroids improve the arrhythmic burden but promote fibrosis within active granulomas, fostering reentrant circuits for VT or flutters, especially in the para-tricuspid area [25].

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic Lupus Erythematosus (SLE), often regarded as a prototype autoimmune disease, presents a spectrum of cardiac rhythm disorders, with sinus tachycardia, atrial fibrillation (AF), and atrial premature complexes being the most prevalent (15–50% incidence). On the other hand, conduction defects are prevalent in SLE patients (34–70%) [26,27]. These arrhythmias' pathophysiology is complex, involving initial inflammatory cell infiltration and subsequent myocardial necrosis and fibrotic replacement; these mechanisms are transient and exacerbated during lupus myocarditis in SLE flares [28]. As mentioned above, emerging evidence suggests a possible role of autoantibodies, particularly Anti-Ro/SSA, leading to calcium channel downregulation and altered protein expression, resulting in dysregulated intracellular calcium homeostasis and cardiomyocyte apoptosis [29], also the anti-U1-nuclear ribonuclear antibodies were associated with AV blocks. Small vessel vasculitis and fibrotic tissue infiltration contribute to reentrant circuits and sinus or atrioventricular (AV) node dysfunction. QT interval prolongation, dispersion, and reduced heart rate variability are frequent in anti-Ro/SSA-positive patients, with an increased risk of TV and SCD [26,27]. Standard SLE medications, such as glucocorticosteroids and anti-malarial drugs, may induce tachyarrhythmias and QT prolongation. However, chloroquine exhibits a protective effect by modulating the myocardial action potential dynamics, exerting antifibrillatory effects by blocking the Kir2.1 potassium channel. Mycophenolate mofetil, tacrolimus, and rituximab can cause tachycardia. Methotrexate and cyclophosphamide may rarely trigger ventricular arrhythmias [3,30].

RHEUMATOID ARTHRITIS (RA)

In patients with RA, the rheumatoid factors and citrullinated proteins in cardiac tissue are present in approximately one-quarter of cases. The risk of AF is 40% higher than in the general population, especially in patients with high inflammation markers (sedimentation rates >60mm/h or TNF-α). The pathophysiology involves systemic inflammation, ischemic heart disease, and heart failure, which contribute to increased circulating levels of inflammatory proteins and trigger arrhythmogenic foci [31]. Complete AV block is rare but is more prevalent in patients with subcutaneous nodules, implicating rheumatoid granulomas and non-specific inflammatory lesions in the genesis of conduction disturbances. Ventricular arrhythmias such as premature ventricular contractions (PVCs) and VT are observed in diffuse cardiac involvement due to coronary vasculitis and atherosclerotic disease, which lead to perfusion defects of the myocardium with proarrhythmic effects [12]. Moreover, antibodies targeting the cardiac conduction system, detected in 35% of RA patients, potentially exacerbate conduction abnormalities by increasing P-wave dispersion and left atrial diameter. Dysregulated autonomic tone, characterized by heightened sympathetic and diminished parasympathetic activity, may further predispose RA patients to VT. Notably, Early initiation of disease-modifying antirheumatic drugs (DMARDs) demonstrates promising effects in ameliorating lipid profiles, mitigating atherosclerosis, and reducing endothelial dysfunction by quelling inflammation. Anti-inflammatory agents like infliximab may pose a risk for new-onset ventricular tachyarrhythmias [32].

SYSTEMIC SCLEROSIS

Systemic Sclerosis (SSc) patients exhibit a higher mean heart rate and higher PVC burden in 20–67% of patients, and 7–28% of the patients have VT [33,34]. Myocardial fibrosis is a primary contributor to these cardiac rhythm disorders, with a six-fold increase in ventricular arrhythmias in severe cases compared to milder ones [35]. Supraventricular arrhythmias, such as AF and flutter, are prevalent (20–30%), especially in limited SSc cases, often attributed to myocardial fibrosis and valvular regurgitation [12]. Conduction system abnormalities affect approximately 25% of SSc patients, with first-degree AV block, bundle branch blocks, and non-specific intraventricular conduction delays [33]. The overproduction of anti-β1-adrenergic receptor autoantibodies contributes to autonomic dysfunction, potentially preceding myocardial fibrosis implicated in the pathogenesis of arrhythmias. Frequent PVC is associated with increased mortality, 50% during 33 months of

follow-up, highlighting their prognostic significance [21].

ANKYLOSING SPONDYLITIS

Patients exhibit susceptibility to AV re-entry tachycardia compared to the general population, reported to be 6.24 per 1,000 individuals. Moreover, patients demonstrate an elevated burden of PVC and premature atrial contractions (PAC), which correlate with increased QT dispersion. The pathogenesis is secondary to inflammatory processes, fibromuscular proliferation, fibrotic scarring, enhanced automaticity, and triggered activity. Notably, the human leukocyte antigen (HLA) B27 is implicated in arrhythmogenesis by augmenting platelet adhesion to vessel walls, thereby contributing to perfusion defects and scarring [3].

PSORIASIS

Patients diagnosed with psoriasis are more susceptible to AF compared to the general population, with an adjusted risk from 1.50 to 2.98 under 50 and from 1.16 to 1.29 in those aged 50 or older. This increased risk is primarily attributed to chronic inflammation mediated by TNF-α, IL-6, and IL-17. Factors contributing to structural remodeling in psoriasis, such as platelet-derived growth factor α (PDGFα) that promote cell proliferation and collagen expression in cardiac fibroblasts, which contribute to electrical remodeling, associated with TNF-α mediated disruption of the calcium influx into pulmonary vein cardiomyocytes, favoring the arrhythmia incidence. Treatment with methotrexate and TNF inhibitors has been associated with a reduced risk of cardiovascular disease morbidity and mortality, whereas ustekinumab appears to have a neutral effect. Statins have been shown to reduce the incidence of both AF and psoriasis [36,37].

IDIOPATHIC INFLAMMATORY MYOPATHIES

In patients with polymyositis and dermatomyositis, cardiac involvement is not uncommon and significantly impacts survival rates, with reported prevalence ranging from 9% to 72%. Myocarditis, focal fibrosis, vasculitis, and abnormalities in vessel structure (e.g., intimal proliferation, medial sclerosis) are the proposed mechanisms underlying abnormal electrical activity by increased automaticity [38]. Electrocardiogram (ECG) and Holter monitoring studies have revealed frequent PAC, atrial tachycardia, and paroxysmal AF. Various conduction abnormalities are observed, including bundle branch block, fascicular block, and first-, second-, and rarely third-degree AV block [39].

ANTI-NEUTROPHIL CYTOPLASMIC - ANTIBODY-ASSOCIATED VASCULITIS

Clinically significant cardiac involvement in ANCA-associated vasculitis is rare but carries considerable prognostic implications, mainly due to its association with AF, which independently predicts worse survival rates. Vascular inflammation increases arterial stiffness, culminating in end-organ ischemia [40]. Bundle branch blocks and AV blocks have been reported to be associated with granulomatous inflammation affecting the AV node [12].

GRAVES' DISEASE

Graves' disease (GD) is characterized by hyperthyroidism resulting from circulating thyrotropin receptor antibodies. The most prevalent cardiac rhythm disorder is AF, associated with a decreased atrial refractory period due to augmented sympathetic tone and reduced heart rate variability, increasing automaticity in the pulmonary vein tissue. Thyroid hormone decreases the expression of L-type calcium channel mRNA and increases the expression of the Kv1.5 potassium channel, which contributes to the decreased atrial refractory period. Autoantibodies to β adrenergic and M2 muscarinic cholinergic receptors also increase sympathetic function and decrease the atrial refractory period. Ventricular arrhythmias in hyperthyroidism are linked to thyroid hormone effects on cardiac myocyte Na/K-ATPase, which increases intracellular potassium levels, hyperpolarizes the membrane, and prolongs repolarization, leading to a prolonged QTc interval. Restoration of euthyroidism has been associated with improvements in rhythm control. Prednisone therapy has been beneficial, with a high reversion rate and relatively short reversion time [41,42].

INFLAMMATORY BOWEL DISEASE

Patients with Ulcerative colitis and Crohn's disease have a chronic inflammatory condition prone to AF; its incidence increases more than twofold during an active flare of Inflammatory Bowel Disease (IBD) due to inflammatory cytokines, especially IL-6, which significantly correlates with increased Left Atrial size by stimulating matrix metalloproteinase-2, inducing myocarditis, and electrical changes in the atrium. Furthermore, electro-mechanical delay triggers AF. The observed QT interval prolongation and dispersion in IBD patients using cardiotoxic medications like infliximab or ciprofloxacin [3,43].

Biomarkers For Immune-Mediated Arrhythmias

Identifying biomarkers that reflect or mediate arrhythmogenic mechanisms, regardless of the

presence or absence of structural heart disease, is a crucial clinical need. Those biomarkers are indicative of inflammation, fibrosis, and autoimmunity and predict the risk of arrhythmias [14].

In patients with dilated cardiomyopathy (DCM), the presence of anti-α1C Ca+ predicts a prolonging action potential duration and QT interval, inducing early afterdepolarizations and triggering ventricular tachycardia, ultimately culminating in sudden cardiac death and remaining an independent risk factor for sudden cardiac death in DCM patients [44]. The Fibroblast growth factor 23 (FGF-23) has shown robust associations with AF with an odds ratio (OR) of 1.7 (95%CI: 1.36–2.34), and the inclusion of these biomarkers alongside clinical risk factors has demonstrated improved AF prediction compared to using clinical risk factors alone [45]. TNF-α and IL-6 indicate inflammation with QT prolongation [46], increasing the risk for Torsade de Pointes (TdP), irrespective of the underlying inflammatory etiology [7]. The pro-fibrotic protein Galectin-3 (Gal-3) has been implicated in arrhythmogenesis through structural and electrophysiological remodeling; elevated levels have been independently linked to left atrial appendage (LAA) thrombi [14]. Growth differentiation factor-15 (GDF-15) is activated in response to cellular ischemia, has been associated with paroxysmal AF, and is linked to LAA thrombi, and elevated concentrations of soluble ST2 (sST2), an inhibitor of IL-33 proinflammatory signaling, have shown significant associations with new-onset AF [14].

Perspectives of Biological Therapy for the Management Cardiac Arrhythmias

Current management strategies for cardiac arrhythmias encompass a range of interventions, including anti-arrhythmic drugs, autonomic modulation, implantable cardioverter–defibrillator (ICD) implantation, cardiac stereotactic body radiotherapy (SBRT), and catheter ablation, there is a clear need for alternative approaches that can modify arrhythmia substrates without adversely affecting myocardial viability. Therefore, therapeutic interventions targeting procedure-related inflammation promise to reduce recurrence [12,47]. Cell-based molecular therapies have emerged as promising strategies to restore gene expression, attenuate cardiomyocyte death, modulate immune responses, and mitigate myocardial scarring, thereby improving cardiac function [47,48].

GENE THERAPY

The strategy and outcomes of gene therapy strategies can be categorized into three groups:

- Gene transfer: Aim to restore or increase a gene expression.
- Gene silencing: Reduce the expression of defective alleles or specific pathways
- Gene editing: DNA correction or manipulation.

Gene editing: The emergence of clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene editing tools is a promising method for the management of monogenic disorders, like transcriptional regulation and RNA editing, expanding their potential utility in the biological pacemaker development [49]. Typically, CRISPR-Cas9 components are delivered via Adeno-associated virus, nanoparticles, polymeric nanoparticles, and exosomes are being explored as potential carriers; however, delivery efficiency and long-term expression need to be addressed [49–51].

Myocardial gene transfer: Addressing the genetic defect, the therapeutic intervention replaces or removes a disease-causing gene at the level of the myocardium, thereby eliminating a fundamental incipient for a given condition. The vectors can be categorized as viral (gene transduction) and non-viral (transfection), which serve as carriers for therapeutic genes [52].

- Non-viral vectors: Naked plasmid DNA is a commonly used option due to its versatility, nonimmunogenicity, and ease of production. It remains the most accessible tool for gene transfer in vivo.
  - Plasmids are circular DNA constructs that can be customized with a versatile combination of transgenes and regulatory elements. Compared to other vectors, naked plasmids can hold significantly larger quantities of genetic information. Plasmids are also easy to produce, with adequate infrastructure for clinical-grade plasmids already in place. Despite this, the transducing cells need enhancements for effective gene uptake [53].
  - Lipid-based nanoparticles represent another non-viral vector; nanoparticles offer biocompatibility and good cellular uptake and can be deployed with targeting ligands to enhance tissue specificity. The liposomal delivery mechanism for small molecule drugs is already in clinical use as a chemotherapeutic vehicle, and lipid-based nanoparticles containing a genetic construct have a demonstrated ability for transducing cardiac cells, offering good

cellular uptake and the potential for tissue-specific targeting; however, challenges such as off-target effects and rapid clearance from to rapid clearance by the reticuloendothelial system remains a limitation [54].

- Modified-messenger RNA (modRNA) is a promising non-viral vector due to its transient but efficient expression profile; modRNA has advantages and disadvantages as a gene delivery tool compared to DNA vectors. One advantage is that mRNA does not require localization of the nucleus or transcription process. The modRNA gene delivery has minimal risk of integration into the host genome, is highly efficient with robust transient expression with no sign of innate immune response. The modRNA is translated in minutes, lasting up to 10 days in vivo. The use of modRNA in the heart is mainly for myocardial ischemia/reperfusion injury in the ventricle because of its transient pharmacokinetic profile. The disadvantages are the unstable modRNA generation and the need for repeated delivery due to its short expression pattern [55].

- Viral vectors: Viral vectors are live, replication-deficient viruses that have been genetically modified to replace the native viral genes with therapeutic transgenes. Any cell that the vector infects integrates the transgene payload to produce or inhibit a genetic product. Compared to non-viral plasmids, which must be delivered directly to the tissue of interest, viral vectors have the theoretical advantage of minimally invasive delivery via the bloodstream. Adeno-associated virus (AAV), adenovirus (Ad), and lentivirus (LV) have gained attention for their ability to deliver genes efficiently [56].
  - Adeno-associated virus: is a non-enveloped, nonintegrating, single-stranded DNA parvovirus. AAV emerged as a gene therapy vector development focus due to its low immunogenicity, long-expression duration potential, and robust safety profile. It offers the advantage of low immunogenicity and prolonged transgene expression; however, challenges such as limited cargo capacity and preexisting neutralizing antibodies in some populations must be addressed. Notably, AAV alone is incapable of productive replication and requires coinfection with a helper virus, usually adenovirus or herpesvirus. The lack of self-replication machinery increases AAV's safety and limits its genome size. When including a cardiac-specific promoter, many transgenes exceed an AAV construct's maximum size, which limit the desired effect, which also can be delayed as gene expression requires converting the single-stranded viral genome to the double-stranded host genome [52].
  - adenovirus vectors: are simple to produce, efficiently transduce both dividing and nondividing cells and have a packaging capacity for moderate-sized genes. However, in the heart, gene expression after Ad vector transduction is robust but transient, and Ads can trigger innate immune response and toxicity due to viral gene products [57].
  - Lentivirus vectors are enveloped, integrating single-stranded RNA retroviruses. In gene therapy, LV vectors are usually derived from the HIV-1 virion, modified to be replication-defective to safeguard against off-target continued infection. Retroviral vectors typically require active cellular division to integrate and express a transgene. However, the machinery of HIV conveys an ability to transduce intact nuclear membranes in post-mitotic cells (such as cardiomyocytes) and accomplishes long-term gene expression with moderate packaging capacities. However, there are concerns regarding immune responses and safety profiles [58].

Gene delivery: The therapeutic intravenous administration (IV) is the least invasive method but lacks specificity, resulting in systemic dispersion of the vector with the transduction of numerous off-target organs [52,58]. Site-directed vector engineering strategies are being explored to enhance specificity. Cardiac perfusion via intracoronary injection allows selective perfusion of the cardiac vasculature, maximizing tissue exposure to the vector. However, vascular permeability and rapid blood flow clearance limitations may affect efficacy, as observed in clinical trials like CUPID2 (AAV / SERCA2a coronary injection in patients with heart failure) [59]. Retrograde infusion via coronary sinus injection offers a potentially safer alternative, although careful regulation of injection pressure is necessary to prevent complications. Epicardial gene painting involves applying a vector-protease-polymer gel directly onto the atrial epicardium, facilitating transmural gene transfer. At the same time, the invasiveness of the surgical procedure and challenges in accessing specific cardiac structures may limit its applicability [52]. Direct myocardial injection provides precise delivery to targeted

areas but is limited by its localized effect, challenging widespread transduction. Electroporation, initially used for myocardial ablation, shows promise for plasmid DNA delivery and can enhance gene uptake; these micropores enable diffusion of surrounding plasmid into electroporated cells, and the rate of gene uptake in vivo is 15–20 fold higher when electroporation is used versus standard plasmid DNA delivery alone but carries risks of ventricular fibrillation if not carefully synchronized with cardiac rhythm [60].

Targets for arrhythmia control in gene therapy:

- Electrical remodeling typically involves shortening of the atrial action potential duration (APD) due to alterations in ion currents, including decreased L-type calcium current and increased inward-rectifier current (IK1), along with constitutive activation of acetylcholine-induced potassium current (IKACh). Transfection of KCNE2 and KCNH2 variants has shown promise in prolonging APD and reducing AF burden in animal models. Similarly, genetic suppression of TASK-1 using atrial anti–TASK–1 small interfering RNA (siRNA) has demonstrated efficacy in prolonging atrial APD [56,57].
- Abnormal calcium handling contributes to ectopic activity, particularly sarcoplasmic reticulum (SR) calcium leak via the ryanodine receptor type 2 (RyR2). Targeting RyR2 phosphorylation sites or utilizing modified forms of calmodulin (CaM) has shown potential for attenuating SR calcium leak and reducing AF susceptibility [52,61].
- Autonomic nerve remodeling, characterized by vagal stimulation-induced shortening of the atrial effective refractory period, presents another avenue for gene therapy intervention. Inhibition of specific components of the G-protein autonomic pathway, such as Gαi and Gαo, has demonstrated efficacy in modulating atrial electrophysiology and reducing AF inducibility in animals [52].
- Gap junction remodeling, represented by reduced expression or abnormal localization of connexins (Cxs), contributes to impaired electrical conduction and increased AF risk. Targeting Cxs, such as Cx40 and Cx43, has been shown to improve conduction and reduce arrhythmia burden [60,61].
- Structural remodeling, characterized by atrial fibrosis and TGF-β upregulation, represents another potential target for gene therapy. Inhibition of TGF-β signaling has shown promise in reducing fibrosis and related arrhythmias [52].
- In catecholaminergic polymorphic ventricular tachycardia (CPVT), strategies include replacement of wild-type genes, silencing of mutant alleles, CRISPR/Cas9 editing, and suppression of downstream molecules within associated pathways. These approaches have shown promise in preclinical models [48].

Exosome Therapy for Ventricular arrhythmias: The therapeutic potential of cell-based therapy in stimulating cardiac regeneration, primarily through indirect paracrine effects rather than direct remuscularization, is obtained through Exosomes, which are small extracellular vesicles secreted by progenitor and stromal cells, have emerged as key mediators of this regenerative process, delivering bioactive molecules, including nucleic acids, proteins, lipids, and metabolites, collectively termed the "regenerative cargo," which exert anti-apoptotic, anti-inflammatory, and anti-fibrotic effects in diseased tissue, contributing to cardiac repair and functional recovery. In models of acute myocardial infarction, exosome administration into the border zone has been associated with improved cardiac function, reduced proinflammatory cytokine levels, and decreased scar formation, leading to increased viable myocardium, improving the associated arrhythmias, and reduced ventricular arrhythmias. In arrhythmogenic cardiomyopathy, characterized by myocyte loss, hyperinflammation, and fibrofatty replacement, exosome treatment prevents abnormal biventricular remodeling and reduces arrhythmia inducibility. In porcine models, exosome treatment altered wavefront propagation, decreased fibrosis, and reduced arrhythmia inducibility, suggesting a potential role in modifying the arrhythmogenic substrate [47].

Biological pacemakers: Somatic reprogramming techniques emerged as a promising strategy for converting normal working myocytes into sinoatrial node-like cells via gene therapy. One approach is adenovirus-based gene transfer for the expression of Kir2, which suppresses IK1, inducing a biological pacemaker. Another approach has been overexpressing HCN2, enhancing If currents to create biological pacemakers. Another mechanism is the endogenous suppressive microRNAs TBX18-induced reprogramming that converts cardiomyocytes into functional SAN-like cells, mimicking the physiological and morphological characteristics of native pacemaker cells [62].

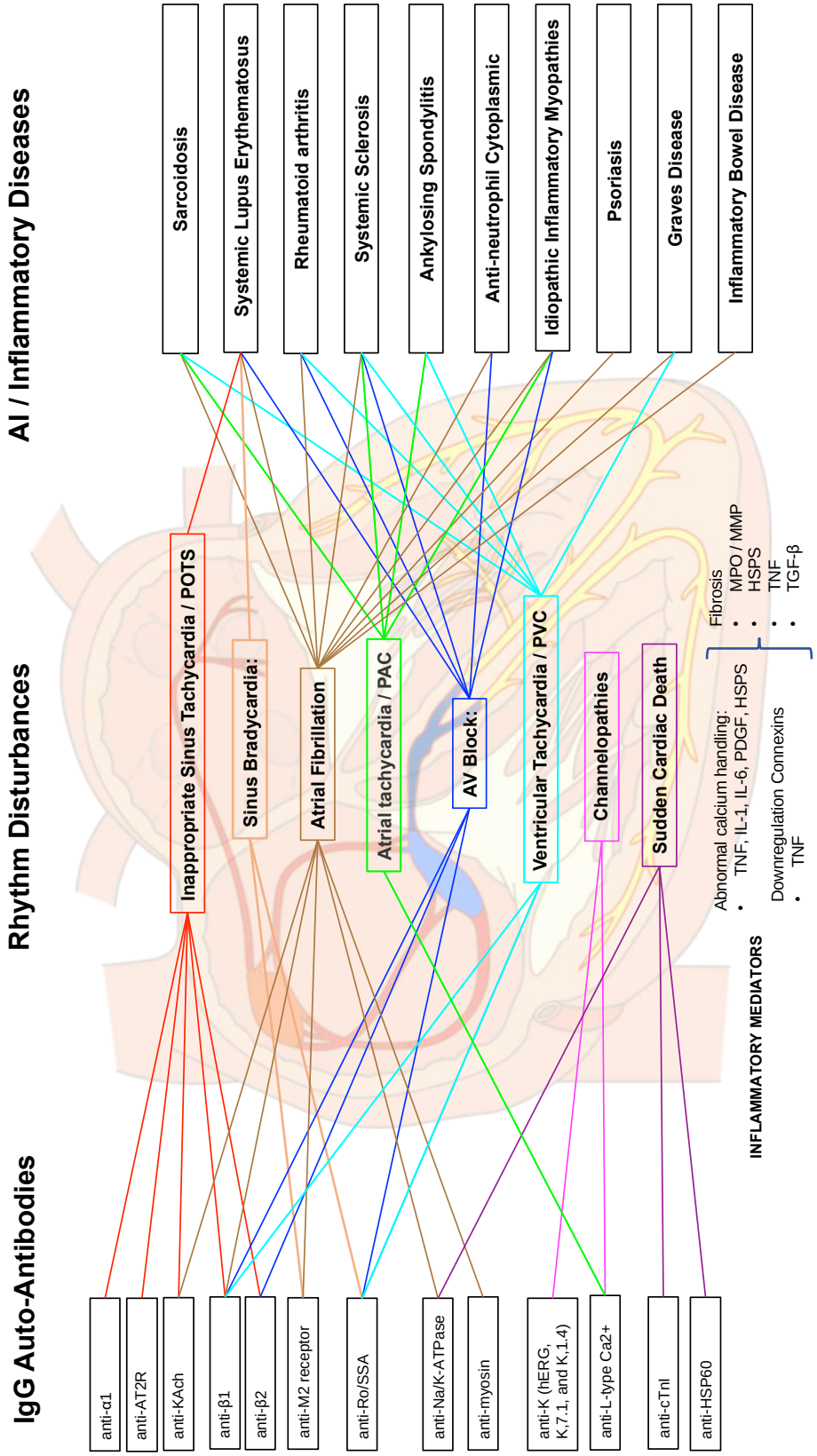
Conflicts of Interest:

The author have no disclosures or conflicts of interest related to the contents of this manuscript.

Conclusions

Arrhythmias represent significant and frequent manifestations of cardiac involvement in patients with AI diseases. The manifestations are wide, and

the mechanism is diverse. Early recognition and understanding of the mechanisms underlying arrhythmias and integration of newer diagnostic modalities will enhance patient outcomes. Life-threatening arrhythmias are paramount to enhancing and improving the prognosis. Emerging gene and cell-based therapies to specific targets will offer alternatives to the current standard of care in patients with arrhythmias.



Text: Relationship of Cardiac Rhythm disturbance and the autoinmune / inflammatory disease, and causative auto antibodies. Abreviations: Ig: immunoglobulin; POTS: postural orthostatic tachycardia syndrome; PAC: premature atrial complex; PVC: premature ventricular complex; AV: atrioventricular; Anti-Ro/SSA: anti-Ro/Sjogren's syndrome-related antigen A; hERG, human ether-a-go-go-related gene K-channel; KAch, acetylcholine-activated current; TNF: tumor necrosis factor; IL: interleukin; L-type Ca: L calcium currents; IKACh: acetylcholine-activated potassium currents; M2: muscarinic cholinergic type 2 receptor; Gi: inhibitory G protein; Na/K-ATPase: sodium-potassium pump.

Bibliography

1. Lerner, A., Jeremias, P. & Matthias, T. The world incidence and prevalence of autoimmune diseases is increasing. *International Journal of Celiac Disease* **3**, 151–155 (2015).
2. Lee, H. C. & Melduni, R. M. Autoimmunity and cardiac arrhythmias in endemic pemphigus foliaceus—Association, correlation, or causation? *Heart Rhythm* vol. 15 732–733 Preprint at https://doi.org/10.1016/j.hrthm.2018.01.023 (2018).
3. Gawałko, M. *et al*. Cardiac arrhythmias in autoimmune diseases. *Circulation Journal* vol. 84 685–694 Preprint at https://doi.org/10.1253/circj.CJ-19-0705 (2020).
4. Lazzerini, P. E., Capecchi, P. L., Laghi-Pasini, F. & Boutjdir, M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nature Reviews Cardiology* vol. 14 521–535 Preprint at https://doi.org/10.1038/nrcardio.2017.61 (2017).
5. Eisen, A., Arnson, Y., Dovrish, Z., Hadary, R. & Amital, H. Arrhythmias and Conduction Defects in Rheumatological Diseases-A Comprehensive Review. *Seminars in Arthritis and Rheumatism* vol. 39 145–156 Preprint at https://doi.org/10.1016/j.semarthrit.2008.05.001 (2009).
6. Lee, H. C., Huang, K. T. L., Wang, X. L. & Shen, W. K. Autoantibodies and cardiac arrhythmias. *Heart Rhythm* **8**, 1788–1795 (2011).
7. Lazzerini, P. E. *et al*. Autoantibody-mediated cardiac arrhythmias: Mechanisms and clinical implications. *Basic Research in Cardiology* vol. 103 1–11 Preprint at https://doi.org/10.1007/s00395-007-0686-8 (2008).
8. Hernández, C. C. *et al*. Autoantibodies enhance agonist action and binding to cardiac muscarinic receptors in chronic Chagas' disease. *Journal of Receptors and Signal Transduction* **28**, 375–401 (2008).
9. Lazzerini, P. E., Laghi-Pasini, F., Boutjdir, M. & Capecchi, P. L. Anti-Ro/SSA Antibodies and the Autoimmune Long-QT Syndrome. *Frontiers in Medicine* vol. 8 Preprint at https://doi.org/10.3389/fmed.2021.730161 (2021).
10. Schulze, W., Kunze Phd, R. & Wallukat, G. *Pathophysiological Role of Autoantibodies against G-Protein-Coupled Receptors in the Cardiovascular System*. *Exp Clin Cardiol* vol. 10 (2005).
11. Lazzerini, P. E. *et al*. Anti-Ro/SSA Antibodies Blocking Calcium Channels as a Potentially Reversible Cause of Atrioventricular Block in Adults. *JACC Clin Electrophysiol* **9**, 1631–1648 (2023).
12. Plastiras, S. C. & Moutsopoulos, H. M. Arrhythmias and conduction disturbances in autoimmune rheumatic disorders. *Arrhythm Electrophysiol Rev* **10**, 17–25 (2021).
13. Chiale, P. A. *et al*. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac β andrenergic receptors. *Heart Rhythm* **3**, 1182–1186 (2006).
14. Hammerer-Lercher, A., Namdar, M. & Vuilleumier, N. Emerging biomarkers for cardiac arrhythmias. *Clinical Biochemistry* vol. 75 1–6 Preprint at https://doi.org/10.1016/j.clinbiochem.2019.11.012 (2020).
15. Maguy, A., Mahendran, Y., Tardif, J. C., Busseuil, D. & Li, J. Autoimmune Atrial Fibrillation. *Circulation* **148**, 487–498 (2023).
16. Boccellino, M. *et al*. International Journal of Molecular Sciences Review Autoantibodies in Atrial Fibrillation-State of the Art. *Int. J. Mol. Sci* **2023**, 1852 (2023).
17. Maguy, A., Tardif, J. C., Busseuil, D., Ribi, C. & Li, J. Autoantibody Signature in Cardiac Arrest. *Circulation* **141**, 1764–1774 (2020).
18. Capecchi, P. L. *et al*. Autoimmune and inflammatory K+ channelopathies in cardiac arrhythmias: Clinical evidence and molecular mechanisms. *Heart Rhythm* **16**, 1273–1280 (2019).
19. Cimaz, R. *et al*. QT INTERVAL PROLONGATION IN ASYMPTOMATIC ANTI-SSA/Ro-POSITIVE INFANTS WITHOUT CONGENITAL HEART BLOCK. *Arthritis Rheum* **43**, 1049–1053 (2000).
20. Lazzerini, P. E., Laghi-Pasini, F., Boutjdir, M. & Capecchi, P. L. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nature Reviews Immunology* vol. 19 63–64 Preprint at https://doi.org/10.1038/s41577-018-0098-z (2019).
21. Lazzerini, P. E. *et al*. Comparison of Frequency of Complex Ventricular Arrhythmias in Patients With Positive Versus Negative Anti-Ro/SSA and Connective Tissue Disease. *American Journal of Cardiology* **100**, 1029–1034 (2007).
22. Labovsky, V., Smulski, C. R., Gómez, K., Levy, G. & Levin, M. J. Anti-β1-adrenergic receptor autoantibodies in patients with chronic Chagas

heart disease. *Clin Exp Immunol* **148**, 440–449 (2007).

23. Baba, A., Yoshikawa, T. & Ogawa, S. Autoantibodies Produced Against Sarcolemmal Na-K-ATPase: Possible Upstream Targets of Arrhythmias and Sudden Death in Patients With Dilated Cardiomyopathy. *J Am Coll Cardiol* **40**, 1153–1162 (2002).
24. Ryabkova, V. A. *et al.* Lethal immunoglobulins: Autoantibodies and sudden cardiac death. *Autoimmunity Reviews* vol. 18 415–425 Preprint at https://doi.org/10.1016/j.autrev.2018.12.005 (2019).
25. Shah, H. H. *et al.* Cardiac sarcoidosis: a comprehensive review of risk factors, pathogenesis, diagnosis, clinical manifestations, and treatment strategies. *Frontiers in Cardiovascular Medicine* vol. 10 Preprint at https://doi.org/10.3389/fcvm.2023.1156474 (2023).
26. Giannelou, M. & Mavragani, C. P. Cardiovascular disease in systemic lupus erythematosus: A comprehensive update. *Journal of Autoimmunity* vol. 82 1–12 Preprint at https://doi.org/10.1016/j.jaut.2017.05.008 (2017).
27. Bourré-Tessier, J. *et al.* Electrocardiographic findings in systemic lupus erythematosus: Data from an international inception cohort. *Arthritis Care Res (Hoboken)* **67**, 128–135 (2015).
28. Santos-Pardo, I. *et al.* Anti-Ro/SSA antibodies and cardiac rhythm disturbances: Present and future perspectives. *International Journal of Cardiology* vol. 184 244–250 Preprint at https://doi.org/10.1016/j.ijcard.2014.11.002 (2015).
29. Akuka, A. *et al.* Association of anti-Ro seropositivity with cardiac rhythm and conduction disturbances. *Eur Heart J* **43**, 4912–4919 (2022).
30. Myung, G. *et al.* Prevalence of resting-ECG abnormalities in systemic lupus erythematosus: a single-center experience. *Clin Rheumatol* **36**, 1311–1316 (2017).
31. Engelmann, M. D. M. & Svendsen, J. H. Inflammation in the genesis and perpetuation of atrial fibrillation. *European Heart Journal* vol. 26 2083–2092 Preprint at https://doi.org/10.1093/eurheartj/ehi350 (2005).
32. Wen, S. N. *et al.* Catheter ablation of atrial fibrillation in patients with rheumatoid arthritis. *J Cardiol* **66**, 320–325 (2015).
33. Mavrogeni, S. *et al.* Cardiac magnetic resonance predicts ventricular arrhythmias in scleroderma: The Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS). *Rheumatology (United Kingdom)* **59**, 1938–1948 (2020).
34. Wozniak, J. *et al.* Evaluation of heart rhythm variability and arrhythmia in children with systemic and localized scleroderma. *Journal of Rheumatology* **36**, 191–196 (2009).
35. Vrancianu, C. A. *et al.* Arrhythmias and Conduction Disturbances in Patients with Systemic Sclerosis—A Systematic Literature Review. *International Journal of Molecular Sciences* vol. 23 Preprint at https://doi.org/10.3390/ijms232112963 (2022).
36. Simsek, H. *et al.* Increased risk of atrial and ventricular arrhythmia in long-lasting psoriasis patients. *The Scientific World Journal* **2013**, (2013).
37. Ungprasert, P., Srivali, N. & Kittanamongkolchai, W. Psoriasis and risk of incident atrial fibrillation: A systematic review and meta-analysis. *Indian Journal of Dermatology, Venereology and Leprology* vol. 82 489–497 Preprint at https://doi.org/10.4103/0378-6323.186480 (2016).
38. Lu, Z., Guo-Chun, W., Li, M. & Ning, Z. Cardiac involvement in adult polymyositis or dermatomyositis: A systematic review. *Clinical Cardiology* vol. 35 685–691 Preprint at https://doi.org/10.1002/clc.22026 (2012).
39. Lundberg, I. E. Cardiac involvement in autoimmune myositis and mixed connective tissue disease. *Lupus* vol. 14 708–712 Preprint at https://doi.org/10.1191/0961203305lu2205oa (2005).
40. Miloslavsky, E. & Unizony, S. The Heart in Vasculitis. *Rheumatic Disease Clinics of North America* vol. 40 11–26 Preprint at https://doi.org/10.1016/j.rdc.2013.10.006 (2014).
41. Jia, G. & Sowers, J. R. Autoantibodies of β-adrenergic and M2 cholinergic receptors: atrial fibrillation in hyperthyroidism. *Endocrine* vol. 49 301–303 Preprint at https://doi.org/10.1007/s12020-015-0556-3 (2015).
42. Reddy, V., Taha, W., Kundumadam, S. & Khan, M. Atrial fibrillation and hyperthyroidism: A literature review. *Indian Heart Journal* vol. 69 545–550 Preprint at https://doi.org/10.1016/j.ihj.2017.07.004 (2017).
43. Kristensen, S. L. *et al.* Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: A nationwide study. *Europace* **16**, 477–484 (2014).

44. Qu, Y. S. *et al.* Autoimmune Calcium Channelopathies and Cardiac Electrical Abnormalities. *Frontiers in Cardiovascular Medicine* vol. 6 Preprint at https://doi.org/10.3389/fcvm.2019.00054 (2019).
45. Chua, W. *et al.* Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. *Eur Heart J* **40**, 1268–1276 (2019).
46. Adlan, A. M., Panoulas, V. F., Smith, J. P., Fisher, J. P. & Kitas, G. D. Association between corrected QT interval and inflammatory cytokines in rheumatoid arthritis. *Journal of Rheumatology* **42**, 421–428 (2015).
47. Lin, Y. N., Miguel-dos-Santos, R. & Cingolani, E. Biological Modification of Arrhythmogenic Substrates by Cell-Free Therapeutics. *Heart Lung Circ* **32**, 844–851 (2023).
48. Pérez, P. R., Hylind, R. J., Roston, T. M., Bezzerides, V. J. & Abrams, D. J. Gene Therapy for Catecholaminergic Polymorphic Ventricular Tachycardia. *Heart Lung Circ* **32**, 790–797 (2023).
49. Mesquita, T., Miguel-Dos-Santos, R. & Cingolani, E. Biological Pacemakers: Present and Future. *Circ Res* **134**, 837–841 (2024).
50. Ryan, T. & Roberts, J. D. Emerging Targeted Therapies for Inherited Cardiomyopathies and Arrhythmias. *Cardiac Electrophysiology Clinics* vol. 15 261–271 Preprint at https://doi.org/10.1016/j.ccep.2023.04.006 (2023).
51. McRae, C., Kapoor, A., Kanda, P., Hibbert, B. & Davis, D. R. Systematic review of biological therapies for atrial fibrillation. *Heart Rhythm* **16**, 1399–1407 (2019).
52. Yoo, S., Geist, G. E., Pfenniger, A., Rottmann, M. & Arora, R. Recent advances in gene therapy for atrial fibrillation. *Journal of Cardiovascular Electrophysiology* vol. 32 2854–2864 Preprint at https://doi.org/10.1111/jce.15116 (2021).
53. Su, C.-H., Wu, Y.-J., Wang, H.-H. & Yeh, H.-I. Nonviral gene therapy targeting cardiovascular system. *Am J Physiol Heart Circ Physiol* **303**, 629–638 (2012).
54. Turnbull, I. C. *et al.* Myocardial delivery of lipidoid nanoparticle carrying modRNA induces rapid and transient expression. *Molecular Therapy* **24**, 66–75 (2016).
55. Kaur, K. & Zangi, L. Modified mRNA as a Therapeutic Tool for the Heart. *Cardiovasc Drugs Ther* **34**, 871–880 (2020).
56. Zhao-Fleming, H. H. *et al.* Characterization of cardiac bradyarrhythmia associated with LGI1-IgG autoimmune encephalitis. *Front Immunol* **13**, (2022).
57. Greener, I. & Donahue, J. K. Gene therapy strategies for cardiac electrical dysfunction. *Journal of Molecular and Cellular Cardiology* vol. 50 759–765 Preprint at https://doi.org/10.1016/j.yjmcc.2010.07.022 (2011).
58. Rincon, M. Y., VandenDriessche, T. & Chuah, M. K. Gene therapy for cardiovascular disease: Advances in vector development, targeting, and delivery for clinical translation. *Cardiovascular Research* vol. 108 4–20 Preprint at https://doi.org/10.1093/cvr/cvv205 (2015).
59. Greenberg, B. *et al.* Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure. The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b). *JACC Heart Fail* **2**, 84–92 (2014).
60. Greener, I. D. *et al.* Connexin43 gene transfer reduces ventricular tachycardia susceptibility after myocardial infarction. *J Am Coll Cardiol* **60**, 1103–1110 (2012).
61. Driessen, H. E., Van Veen, T. A. B. & Boink, G. J. J. Emerging molecular therapies targeting myocardial infarction-related arrhythmias. *Europace* vol. 19 518–528 Preprint at https://doi.org/10.1093/europace/euw198 (2017).
62. Kapoor, N., Liang, W., Marbán, E. & Cho, H. C. Direct conversion of quiescent cardiomyocytes to pacemaker cells by expression of Tbx18. *Nat Biotechnol* **31**, 54–62 (2013).