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Review

Mitochondrial Calcium Response Mismatch in Metabolic Atrial Fibrillation: A Proposed Mechanistic Framework Linking Metabolic Stress to Atrial Fibrillation Vulnerability, Burden, and Recurrence

Jie Cai †, Shi Qiu †, Chao Wang, Jianbing Huang, Yanqing Zhang, Zhaolei Jiang * and Fangbao Ding *

Department of Cardiothoracic Surgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China; caijie@xinhuamed.com.cn (J.C.); oliveira@sjtu.edu.cn (S.Q.); wc168198@sjtu.edu.cn (C.W.); huangjianbing@xinhuamed.com.cn (J.H.); alexcheung@sjtu.edu.cn (Y.Z.)
* Correspondence: jiangzhaolei@xinhuamed.com.cn (Z.J.); dingfangbao@xinhuamed.com.cn (F.D.)
† These authors contributed equally to this work.

Abstract

Obesity and metabolic syndrome are increasingly recognized as major drivers of atrial fibrillation (AF), and patients with this phenotype commonly exhibit a higher AF burden, more rapid progression from paroxysmal to persistent disease, and an increased risk of recurrence after catheter ablation. Conventional explanations, including structural remodeling, inflammation, and electrophysiological heterogeneity, account for part of this phenotype but do not fully explain why metabolic AF is often less responsive to conventional rhythm-control strategies. Here, we discuss that workload-inappropriate mitochondrial calcium responsiveness represents a candidate intermediate phenotype linking metabolic stress to atrial arrhythmogenesis. Under physiological conditions, mitochondrial calcium uptake couples excitation to energy production by synchronizing ATP generation, redox buffering, and ion homeostasis with beat-to-beat calcium cycling. In the metabolically stressed atrium, however, lipotoxicity, substrate inflexibility, oxidative stress, chronic low-grade inflammation, and disruption of sarcoplasmic reticulum–mitochondrial microdomains may impair or destabilize workload-responsive mitochondrial Ca^{2+} handling. This may create a state of energy–calcium mismatch in which atrial excitation is no longer matched by adequate metabolic support. The downstream consequences are predicted to include ATP insufficiency, impaired calcium reuptake, sodium–calcium disequilibrium, reactive oxygen species amplification, reduced stress tolerance, and progressive structural remodeling, together creating both triggers and substrate for AF. We further discuss how this framework can be tested through functional readouts, such as mitochondrial respiratory reserve, NAD(P)H/FAD redox recovery, redox stress markers, mitochondrial and cytosolic Ca^{2+} dynamics, and circulating mitochondrial injury signals, and how these measures may align with clinically relevant endpoints including AF burden and post-ablation recurrence. The model may be particularly relevant in patients with heart failure with preserved ejection fraction (HFpEF), in whom metabolic overload, inflammation, microvascular dysfunction, impaired oxygen delivery, and atrial pressure stress converge and may reduce atrial metabolic reserve; however, direct evidence that HFpEF represents an atrial mitochondrial Ca^{2+}-mismatch phenotype remains limited. Taken together, this electro–metabolic framework provides a testable mechanistic model for metabolic AF and generates clinically relevant predictions that require prospective validation.

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1. Introduction

Atrial fibrillation (AF) is increasingly understood not merely as a disorder of impulse initiation and propagation but as a manifestation of a broader atrial cardiomyopathic substrate by integrated abnormalities in atrial structure, electrophysiology, contractile function, cellular metabolism, and stress adaptation [1,2]. This concept is particularly relevant in patients with obesity and metabolic syndrome, in whom AF often follows a more substrate-driven clinical course marked by higher arrhythmia burden, accelerated progression toward persistent forms, and reduced durability of rhythm-control strategies, particularly a higher risk of recurrence after catheter ablation [3,4]. These patients frequently require repeated intervention, and their response to trigger-focused strategies such as pulmonary vein isolation is often incomplete, suggesting that the underlying atrial substrate has already undergone extensive pathological remodeling [5].

Current mechanistic models of AF emphasize an interacting network of atrial remodeling processes, including fibrosis, inflammation, ion-channel remodeling, autonomic imbalance, and altered calcium handling [6]. Although each of these processes undoubtedly contributes to AF vulnerability and burden, they do not fully explain why the metabolically stressed atrium appears especially prone to persistent and recurrent disease. A missing link may lie in the failure of the atrium to match energy supply with the demands of electrical and contractile activity. In normal atrial myocardium, mitochondrial Ca^{2+} uptake couples cytosolic Ca^{2+} transients to an adaptive increase in oxidative metabolism [7]. However, studies of metabolic syndrome have identified impaired mitochondrial Ca^{2+} uptake in human atrial tissue and experimental models, while investigations of atrial myocytes from patients with AF have demonstrated blunted workload-dependent mitochondrial Ca^{2+} accumulation and impaired redox recovery [8,9]. These structural characteristics and disease-related findings highlight the relevance of mitochondrial Ca^{2+} responsiveness to atrial excitation–metabolism coupling in metabolic AF.

This coupling becomes particularly important during acute increases in workload, as cardiomyocyte-specific loss of MCU blunts β-adrenergic contractile responsiveness, mitochondrial dehydrogenase activation, bioenergetic reserve, and rapid workload adaptation [10,11]. In atrial disease models, tachypacing causes dysregulated mitochondrial Ca^{2+} handling together with reductions in mitochondrial membrane potential, respiration, and ATP production [12]. Disruption of sarcoplasmic reticulum–mitochondrial contacts and reduced expression of the tethering protein MFN2 have also been observed in experimental AF and human atrial tissue, particularly in the presence of diabetes [13]. In patients with metabolic syndrome and high-fat/high-sucrose-fed mice, increased expression of MICU regulatory subunits was associated with impaired MCUC-mediated mitochondrial Ca^{2+} uptake, whereas pharmacological restoration of MCUC activity abolished AF occurrence in the mouse model [8]. More recently, atrial cardiomyocytes from patients with AF were shown to exhibit blunted mitochondrial Ca^{2+} accumulation during increased workload, impaired NAD(P)H/FAD regeneration, and spatial disorganization of sarcoplasmic reticulum–mitochondrial contacts that may impair Ca^{2+} transfer [9].

Collectively, previous studies have established that mitochondrial Ca^{2+} handling, SR–mitochondrial communication, and Ca^{2+}-dependent metabolic adaptation are disrupted in AF and metabolic disease. Building on these observations, we define "mitochondrial calcium response mismatch" as an inappropriate mitochondrial Ca^{2+} response and down-

stream metabolic adaptation relative to excitation-induced cytosolic Ca^{2+} cycling and energetic demand, potentially encompassing insufficient responsiveness or excessive Ca^{2+} accumulation. Operationally, the proposed relationship can be evaluated as a sequence of measurable inputs and outputs: cytosolic Ca^{2+} signals/pacing demand → mitochondrial Ca^{2+} response → NAD(P)H/FAD redox response → ATP availability and metabolic adaptation. Mismatch may therefore reflect attenuated mitochondrial Ca^{2+} responses for a given cytosolic Ca^{2+} input, or insufficient redox and ATP-related adaptation despite relatively preserved mitochondrial Ca^{2+} responses. This framework shifts the focus from isolated mitochondrial abnormalities to the relative adequacy of the mitochondrial response in relation to cellular demand (Figure 1).

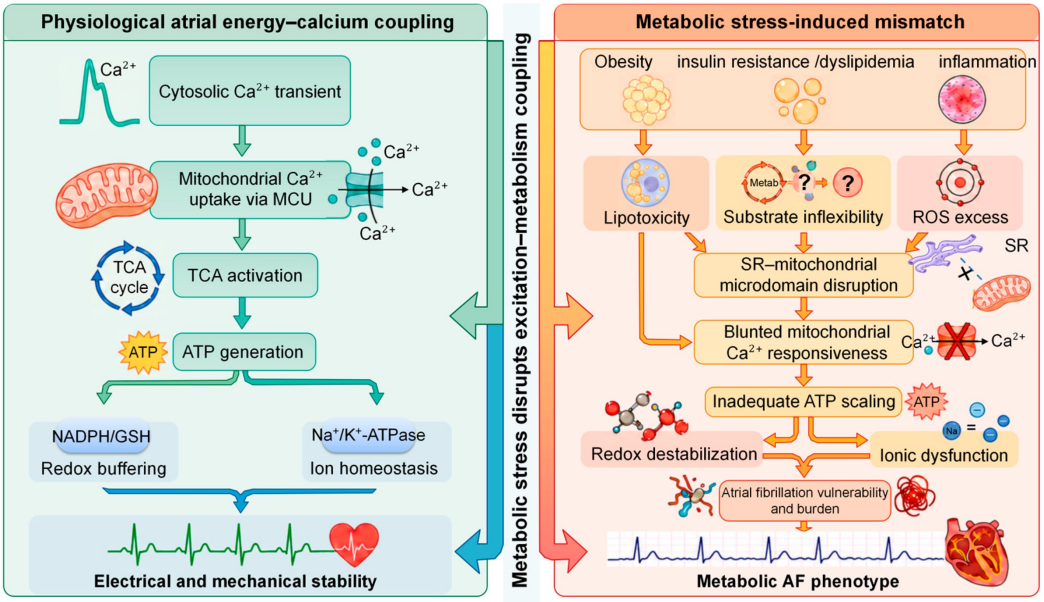


Figure 1. Conceptual framework of mitochondrial calcium response mismatch in metabolic AF. Under physiological conditions, cytosolic Ca^{2+} transients are coupled to mitochondrial Ca^{2+} uptake, thereby linking atrial excitation to ATP generation, redox buffering, and ion homeostasis. Under metabolic stress, lipotoxicity, metabolic inflexibility, oxidative stress, chronic inflammation, and disruption of sarcoplasmic reticulum–mitochondrial microdomains blunt mitochondrial calcium responsiveness, producing a state of energy–calcium mismatch, thereby promoting atrial fibrillation vulnerability and burden within the metabolic AF phenotype. Solid arrows indicate relationships supported by experimental and/or clinical evidence, whereas dashed open arrows indicate proposed relationships supported predominantly by indirect or convergent evidence. Green and blue elements represent physiological energy–calcium coupling, whereas orange and red elements indicate metabolic stress-associated alterations and pathological consequences.

2. Physiological Basis of Energy–Calcium Coupling in the Atrial Myocardium

During each heartbeat, cytosolic Ca^{2+} transients initiate myofilament contraction, while a fraction of this Ca^{2+} signal is relayed to mitochondria through the mitochondrial calcium uniporter (MCU) complex [8,14]. Matrix Ca^{2+} activates Ca^{2+}-sensitive dehydrogenases of the tricarboxylic acid cycle, including pyruvate, isocitrate, and alpha-ketoglutarate dehydrogenases, thereby increasing reducing-equivalent supply to oxidative phosphorylation [15,16]. Direct causal support comes from adult cardiomyocyte-specific Mcu deletion in mice, which blunts acute workload-induced metabolic and contractile adaptation [10,11], and from a metabolic-syndrome mouse model in which impaired atrial mitochondrial Ca^{2+} uptake was accompanied by increased AF susceptibility, whereas

pharmacological enhancement of MCU-complex activity restored uptake in vitro and abolished AF occurrence in vivo [8]. Together, these findings indicate that MCU-mediated mitochondrial Ca^{2+} uptake contributes to workload-dependent metabolic adaptation in cardiomyocytes and suggest that impaired atrial mitochondrial Ca^{2+} handling may be associated with increased AF susceptibility.

The responsiveness of this pathway is determined by the Ca^{2+}-dependent gating properties of the mitochondrial calcium uniporter complex [16]. Ca^{2+} crosses the outer mitochondrial membrane primarily through voltage-dependent anion channels and subsequently enters the matrix through the uniporter complex in the inner mitochondrial membrane [17,18]. MICU1 and MICU2 act as Ca^{2+}-sensing regulatory subunits through their EF-hand domains and determine the activation threshold and cooperativity of mitochondrial Ca^{2+} uptake [16,19,20]. At resting cytosolic Ca^{2+} concentrations, the MICU regulatory complex limits constitutive Ca^{2+} entry, whereas elevations in cytosolic Ca^{2+} promote cooperative activation of the uniporter [19,20]. During excitation, local Ca^{2+} concentrations rise substantially at sarcoplasmic-reticulum–mitochondrial contact sites, enabling mitochondrial Ca^{2+} uptake to increase in parallel with cellular workload [21,22]. The magnitude and kinetics of this response are further influenced by the amplitude and frequency of cytosolic Ca^{2+} transients, the spatial organization of Ca^{2+} microdomains, the mitochondrial membrane potential, and the relative abundance of MCU and its MICU regulatory subunits. Mitochondrial Ca^{2+} sensitivity should therefore be viewed as a dynamic property of the entire transport system rather than an intrinsic property of the MCU pore alone. Although these regulatory principles are well established in mammalian cells, their quantitative activation thresholds in human atrial myocytes remain insufficiently defined.

The physiological significance of regulated mitochondrial Ca^{2+} uptake extends to the coordination of ATP supply and redox homeostasis with myocardial workload. Together with ADP-dependent stimulation of respiration, Ca^{2+}-dependent NADH regeneration supports oxidative phosphorylation during increased energy demand, thereby contributing to the ATP supply required for sarcoplasmic reticulum Ca^{2+} reuptake by SERCA and maintenance of transsarcolemmal ion gradients by the Na^+/K^+-ATPase [23,24]. Ca^{2+}-dependent metabolic regulation also influences redox homeostasis: NADH supplies electrons to the respiratory chain, whereas NADPH supports glutathione- and thioredoxin-dependent antioxidant systems [25,26]. Nicotinamide nucleotide transhydrogenase (NNT) contributes to NADPH regeneration but can operate in reverse under adverse energetic conditions, consuming NADPH to regenerate NADH [25,26]. Consequently, the net effect of mitochondrial Ca^{2+} signaling on reactive oxygen species (ROS) depends on the balance between oxidant generation and antioxidant capacity rather than on Ca^{2+} uptake alone. Consistent with the importance of these processes in atrial myocardium, atrial tissue from patients with AF and concomitant heart failure exhibited ATP depletion, reduced oxidative phosphorylation complex abundance, and increased oxidative-stress indicators [27]. These observations do not, however, establish impaired MCU-mediated uptake as their cause. Mitochondrial Ca^{2+} efflux through NCLX further regulates matrix Ca^{2+} load. In adult mouse hearts, NCLX deletion caused mitochondrial Ca^{2+} overload, increased superoxide generation, and severe myocardial dysfunction, whereas NCLX overexpression enhanced Ca^{2+} clearance and protected against ischemic injury [28]. Together, these findings suggest that regulated mitochondrial Ca^{2+} uptake and efflux contribute to metabolic and redox homeostasis, rather than implying that greater Ca^{2+} uptake is invariably beneficial.

Taken together, these mechanisms provide a physiological basis for the coordination of mitochondrial Ca^{2+} signaling with the metabolic demands of atrial excitation and Ca^{2+} cycling. In this context, mitochondrial Ca^{2+} responsiveness refers to the capacity of mitochondrial Ca^{2+} uptake and clearance to adapt to changes in cytosolic Ca^{2+} signaling

and cellular workload, while supporting oxidative metabolism and maintaining redox homeostasis without excessive Ca^{2+} accumulation. Importantly, an appropriate response does not necessarily imply greater Ca^{2+} uptake, but rather a coordinated adjustment of mitochondrial Ca^{2+} handling to changing cellular demands. The extent to which alterations in this response contribute to energetic deficits, redox imbalance, and abnormal Ca^{2+} handling in human atrial myocardium remains to be established. This relationship could be investigated during controlled workload transitions by assessing mitochondrial and cytosolic Ca^{2+} dynamics, NAD(P)H/FAD redox responses, and complementary measures of ATP production, respiration, and ROS generation in human atrial myocytes.

3. How Metabolic Syndrome Blunts Mitochondrial Calcium Responsiveness

Altered regulation of the mitochondrial calcium uniporter complex (MCUC) may represent an important mechanism linking metabolic syndrome to impaired atrial mitochondrial Ca^{2+} responsiveness. In patients with metabolic syndrome, right-atrial tissue exhibited reduced mitochondrial Ca^{2+} uptake and increased MICU regulatory-subunit expression compared with tissue from patients without metabolic syndrome [8]. Consistently, mice fed a high-fat/high-sucrose diet showed impaired atrial mitochondrial Ca^{2+} uptake after 2 and 12 weeks, accompanied by increased AF susceptibility [8]. Importantly, pharmacological enhancement of MCUC activity restored mitochondrial Ca^{2+} uptake in vitro and abolished AF occurrence in the dietary mouse model [8]. Mechanistically, MICU regulatory subunits control the activation threshold and cooperativity of mitochondrial Ca^{2+} uptake [19,20]. A recent study further demonstrated that MICU1 forms a complex with MCU in nonfailing human left-ventricular tissue, while genetic and pharmacological experiments in mice established the regulatory roles of MICU1 and MICU2 in cardiomyocyte mitochondrial Ca^{2+} influx [29]. Together, these findings suggest that altered MICU-dependent regulation may contribute to impaired atrial mitochondrial Ca^{2+} responsiveness under metabolic stress.

A second factor is metabolic inflexibility: after prolonged high-fat feeding, mouse atria accumulated long-chain lipids, activated beta-oxidation, and increased palmitoyl-CoA-supported mitochondrial respiration [30]. Similarly, studies of cardiac metabolism in type 2 diabetes have reported increased fatty-acid oxidation accompanied by reduced glucose oxidation [31,32]. In contrast, experimentally induced ceramide accumulation in human induced pluripotent stem cell-derived cardiomyocytes reduced ATP-linked oxygen consumption, beta-oxidation, and respiratory capacity, whereas inhibition of ceramide synthesis partially restored mitochondrial and metabolic indices [33]. These findings indicate that metabolic stress can alter substrate utilization and compromise mitochondrial bioenergetics through distinct mechanisms. Because fatty-acid oxidation has a higher oxygen cost per unit of ATP than glucose oxidation, a fatty-acid-biased atrium may have less flexibility when workload rises abruptly or oxygen delivery is constrained [24,31,32]. Metabolic inflexibility and lipotoxic mitochondrial injury may therefore limit the energetic adaptation associated with mitochondrial Ca^{2+} signaling, even when Ca^{2+} uptake is relatively preserved, rather than necessarily causing a primary defect in MCUC gating.

Chronic oxidative stress represents a third mechanism: obesity, insulin resistance, and hyperglycemia are associated with increased reactive oxygen species (ROS) production and disturbances in mitochondrial redox homeostasis [34,35]. In right-atrial tissue from patients with AF, mitochondrial electron transport chain dysfunction was accompanied by increased mitochondrial superoxide production and oxidative damage [36]. In addition, increased atrial RyR2 oxidation was observed in patients with chronic AF, while experiments in mice demonstrated that abnormal intracellular Ca^{2+} release was associated with mitochondrial dysfunction, increased ROS production, and greater AF susceptibility. Ge-

netic suppression of mitochondrial ROS production or pharmacological inhibition of RyR2 leakage prevented AF in these mouse models [37]. Importantly, oxidation does not uniformly suppress the MCU complex; direct experiments showed that S-glutathionylation of MCU at Cys-97 increased channel activity, mitochondrial Ca^{2+} uptake, mitochondrial ROS, and Ca^{2+}-overload-induced cell death [38]. Excessive mitochondrial Ca^{2+} accumulation may also result from impaired Ca^{2+} efflux. Experimental evidence indicates that disruption of mitochondrial Na^{+}/Ca^{2+} exchange can cause Ca^{2+} overload, promote mitochondrial permeability transition, and induce cardiomyocyte injury [28]. Thus, mitochondrial Ca^{2+} dysregulation may involve either insufficient responsiveness or excessive accumulation, although the contribution of the latter to human metabolic AF remains uncertain. Together, these findings indicate that mitochondrial Ca^{2+} homeostasis may be disrupted through altered uptake or efflux, leading to either insufficient responsiveness or excessive accumulation, with potentially detrimental consequences for mitochondrial function and cellular Ca^{2+} handling.

Chronic low-grade inflammation may add another layer of dysregulation, as obesity and diabetes are associated with inflammatory signaling, including NLRP3 inflammasome activation, in AF [39]. In human atrial specimens, macrophage subpopulations were predominantly localized to epicardial adipose tissue. In high-fat-diet-fed mice, atrial adiposity was accompanied by macrophage recruitment, whereas depletion of $CCR2^{+}$ monocyte-derived macrophages prevented fibro-fatty remodeling, atrial dilation, and AF [40]. A further mechanistic link between inflammation and atrial Ca^{2+} handling comes from increased NLRP3 inflammasome activity in atrial cardiomyocytes from patients with paroxysmal or chronic AF. Cardiomyocyte-specific NLRP3 activation in mice also promoted abnormal sarcoplasmic reticulum Ca^{2+} release and increased AF susceptibility [41]. These findings demonstrate that inflammatory signaling can contribute to atrial remodeling and abnormal intracellular Ca^{2+} handling, although they do not directly establish impaired mitochondrial Ca^{2+} uptake. Chronic inflammation may therefore contribute to mitochondrial calcium response mismatch by altering intracellular Ca^{2+} signaling and potentially compromising mitochondrial metabolic adaptation.

Taken together, alterations in MCUC regulation, substrate utilization, redox homeostasis, and inflammatory signaling may disturb different steps linking cytosolic Ca^{2+} signals to mitochondrial Ca^{2+} uptake and metabolic adaptation. The spatial organization of the sarcoplasmic reticulum (SR) and mitochondria provides an important context for this coupling. Reduced SR–mitochondrial contacts and MFN2 expression have been observed in right-atrial appendages from patients with persistent AF, with more pronounced abnormalities in those with concomitant diabetes [13]. In atrial myocytes from patients with AF, disrupted SR–mitochondrial spatial association was accompanied by blunted mitochondrial Ca^{2+} accumulation during increased workload and impaired NAD(P)H/FAD redox recovery [9]. These findings suggest that the spatial delivery of Ca^{2+} signals, mitochondrial Ca^{2+} handling, and downstream metabolic adaptation may all influence the adequacy of the mitochondrial response. However, whether the metabolic and inflammatory disturbances discussed above directly cause SR–mitochondrial disorganization remains unclear. Thus, mitochondrial calcium response mismatch should be understood not simply as reduced Ca^{2+} uptake, but as an inadequate or dysregulated mitochondrial Ca^{2+}–metabolic response relative to ongoing atrial demand. Physiological atrial coupling and the corresponding disease-associated or experimental alterations are summarized in Table 1.

Table 1. Physiological atrial energy–calcium coupling and disease-associated or experimental alterations.

Domain	Physiologically Coupled Atrium	Disease-Associated or Experimental Finding	Consequence	Reference
Mitochondrial Ca^{2+} uptake	Regulated Ca^{2+} uptake	Blunted mitochondrial Ca^{2+} response	Dysregulated Ca^{2+} responsiveness	[8,9]
Substrate utilization	Adjustable substrate use	Increased fatty-acid utilization	Potentially altered metabolic adaptation	[30]
Energetic adaptation	ATP supply matched to demand	Reduced reserve after Mcu deletion	Potential energy–demand mismatch	[10]
Redox regulation	Adaptive redox balance	Blunted recovery or increased ROS	Dysregulated Ca^{2+}–redox coupling	[9,36]
Inflammation-related signaling	No sustained inflammatory activation	NLRP3-linked SR Ca^{2+} abnormalities	Mitochondrial effects remain uncertain	[41]
SR–mitochondrial organization	Preserved spatial association	Reduced contacts or disorganization	Potentially altered local Ca^{2+} signaling	[9,13]

Abbreviations: ATP, adenosine triphosphate; Ca^{2+}, calcium; ROS, reactive oxygen species; SR, sarcoplasmic reticulum.

4. From Mismatch to Atrial Fibrillation

When mitochondrial Ca^{2+} handling and metabolic adaptation become mismatched to atrial excitation and workload, energetic and redox responses may become inadequate or dysregulated. This state of energy–calcium mismatch may contribute to an arrhythmogenic substrate for AF through several interrelated mechanisms.

First, mitochondrial calcium response mismatch may promote AF initiation by compromising the energetic adaptation required for atrial excitation and Ca^{2+} cycling. In high-fat/high-sucrose-fed mice, impaired atrial mitochondrial Ca^{2+} uptake was accompanied by increased inhibitory phosphorylation of pyruvate dehydrogenase, whereas pharmacological enhancement of uptake suppressed AF occurrence [8]. These findings link altered mitochondrial Ca^{2+} handling to metabolic remodeling and AF susceptibility, although a consequent reduction in ATP availability has not been directly established. In isolated atrial myocytes, experimental inhibition of mitochondrial ATP synthesis enhanced pacing-induced Ca^{2+} alternans [42], supporting a role for mitochondrial energetic function in maintaining stable Ca^{2+} cycling. ATP-dependent processes, including Na^+/K^+-ATPase activity and SERCA-mediated sarcoplasmic reticulum (SR) Ca^{2+} reuptake, require adequate energy supply [42,43]. Importantly, studies of atrial myocytes from patients with chronic AF demonstrated that increased SR Ca^{2+} leak and Na^+/Ca^{2+} exchanger (NCX) function promote delayed afterdepolarizations and triggered activity, providing a mechanism for AF-related ectopic triggers [44]. Under substantial metabolic stress, sarcolemmal ATP-sensitive K^+ channel activation can shorten action potential duration [45]. Experimental studies further demonstrated that spatial heterogeneity in atrial action potential duration supports reentrant rotors and sustained AF, whereas reducing this heterogeneity suppresses AF [46]. Thus, impaired energetic adaptation provides a plausible forward mechanism through which mitochondrial calcium response mismatch may facilitate arrhythmogenic Ca^{2+} handling, electrical instability, and AF initiation, although the complete causal sequence remains to be established in human metabolic AF.

Second, mitochondrial calcium response mismatch may promote AF initiation by compromising redox adaptation and thereby enhancing arrhythmogenic Ca^{2+} handling. In atrial myocytes from patients with AF, blunted workload-induced mitochondrial Ca^{2+} accumulation was accompanied by impaired NAD(P)H/FAD redox recovery [9]. Mitochondrial redox balance is closely linked to respiratory-chain electron transfer, which normally

reduces oxygen to water and generates the proton gradient required for ATP synthesis. Under conditions favoring electron leak, sites within respiratory complexes I and III can instead transfer electrons prematurely to molecular oxygen (O_2), producing superoxide ($O_2\bullet^-$), which is subsequently converted into hydrogen peroxide (H_2O_2) [47]. Increased electron leak can therefore enhance mitochondrial reactive oxygen species (ROS) production; oxidative stress develops when ROS generation exceeds antioxidant clearance [47]. One redox-sensitive target is the type 2 ryanodine receptor (RyR2), the sarcoplasmic reticulum Ca^{2+}-release channel, whose oxidation can promote abnormal diastolic Ca^{2+} leak [37]. RyR2 oxidation was increased in atrial tissue from patients with chronic AF. In mice with genetically induced RyR2-mediated Ca^{2+} leak, mitochondrial ROS and AF susceptibility increased, whereas mitochondria-targeted catalase reduced RyR2 oxidation, Ca^{2+} leak, and AF susceptibility [37]. These findings link mitochondrial oxidative stress and RyR2 dysfunction to AF-related triggers. Oxidative stress may also contribute to atrial electrical and structural remodeling associated with AF maintenance [48]. Thus, impaired redox adaptation provides a second plausible forward mechanism linking mitochondrial calcium response mismatch to AF initiation; however, whether the mismatch itself directly increases electron leak and initiates this sequence remains unproven in human metabolic AF.

Importantly, the relationship between mitochondrial calcium response mismatch and AF is likely bidirectional. In the normal heart, acute workload increases recruit MCU-dependent mitochondrial Ca^{2+} uptake to augment oxidative metabolism and ATP production [10,11]. This response is compromised in AF: atrial myocytes from patients with AF show blunted mitochondrial Ca^{2+} accumulation during workload transitions, impaired NAD(P)H/FAD regeneration, and increased proarrhythmic Ca^{2+} release; enhancing mitochondrial Ca^{2+} uptake reduces abnormal Ca^{2+} events [9]. Once AF develops, rapid and irregular atrial activation may impose additional metabolic stress. At the same mean contraction rate, irregular pacing increases diastolic Ca^{2+}, activates CaMKII and AMPK, promotes fatty-acid uptake and lipid accumulation, and reduces glucose uptake [49]. Rapid atrial pacing also depletes ATP, suppresses mitochondrial biogenesis and respiratory-chain expression, and produces mitochondrial ultrastructural injury [50]. It also increases atrial peroxynitrite formation and electrical remodeling, which are attenuated by antioxidant treatment [51]. These abnormalities may reinforce one another because mitochondrial ROS and RyR2-mediated Ca^{2+} leak form a reciprocal amplification loop [37]. Thus, mitochondrial dysfunction may facilitate AF initiation, while AF-related rapid and irregular activation further worsens energetic, redox, Ca^{2+}-handling, and mitochondrial abnormalities, potentially increasing AF burden and facilitating progression from paroxysmal to persistent AF, although these clinical extensions remain to be tested directly. The downstream arrhythmogenic pathways and the proposed feedback loop linking mitochondrial calcium response mismatch to AF are schematically illustrated in Figure 2.

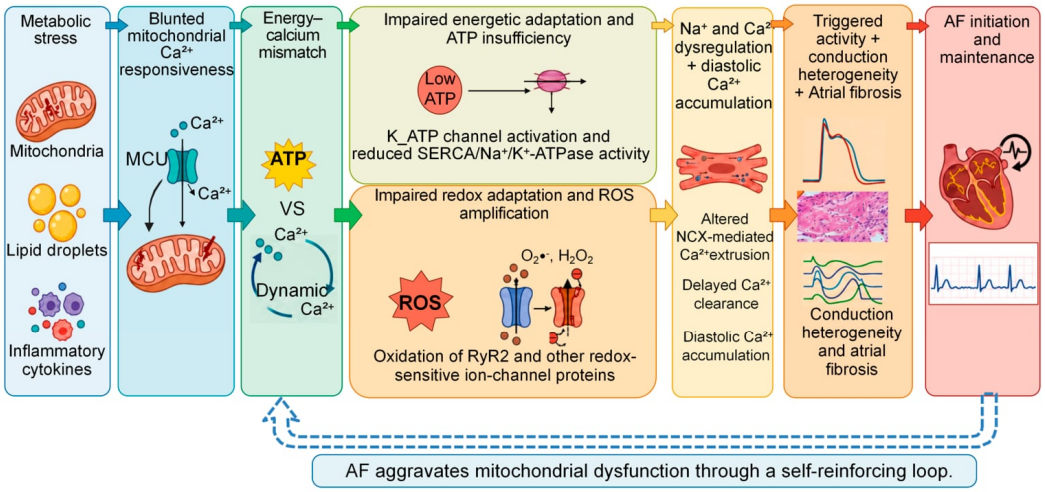


Figure 2. Proposed bidirectional framework linking mitochondrial calcium response mismatch to AF initiation and maintenance. Metabolic stress may blunt mitochondrial Ca^{2+} responsiveness, thereby uncoupling atrial excitation-dependent Ca^{2+} signaling from metabolic adaptation. Mitochondrial calcium response mismatch may impair energetic adaptation and ATP-dependent ion transport, disrupt redox adaptation, and amplify mitochondrial reactive oxygen species (ROS). These interrelated pathways promote Na^+ and Ca^{2+} dysregulation, arrhythmic triggers, conduction heterogeneity, and atrial fibrosis, thereby facilitating AF initiation and maintenance. Once AF develops, rapid and irregular atrial activation may further aggravate mitochondrial dysfunction, forming a self-reinforcing feedback loop. Solid arrows denote comparatively well-supported relationships based on experimental and/or clinical evidence, whereas the dashed open arrow denotes a proposed feedback relationship supported by convergent but predominantly indirect evidence. Colored boxes are used to distinguish different mechanistic stages, illustrating the progression from upstream metabolic stress and mitochondrial dysfunction to downstream arrhythmogenic consequences and AF initiation and maintenance.

5. Mitochondrial Calcium Response Mismatch in Relation to Established AF Mechanisms

Atrial fibrillation arises from multiple interacting mechanisms, and mitochondrial calcium response mismatch should be considered alongside established pathways rather than as their common upstream cause. Atrial fibrosis disrupts electrical conduction and promotes conduction heterogeneity, providing a structural substrate for re-entry [52]. Atrial stretch and mechanical remodeling can independently alter electrophysiological properties through mechano-electrical feedback [53], while autonomic modulation influences atrial conduction dynamics and wavefront propagation [54]. In a high-fat-diet rat model, increased atrial sympathetic and parasympathetic nerve densities were accompanied by shortened atrial effective refractory periods and increased AF inducibility, providing experimental evidence linking metabolic stress to atrial autonomic remodeling [55]. These mechanisms may promote AF without requiring impaired mitochondrial Ca^{2+} responsiveness. Nevertheless, changes in atrial electrical activity and mechanical workload may alter cellular energetic demand, creating conditions in which mitochondrial metabolic adaptation becomes relevant. Thus, mitochondrial calcium response mismatch may interact with structural, mechanical, and autonomic remodeling without necessarily preceding or mediating these processes.

Inflammatory and adipose-derived pathways provide additional mechanisms linking metabolic disturbances to AF. Experimental activation of cardiomyocyte NLRP3 inflammasome signaling promotes abnormal Ca^{2+} handling, electrical remodeling, and AF susceptibility [41]. Human epicardial adipose tissue can promote atrial fibrosis through the secretion of profibrotic factors [56], while its accumulation and infiltration are associ-

ated with atrial conduction abnormalities [57]. These pathways can contribute to atrial remodeling without mitochondrial Ca^{2+} mismatch being an established prerequisite. Moreover, mitochondrial-related dysfunction in AF involves mechanisms beyond altered Ca^{2+} handling, including oxidative DNA damage and PARP1-mediated NAD^+ depletion [58]. Metabolic remodeling may also involve changes in substrate utilization and myofibrillar energetics [1]. Accordingly, mitochondrial Ca^{2+} dysregulation may represent one component of a broader network of interacting metabolic and mitochondrial abnormalities rather than a mechanism that accounts for all mitochondrial dysfunction in AF.

The distinctive feature of the mitochondrial calcium response mismatch framework lies in its emphasis on the dynamic coupling between cytosolic Ca^{2+} signals, mitochondrial Ca^{2+} handling, and metabolic adaptation to changing atrial workload. Whereas conventional descriptions of mitochondrial dysfunction often emphasize abnormalities in respiratory capacity, ATP availability, or oxidative stress, the proposed framework focuses on whether mitochondrial Ca^{2+} uptake and the resulting metabolic responses are appropriately matched to excitation-induced demand. This distinction allows consideration of impaired mitochondrial Ca^{2+} uptake and inadequate downstream metabolic adaptation as potentially different components of the mismatch. Evidence of impaired mitochondrial Ca^{2+} handling in human atrial tissue from patients with metabolic syndrome and atrial myocytes from patients with AF, together with experimental findings showing reduced AF susceptibility following enhancement of mitochondrial Ca^{2+} uptake in mouse models, provides a rationale for investigating this relationship [8,9]. Rather than replacing established structural, inflammatory, autonomic, or mechanical mechanisms of AF, this framework provides a complementary perspective on how metabolic stress may compromise atrial adaptation to changing workload. Whether such mismatch represents an independent causal mechanism or a convergent consequence of other pathological processes remains to be established.

6. Aligning Functional Readouts with Clinical Endpoints

To translate mitochondrial Ca^{2+} response mismatch into an experimentally and clinically testable framework, functional measures should be distinguished according to both their position in the proposed pathway and their current level of validation. Direct readouts assess mitochondrial Ca^{2+} responsiveness to changes in cellular demand, whereas downstream readouts reflect subsequent metabolic or mitochondrial consequences, and surrogate readouts capture more distal cellular or atrial dysfunction. These measures should also be differentiated as established clinical readouts, candidate biomarkers, or experimental/hypothesis-generating measures. At present, mitochondrial Ca^{2+}-related measurements remain largely investigational in AF and have not been established for routine clinical assessment [59,60].

Because mitochondrial Ca^{2+} response mismatch concerns the adequacy of adaptation to changing cellular demand, it should be tested dynamically rather than inferred from resting measurements alone. In isolated atrial cardiomyocytes or ex vivo atrial preparations, measurements can be obtained at baseline, during increased workload induced by graded pacing and/or β-adrenergic stimulation, and during recovery. Cytosolic Ca^{2+} transients define the excitation-related input, whereas mitochondrial Ca^{2+} accumulation and kinetics provide the most direct readout of mitochondrial responsiveness. Under the same standardized stress, NAD(P)H/FAD dynamics and, where technically feasible, ATP availability and cellular function can be assessed simultaneously or in matched parallel experiments. This approach is experimentally feasible: in patient-derived atrial myocytes, increasing pacing from 0.5 to 3 Hz followed by isoproterenol stimulation enabled concurrent assessment of cytosolic Ca^{2+}, mitochondrial Ca^{2+}, and NAD(P)H/FAD, revealing blunted mitochondrial

Ca^{2+} accumulation and impaired redox regeneration in AF [9]. Response amplitude and recovery kinetics may therefore provide dynamic measures of the proposed mismatch.

Downstream measures can further characterize the metabolic and injury consequences of mitochondrial Ca^{2+} maladaptation, but they should not be interpreted as direct measures of the mismatch itself. Experimental tachypacing and human atrial studies have linked AF with altered ATP content, mitochondrial respiration, and oxidative phosphorylation, supporting their use as downstream energetic readouts, although their value for predicting AF burden or recurrence remains unvalidated [12]. Oxidative stress markers, including mitochondrial superoxide and lipid peroxidation products, are also increased in human AF atrial tissue, but they reflect a broader downstream injury response rather than mitochondrial Ca^{2+} mismatch specifically [36]. Circulating mt-cfDNA is more clinically accessible and has recently been associated with post-ablation AF recurrence; however, this evidence remains preliminary, and its atrial and mechanistic specificity is limited [61]. These measures are therefore best considered candidate or experimental biomarkers rather than validated clinical indicators of mitochondrial Ca^{2+} response mismatch.

Clinically accessible measures of atrial mechanical function may provide a downstream bridge between mitochondrial dysfunction and clinically relevant AF outcomes. Left atrial strain, particularly reservoir strain, can be assessed non-invasively by echocardiography and has been associated with AF recurrence after rhythm-control interventions [12]. In patients undergoing ablation for long-standing persistent AF, left atrial reservoir and contractile strain were also associated with post-ablation rhythm outcomes, with contractile strain independently associated with recurrence [62]. Left atrial appendage flow velocity, measured by transesophageal echocardiography, has likewise been associated with post-ablation recurrence, although the certainty of the meta-analytic evidence remains limited [63]. These measures should therefore be regarded as established clinical functional readouts of atrial dysfunction, but only candidate surrogates of mitochondrial Ca^{2+} response mismatch. Their translational value will depend on whether mechanistically proximal measures of mitochondrial adaptation show consistent associations with atrial mechanical dysfunction and clinically meaningful endpoints such as AF burden, progression, recurrence, and response to rhythm-control therapy. A central testable prediction of this framework is that impaired workload-dependent mitochondrial Ca^{2+} responsiveness, or appropriately validated functional surrogates, will remain associated with AF burden and post-ablation recurrence after adjustment for established clinical and structural risk factors. This prediction requires prospective validation using standardized dynamic metabolic measurements, continuous rhythm monitoring, and detailed assessment of the atrial substrate.

Hierarchical functional readouts, their dynamic assessment, and current translational status are summarized in Table 2.

Table 2. Candidate functional readouts and evidence status for the proposed mitochondrial calcium response mismatch framework in atrial fibrillation.

Mechanistic Level	Functional Readout	What It Reflects	Dynamic Assessment	Evidence Status	References
Upstream demand signal	**Cytosolic Ca^{2+} transients**	Excitation-related Ca^{2+} demand to which mitochondria are expected to respond	Ca^{2+} transient amplitude, integrated signal, and decay kinetics during baseline → graded workload → recovery	**Established experimental readout**; not a mismatch biomarker itself	[9,64]

Table 2. *Cont.*

Mechanistic Level	Functional Readout	What It Reflects	Dynamic Assessment	Evidence Status	References
Direct mechanistic readout	**Mitochondrial Ca^{2+} responsiveness**	Adequacy of mitochondrial Ca^{2+} response to increasing cellular demand	Mitochondrial Ca^{2+} accumulation, amplitude, latency, and recovery kinetics under the same workload protocol	**Experimental mechanistic readout**; most proximal to the proposed mismatch	[9,12]
Immediate downstream metabolic readout	**NAD(P)H/FAD redox dynamics**	Workload-dependent metabolic and redox adaptation	Redox oxidation/depletion during increased workload and amplitude/rate of recovery	**Experimental/hypothesis-generating readout**	[9]
Immediate downstream energetic readout	**ATP availability/ATP dynamics**	Ability of ATP production to match increased energetic demand	ATP level or dynamics at baseline, increased workload, and recovery	**Experimental/hypothesis-generating readout**	[12,27]
Downstream mitochondrial functional readout	**Mitochondrial respiratory function**	Capacity to increase oxidative phosphorylation above basal energetic demand	Respiration at basal and stimulated states where measured; electron transport chain activity assessed separately	**Candidate functional readout**; predictive value for AF recurrence remains unvalidated	[12,36,65]
Downstream redox readout	**Mitochondrial ROS**	Oxidative consequence of impaired mitochondrial adaptation	Stress-induced mitochondrial ROS accumulation during or after workload challenge	**Experimental/candidate readout**; limited specificity	[27,36]
Downstream mitochondrial injury readout	**Mitochondrial injury markers**	Structural and functional mitochondrial injury secondary to sustained metabolic stress	Mitochondrial membrane potential, oxidative injury products, mitochondrial network integrity, or mtDNA damage	**Experimental/candidate readout**	[12,27,36]
Circulating injury surrogate	**Circulating mt-cfDNA**	Release of mitochondrial components associated with cellular/mitochondrial injury	Plasma or serum mt-cfDNA before intervention and during follow-up	**Candidate biomarker**; limited tissue and mechanistic specificity	[61]
Downstream Ca^{2+}-handling phenotype	**Diastolic Ca^{2+} accumulation**	Impaired cytosolic Ca^{2+} homeostasis and enhanced diastolic SR Ca^{2+} leak	Diastolic $[Ca^{2+}]i$ during pacing/workload escalation and recovery	**Established experimental AF phenotype**; not specific to mitochondrial mismatch	[66]
Downstream Ca^{2+}-handling phenotype	**Spontaneous Ca^{2+} waves**	Arrhythmogenic spontaneous SR Ca^{2+} release	Ca^{2+} wave/spark frequency during pacing or adrenergic stress	**Established experimental AF phenotype**	[67,68]
Downstream cellular functional output	**Frequency-dependent atrial mechanical response**	Ability of atrial myocardium to maintain mechanical performance as workload rises	Developed force and diastolic tension during stepwise pacing	**Experimental functional readout**; not specific to mitochondrial mismatch	[69,70]
Clinical organ-level readout	**LA strain/phasic function**	Atrial mechanical function	LASr/LASct at baseline and follow-up	**Associated with AF recurrence**; mismatch link unvalidated	[62,71,72]

Table 2. *Cont.*

Mechanistic Level	Functional Readout	What It Reflects	Dynamic Assessment	Evidence Status	References
Clinical organ-level readout	**LAA flow velocity**	Left atrial appendage mechanical and emptying function	Transesophageal echocardiographic assessment, usually before intervention	**Established clinical functional readout**; Associated with AF recurrence; mismatch link unvalidated	[63]

Abbreviations: AF, atrial fibrillation; ATP, adenosine triphosphate; Ca^{2+}, calcium; FAD, flavin adenine dinucleotide; LA, left atrial; LAA, left atrial appendage; NAD(P)H, reduced nicotinamide adenine dinucleotide phosphate-related autofluorescence signal; ROS, reactive oxygen species.

7. HFpEF as a Potential Clinical Amplifier of Mitochondrial Calcium Response Mismatch

Heart failure with preserved ejection fraction (HFpEF) is closely linked to obesity, insulin resistance or diabetes, hypertension, and systemic inflammation, and AF is highly prevalent among patients with HFpEF [73,74]. These cardiometabolic and inflammatory abnormalities converge on the atrium, creating a clinical setting in which pressure overload, inflammatory signaling, endothelial and microvascular dysfunction, impaired oxygen delivery, and metabolic inflexibility may reduce atrial metabolic reserve and increase AF vulnerability and burden [75,76]. HFpEF may therefore provide a clinical context in which the proposed mitochondrial calcium response mismatch could be amplified, but this convergence does not establish HFpEF as a distinct mitochondrial Ca^{2+}-mismatch phenotype.

In HFpEF, chronic elevation of left ventricular filling pressure increases left atrial wall stress and promotes atrial enlargement, fibrosis, and mechanical dysfunction [77,78]. At the same time, systemic inflammatory activation and microvascular abnormalities may restrict oxygen availability and aggravate mitochondrial inefficiency [79]. The atrium is therefore exposed not only to metabolic toxicity but also to persistent hemodynamic stress [80]. Under such conditions, atrial metabolic reserve may be reduced, potentially limiting the capacity of the atrium to accommodate the additional energetic and calcium-handling demands imposed by rapid or irregular activation. However, whether HFpEF directly impairs workload-dependent mitochondrial Ca^{2+} responsiveness in the human atrium has not been established.

Patients with concomitant HFpEF and AF often experience a more symptomatic clinical course, greater hemodynamic instability, and higher rates of hospitalization [81,82]. Within the present framework, HFpEF is therefore best viewed not as an established mitochondrial Ca^{2+}-mismatch phenotype but as a clinical condition that may amplify the proposed pathway by imposing additional hemodynamic, inflammatory, microvascular, oxygen-delivery, and metabolic constraints on the atrium [79,82]. These converging stresses could reduce atrial tolerance to rapid and irregular activation and thereby favor more sustained arrhythmia, although this proposed mechanistic relationship requires direct validation.

Accordingly, AF management in HFpEF may require a more integrated strategy than rhythm control alone. Interventions that reduce atrial load and improve systemic metabolic function may be particularly relevant in this subgroup, although whether their clinical benefits involve preservation of mitochondrial calcium responsiveness remains to be determined. The proposed amplifying role of HFpEF within this framework is illustrated in Figure 3.

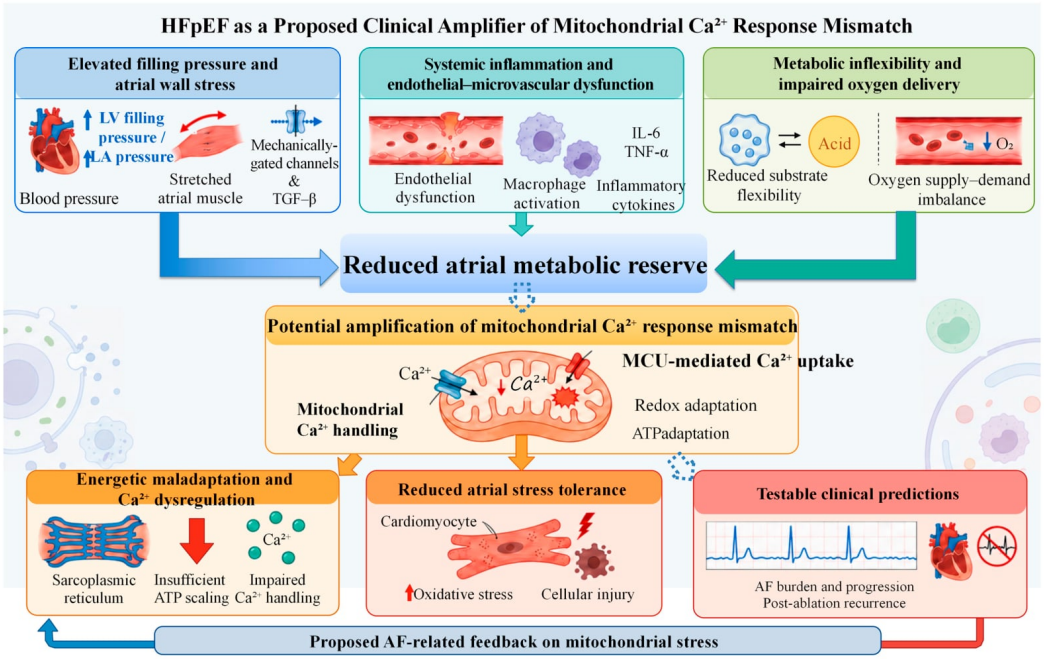


Figure 3. HFpEF as a Proposed Clinical Amplifier of Mitochondrial Calcium Response Mismatch in Metabolic AF. In HFpEF, elevated left ventricular filling pressure and left atrial wall stress, together with systemic inflammation, endothelial–microvascular dysfunction, and impaired oxygen delivery, intensify metabolic stress and further reduce mitochondrial calcium responsiveness. This amplifies energy–calcium mismatch, lowers atrial stress tolerance, and promotes greater AF burden with poorer rhythm-control durability. Colored boxes and solid arrows distinguish the different pathological processes and their proposed directional relationships. Dashed arrows indicate hypothesized mechanistic links, while the bottom feedback arrow illustrates the proposed AF-related feedback on mitochondrial stress.

8. Therapeutic Implications and Future Directions

If impaired mitochondrial calcium responsiveness is a key intermediate phenotype in metabolic AF, then therapeutic strategies should extend beyond suppression of triggers and rate control to restoration of atrial metabolic adaptability. The most immediate and clinically accessible intervention is comprehensive management of the metabolic substrate, consistent with contemporary AF management guidelines aggressive management of the metabolic substrate itself. Weight reduction, glycemic control, improvement of insulin sensitivity, lipid optimization, treatment of sleep-disordered breathing, and blood pressure control are important components of cardiometabolic risk-factor management, although the evidence for improving AF-specific outcomes differs among these interventions [83].

Lifestyle intervention is particularly important. Sustained weight loss and structured risk-factor management have been associated with lower AF burden and improved maintenance of sinus rhythm, while the ARREST-AF randomized clinical trial demonstrated improved freedom from atrial arrhythmia recurrence at 12 months after catheter ablation with structured risk-factor management [84,85]. Exercise training, when appropriately prescribed, has also been shown to reduce AF recurrence and improve symptom severity in a randomized trial [86]. Exercise can induce mitochondrial adaptations in skeletal muscle, including improvements in respiratory function and metabolic capacity [87,88], but these findings do not establish restoration of atrial mitochondrial Ca^{2+} responsiveness. Dietary optimization may contribute to comprehensive cardiometabolic management [83], although direct evidence that specific dietary interventions restore atrial mitochondrial Ca^{2+} responsiveness remains lacking.

Pharmacological therapies with metabolic or cardiorenal benefit may also be relevant. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have demonstrated clinical benefits for heart failure and cardiovascular outcomes across cardiometabolic populations [89] and are recommended for patients with concomitant heart failure and AF to reduce heart failure hospitalization and cardiovascular death [83]. Glucagon-like peptide-1 (GLP-1) receptor agonists have also demonstrated cardiovascular benefits in selected metabolically unhealthy populations [90], while a meta-analysis of randomized trials suggested a lower incidence of AF with semaglutide [91]. However, these cardiometabolic benefits and AF-related findings should not be interpreted as evidence that either drug class directly restores atrial mitochondrial Ca^{2+} responsiveness or corrects the proposed mismatch. Whether modulation of atrial mitochondrial function contributes to their clinical effects remains to be established.

Around the time of catheter ablation, a second therapeutic window may exist. Patients with metabolic AF may be particularly sensitive to peri-procedural oxidative and inflammatory stress [6]. Optimizing peri-procedural management, including maintenance of electrolyte stability, remains clinically relevant; however, the association between pre-procedural serum potassium levels and AF recurrence does not establish that potassium optimization itself prevents recurrence [92]. More specifically, interventions targeting inflammation and oxidative stress have been investigated as potential strategies to reduce early recurrence, but their clinical efficacy remains uncertain. In a randomized, placebo-controlled trial, a 10-day course of colchicine did not reduce atrial arrhythmia recurrence at either 2 weeks or 3 months after catheter ablation [93]. Therefore, targeted peri-ablation anti-inflammatory or antioxidant interventions should be regarded as investigational approaches for preventing AF recurrence rather than established treatments. Whether such interventions can preserve mitochondrial redox adaptation or attenuate mitochondrial calcium response mismatch also requires direct investigation.

Current pharmacological approaches to mitochondrial Ca^{2+} transport remain preclinical and should be interpreted according to the direction of the underlying transport abnormality. In metabolic AF, the most directly relevant evidence comes from kaempferol, an activator of the mitochondrial calcium uniporter complex, which restored impaired mitochondrial Ca^{2+} uptake and abolished AF occurrence in mice exposed to a high-fat/high-sucrose diet [8]. Efsevin, which enhances mitochondrial Ca^{2+} uptake through VDAC2, and kaempferol also suppressed arrhythmogenic Ca^{2+} waves and ventricular tachycardia in catecholaminergic polymorphic ventricular tachycardia models, providing supportive although non-atrial evidence [94]. Conversely, cell-permeable MCU inhibitors such as Ru265 and the MICU1-targeting compounds MCU-i4 and MCU-i11 have been developed primarily as experimental tools for conditions characterized by excessive mitochondrial Ca^{2+} accumulation [95,96]. Mitochondrial Na^+/Ca^{2+} exchange can be inhibited by CGP-37157, which increased mitochondrial Ca^{2+} retention, improved workload-dependent redox and energetic adaptation, and reduced arrhythmias in a preclinical heart-failure model [97]. However, CGP-37157 also affects other Ca^{2+}-handling proteins [98], whereas excessive suppression of mitochondrial Ca^{2+} efflux may itself promote mitochondrial Ca^{2+} overload and cardiac injury [28]. Thus, these findings support restoration of physiological mitochondrial Ca^{2+} responsiveness, rather than uniform activation or inhibition of a single transporter, as the more appropriate therapeutic objective. No direct modulator of MCU or mitochondrial Na^+/Ca^{2+} exchange is currently established for AF treatment.

Future work should therefore move toward a combined "electro-metabolic" treatment model. In this framework, rhythm control remains essential, but it is paired with clinically supported interventions targeting metabolic risk factors and associated conditions, while direct restoration of mitochondrial adaptability remains an experimental therapeutic objec-

tive. Such an approach may be especially valuable in obese patients, those with recurrent AF after ablation, and those with concomitant HFpEF. Whether mitochondrial-targeted interventions provide additional clinical benefits beyond established rhythm-control and risk-factor management strategies requires prospective investigation. Potential therapeutic strategies mapped to the major mechanistic nodes of mitochondrial calcium response mismatch are summarized in Table 3.

Table 3. Therapeutic strategies mapped to mitochondrial calcium response mismatch and their supporting evidence.

Therapeutic Strategy	Main Target	Expected Effect on Mismatch	Relevance to AF Management	Reference
Weight loss, exercise, and dietary optimization	Metabolic stress	Improve metabolic adaptability	Clinical AF evidence for weight loss and exercise	[83–86]
Cardiometabolic risk-factor control	Metabolic substrate	Reduce chronic stress	Clinical management; AF benefit varies	[83,85]
Sleep-disordered breathing treatment	Intermittent hypoxia	Reduce stress exposure	Clinical care; recurrence benefit uncertain	[83,99]
SGLT2 inhibitors/GLP-1 receptor agonists	Systemic metabolism	Improve metabolic environment	Clinical cardiometabolic benefit; AF evidence varies	[83,89–91]
Peri-ablation anti-inflammatory strategies	Procedural inflammation	Limit oxidative stress	Investigational for AF recurrence	[93]
Mitochondrial antioxidants/NAD^+ support	Redox imbalance	Preserve redox adaptation	Mainly mechanistic/preclinical evidence	[37,58]
Mitochondrial Ca^{2+} transport modulators	MCUC/NCLX	Restore adaptive Ca^{2+} handling	Preclinical evidence	[8,94,97]
SR–mitochondrial coupling preservation	Organelle contacts	Maintain local Ca^{2+} transfer	Mechanistic evidence; no established AF therapy	[9,13]

Abbreviations: AF, atrial fibrillation; Ca^{2+}, calcium; GLP-1, glucagon-like peptide-1; MCUC, mitochondrial calcium uniporter complex; NAD^+, oxidized nicotinamide adenine dinucleotide; NCLX, mitochondrial Na^+/Ca^{2+} exchanger; SGLT2, sodium-glucose cotransporter 2; SR, sarcoplasmic reticulum.

9. Perspective and Unresolved Questions

Despite its conceptual appeal, the mitochondrial calcium response mismatch model raises several unresolved questions. One major issue is molecular specificity. It remains unclear which components of the mitochondrial calcium uptake and efflux machinery are most consistently altered in metabolic AF, how these alterations evolve over time, and whether they differ across disease stages or patient subgroups. The relative contributions of the MCU complex, mitochondrial $Na^+/Ca2^+$ exchange/NCLX, permeability transition susceptibility, membrane potential stability, and organelle-contact architecture all require systematic investigation.

A second challenge is standardization of measurement. Mitochondrial calcium responsiveness is currently inferred through diverse experimental metrics, including calcium uptake rate, respiratory reserve, NADH recovery kinetics, ROS dynamics, and organelle-contact architecture. A more unified framework for quantifying this phenotype will be necessary if the concept is to be compared across studies and translated into clinical research. An operational assessment would pair cytosolic Ca^{2+} signals or defined pacing increments with the corresponding mitochondrial Ca^{2+} response, NAD(P)H/FAD redox dynamics, and ATP-related adaptation during controlled workload transitions. Response amplitudes and recovery kinetics could be compared at matched workloads, while response ratios or input–output slopes could be explored when the measurement scales permit. A reduced mitochondrial Ca^{2+} response for a given cytosolic Ca^{2+} input would indicate impaired Ca^{2+}

coupling, whereas a relatively preserved mitochondrial Ca^{2+} response with inadequate redox recovery or ATP-related adaptation would suggest downstream metabolic uncoupling. Quantitative cutoffs for mismatch remain to be established and should not be inferred from single resting measurements.

The mismatch framework generates two specific testable predictions. First, despite differences in the upstream metabolic insult, metabolic AF should converge on a reduced workload-dependent relationship between cytosolic Ca^{2+} signals and mitochondrial Ca^{2+}–metabolic responses, measurable as an attenuated mitochondrial Ca^{2+} response for a given increase in cytosolic Ca^{2+} or workload and/or inadequate NAD(P)H recovery and ATP-related adaptation despite a relatively preserved mitochondrial Ca^{2+} response. Second, interventions targeting MCUC regulation or SR–mitochondrial contacts should improve ATP/redox adaptation and suppress arrhythmogenic Ca^{2+} release only when they restore this dynamic demand–response relationship, whereas altering basal mitochondrial Ca^{2+} levels without restoring dynamic coupling may be insufficient.

A third issue concerns causality and bidirectionality. Metabolic stress may impair mitochondrial calcium responsiveness and thereby promote AF, but AF itself may also worsen mitochondrial dysfunction through tachycardia-induced stress, contractile inefficiency, and oxidative injury. The relationship is therefore likely reciprocal. Direct causal evidence in human metabolic AF remains limited, and the relative contribution of this framework compared with established mechanisms, including fibrosis, inflammation, and electrophysiological remodeling, has not been determined. Future studies must determine whether impaired mitochondrial calcium responsiveness is primarily an initiating event, an amplifying mechanism, a marker of disease severity, or all three depending on disease stage. Time-resolved studies in animal models and longitudinal human cohorts will be crucial.

Finally, clinical translation will require practical biomarkers and intervention trials. Direct assessment of atrial mitochondrial function in patients is difficult, and blood-based surrogates remain imperfect. Nevertheless, advances in metabolic imaging, circulating markers of mitochondrial injury, redox stress, or metabolic inflexibility, and atrial tissue profiling may gradually make this framework testable in the clinic. Interventional studies that combine rhythm control with structured metabolic optimization or mitochondrial-targeted therapies may be especially informative if mechanistic biomarkers are incorporated prospectively.

The current human, animal, and mechanistic evidence supporting the proposed framework, together with key evidence gaps, is summarized in Table 4.

Table 4. Human, animal, and mechanistic evidence relevant to the proposed mitochondrial calcium response mismatch framework in metabolic atrial fibrillation.

Claim	Human Evidence	Animal Evidence	Mechanistic Evidence
Impaired mitochondrial Ca^{2+} uptake in metabolic syndrome	Reduced atrial Ca^{2+} uptake and increased MICU expression [8].	Impaired uptake and increased AF susceptibility; kaempferol suppressed AF [8].	MICU regulates MCU activation threshold and Ca^{2+} influx [19,20,29].
Impaired workload-dependent Ca^{2+}–redox adaptation	Blunted mitochondrial Ca^{2+} accumulation and NAD(P)H/FAD recovery [9].	No directly corresponding evidence.	Enhanced mitochondrial Ca^{2+} uptake reduced arrhythmogenic Ca^{2+} release [9].
MCU supports acute metabolic adaptation	Direct causal evidence in human atria unavailable.	Mcu deletion impaired cardiac metabolic and contractile adaptation [10,11].	MCU couples Ca^{2+} uptake to workload-dependent metabolism [10,11].
Disrupted SR–mitochondrial coupling	Reduced contacts and MFN2 expression in AF atria [9,13].	MFN2 deficiency impaired cardiac function in Drosophila [13].	MFN2 overexpression preserved organelle coupling [13].

Table 4. *Cont.*

Claim	Human Evidence	Animal Evidence	Mechanistic Evidence
Excessive mitochondrial Ca^{2+} causes cardiac injury	Direct evidence in metabolic AF unavailable.	NCLX deletion induced Ca^{2+} overload and cardiac injury [28].	MCU Cys-97 S-glutathionylation enhanced Ca^{2+} uptake, ROS and cell death [38].
Oxidative stress promotes abnormal Ca^{2+} handling	Increased RyR2 oxidation and mitochondrial oxidative damage [36,37].	Reducing mitochondrial ROS or RyR2 leak prevented AF [37].	Mitochondrial ROS and RyR2 leak form an amplification loop [37].
Inflammation promotes atrial remodeling	Increased NLRP3 activity and epicardial macrophage accumulation [40,41].	NLRP3 activation promoted AF; macrophage depletion reduced AF [40,41].	NLRP3 promoted abnormal SR Ca^{2+} release; mitochondrial effects remain unproven [41].
AF aggravates metabolic dysfunction	Altered mitochondrial energetics and lipid metabolism [12,49].	Rapid pacing reduced ATP and mitochondrial biogenesis [50].	Irregular pacing altered substrate uptake; tachypacing impaired mitochondrial function [12,49].
Mismatch–AF outcome relationships remain unvalidated	mt-cfDNA and left atrial strain were associated with recurrence [61,62].	Direct evidence unavailable.	An independent mismatch–outcome relationship remains unvalidated.
1HFpEF may amplify mismatch	HFpEF–AF clinical overlap is documented [73,75].	HFpEF mouse models showed nitrosative stress, without direct atrial mismatch assessment [74].	Hemodynamic and microvascular stress provide a proposed framework [78,80].

10. Conclusions

Metabolic AF is unlikely to be explained by electrical remodeling alone. The concept of mitochondrial calcium response mismatch provides a mechanistically coherent framework linking obesity, insulin resistance, lipotoxicity, oxidative stress, inflammation, and atrial cardiomyopathy to the high-AF burden and high recurrence risk observed in clinical practice. By placing impaired excitation–metabolism coupling at the center of the disease model, this perspective helps explain why the metabolically stressed atrium is electrically unstable and less responsive to rhythm-control strategies. More importantly, it suggests that effective management may require a shift from a purely electrophysiological paradigm toward one that also restores metabolic flexibility, preserves mitochondrial adaptation, and improves atrial stress tolerance. If validated experimentally and clinically, this framework may open a new direction for risk stratification and therapy in metabolic AF.

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References

1. Bode, D.; Pronto, J.R.D.; Schiattarella, G.G.; Voigt, N. Metabolic remodelling in atrial fibrillation: Manifestations, mechanisms and clinical implications. *Nat. Rev. Cardiol.* **2024**, *21*, 682–700. [CrossRef]
2. Qin, X.; Jin, L.; Gong, H.; Zheng, Q. Electro-metabolic coupling in atrial fibrillation: A deeper understanding of the metabolic driver. *Biomed. Pharmacother.* **2024**, *180*, 117536. [CrossRef]
3. Becher, N.; Metzner, A.; Toennis, T.; Kirchhof, P.; Schnabel, R.B. Atrial fibrillation burden: A new outcome predictor and therapeutic target. *Eur. Heart J.* **2024**, *45*, 2824–2838. [CrossRef]
4. Shu, H.; Cheng, J.; Li, N.; Zhang, Z.; Nie, J.; Peng, Y.; Wang, Y.; Wang, D.W.; Zhou, N. Obesity and atrial fibrillation: A narrative review from arrhythmogenic mechanisms to clinical significance. *Cardiovasc. Diabetol.* **2023**, *22*, 192. [CrossRef]
5. Xia, Y.; Li, X.F.; Liu, J.; Yu, M.; Fang, P.H.; Zhang, S. The influence of metabolic syndrome on atrial fibrillation recurrence: Five-year outcomes after a single cryoballoon ablation procedure. *J. Geriatr. Cardiol.* **2021**, *18*, 1019–1028. [CrossRef]
6. McCauley, M.D.; Iacobellis, G.; Li, N.; Nattel, S.; Goldberger, J.J. Targeting the Substrate for Atrial Fibrillation: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **2024**, *83*, 2015–2027.
7. Kosmach, A.; Roman, B.; Sun, J.; Femnou, A.; Zhang, F.; Liu, C.; Combs, C.A.; Balaban, R.S.; Murphy, E. Monitoring mitochondrial calcium and metabolism in the beating MCU-KO heart. *Cell Rep.* **2021**, *37*, 109846. [CrossRef]
8. Fossier, L.; Panel, M.; Butruille, L.; Colombani, S.; Azria, L.; Woitrain, E.; Decoin, R.; Torrente, A.G.; Thireau, J.; Lacampagne, A.; et al. Enhanced Mitochondrial Calcium Uptake Suppresses Atrial Fibrillation Associated with Metabolic Syndrome. *J. Am. Coll. Cardiol.* **2022**, *80*, 2205–2219. [CrossRef]
9. Pronto, J.R.D.; Mason, F.E.; Rog-Zielinska, E.A.; Fakuade, F.E.; Bülow, D.; Tóth, M.; Machwart, K.; Brandes, P.; Wiedmann, F.; Kohlhaas, M.; et al. Impaired Atrial Mitochondrial Calcium Handling in Patients with Atrial Fibrillation. *Circ. Res.* **2025**, *137*, 1333–1352. [CrossRef]
10. Luongo, T.S.; Lambert, J.P.; Yuan, A.; Zhang, X.; Gross, P.; Song, J.; Shanmughapriya, S.; Gao, E.; Jain, M.; Houser, S.R.; et al. The Mitochondrial Calcium Uniporter Matches Energetic Supply with Cardiac Workload during Stress and Modulates Permeability Transition. *Cell Rep.* **2015**, *12*, 23–34. [CrossRef]
11. Kwong, J.Q.; Lu, X.; Correll, R.N.; Schwanekamp, J.A.; Vagnozzi, R.J.; Sargent, M.A.; York, A.J.; Zhang, J.; Bers, D.M.; Molkentin, J.D. The Mitochondrial Calcium Uniporter Selectively Matches Metabolic Output to Acute Contractile Stress in the Heart. *Cell Rep.* **2015**, *12*, 15–22. [CrossRef]
12. Wiersma, M.; van Marion, D.M.S.; Wüst, R.C.I.; Houtkooper, R.H.; Zhang, D.; de Groot, N.M.S.; Henning, R.H.; Brundel, B.J.J.M. Mitochondrial Dysfunction Underlies Cardiomyocyte Remodeling in Experimental and Clinical Atrial Fibrillation. *Cells* **2019**, *8*, 1202. [CrossRef]
13. Li, J.; Qi, X.; Ramos, K.S.; Lanters, E.; Keijer, J.; de Groot, N.; Brundel, B.; Zhang, D. Disruption of Sarcoplasmic Reticulum-Mitochondrial Contacts Underlies Contractile Dysfunction in Experimental and Human Atrial Fibrillation: A Key Role of Mitofusin 2. *J. Am. Heart Assoc.* **2022**, *11*, e024478. [CrossRef]
14. Bertero, E.; Nickel, A.; Kohlhaas, M.; Hohl, M.; Sequeira, V.; Brune, C.; Schwemmlein, J.; Abeßer, M.; Schuh, K.; Kutschka, I.; et al. Loss of Mitochondrial Ca^{2+} Uniporter Limits Inotropic Reserve and Provides Trigger and Substrate for Arrhythmias in Barth Syndrome Cardiomyopathy. *Circulation* **2021**, *144*, 1694–1713. [CrossRef]
15. Balderas, E.; Lee, S.H.J.; Rai, N.K.; Mollinedo, D.M.; Duron, H.E.; Chaudhuri, D. Mitochondrial Calcium Regulation of Cardiac Metabolism in Health and Disease. *Physiology* **2024**, *39*, 247–268. [CrossRef]
16. Garbincius, J.F.; Elrod, J.W. Mitochondrial calcium exchange in physiology and disease. *Physiol. Rev.* **2022**, *102*, 893–992. [CrossRef]
17. De Stefani, D.; Raffaello, A.; Teardo, E.; Szabò, I.; Rizzuto, R. A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. *Nature* **2011**, *476*, 336–340. [CrossRef]
18. Baughman, J.M.; Perocchi, F.; Girgis, H.S.; Plovanich, M.; Belcher-Timme, C.A.; Sancak, Y.; Bao, X.R.; Strittmatter, L.; Goldberger, O.; Bogorad, R.L.; et al. Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter. *Nature* **2011**, *476*, 341–345. [CrossRef]
19. Csordás, G.; Golenár, T.; Seifert, E.L.; Kamer, K.J.; Sancak, Y.; Perocchi, F.; Moffat, C.; Weaver, D.; Perez, S.F.; Bogorad, R.; et al. MICU1 controls both the threshold and cooperative activation of the mitochondrial Ca^{2+} uniporter. *Cell Metab.* **2013**, *17*, 976–987. [CrossRef]
20. Paillard, M.; Csordás, G.; Szanda, G.; Golenár, T.; Debattisti, V.; Bartok, A.; Wang, N.; Moffat, C.; Seifert, E.L.; Spät, A.; et al. Tissue-Specific Mitochondrial Decoding of Cytoplasmic Ca(2+) Signals Is Controlled by the Stoichiometry of MICU1/2 and MCU. *Cell Rep.* **2017**, *18*, 2291–2300. [CrossRef]
21. Min, C.K.; Yeom, D.R.; Lee, K.E.; Kwon, H.K.; Kang, M.; Kim, Y.S.; Park, Z.Y.; Jeon, H.; Kim, D.H. Coupling of ryanodine receptor 2 and voltage-dependent anion channel 2 is essential for Ca^{2+} transfer from the sarcoplasmic reticulum to the mitochondria in the heart. *Biochem J.* **2012**, *447*, 371–379. [CrossRef]

22. Jhun, B.S.; O-Uchi, J.; Rhee, B.; Ahrari, A.; DeMichaelis, N.; Jeon, K.I.; Booth, D.M.; Sheu, S.S. Sarcoplasmic reticulum-mitochondria microdomains: Hugging and kissing in the heart. *Am. J. Physiol. Cell Physiol.* **2025**, *329*, C599–C610. [CrossRef]
23. Kohlhaas, M.; Nickel, A.G.; Maack, C. Mitochondrial energetics and calcium coupling in the heart. *J. Physiol.* **2017**, *595*, 3753–3763. [CrossRef]
24. Honka, H.; Solis-Herrera, C.; Triplitt, C.; Norton, L.; Butler, J.; DeFronzo, R.A. Therapeutic Manipulation of Myocardial Metabolism: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2021**, *77*, 2022–2039.
25. Francisco, A.; Figueira, T.R.; Castilho, R.F. Mitochondrial NAD(P)$^+$ Transhydrogenase: From Molecular Features to Physiology and Disease. *Antioxid. Redox Signal* **2022**, *36*, 864–884. [CrossRef]
26. Murphy, E.; Liu, J.C. Mitochondrial calcium and reactive oxygen species in cardiovascular disease. *Cardiovasc Res.* **2023**, *119*, 1105–1116. [CrossRef]
27. Ozcan, C.; Li, Z.; Kim, G.; Jeevanandam, V.; Uriel, N. Molecular Mechanism of the Association Between Atrial Fibrillation and Heart Failure Includes Energy Metabolic Dysregulation Due to Mitochondrial Dysfunction. *J. Card. Fail* **2019**, *25*, 911–920. [CrossRef]
28. Luongo, T.S.; Lambert, J.P.; Gross, P.; Nwokedi, M.; Lombardi, A.A.; Shanmughapriya, S.; Carpenter, A.C.; Kolmetzky, D.; Gao, E.; van Berlo, J.H.; et al. The mitochondrial Na^+/Ca^{2+} exchanger is essential for Ca^{2+} homeostasis and viability. *Nature* **2017**, *545*, 93–97. [CrossRef]
29. Hasan, P.; Berezhnaya, E.; Rodríguez-Prados, M.; Weaver, D.; Bekeova, C.; Cartes-Saavedra, B.; Birch, E.; Beyer, A.M.; Santos, J.H.; Seifert, E.L.; et al. MICU1 and MICU2 control mitochondrial calcium signaling in the mammalian heart. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2402491121. [CrossRef]
30. Suffee, N.; Baptista, E.; Piquereau, J.; Ponnaiah, M.; Doisne, N.; Ichou, F.; Lhomme, M.; Pichard, C.; Galand, V.; Mougenot, N.; et al. Impacts of a high-fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. *Cardiovasc Res.* **2022**, *118*, 3126–3139. [CrossRef]
31. Chan, J.S.F.; Shafaati, T.; Ussher, J.R. Cardiac substrate metabolism in type 2 diabetes. *Biochem. J.* **2025**, *482*, 499–518. [CrossRef]
32. Panwar, A.; Malik, S.O.; Adib, M.; Lopaschuk, G.D. Cardiac energy metabolism in diabetes: Emerging therapeutic targets and clinical implications. *Am. J. Physiol.-Heart Circ. Physiol.* **2025**, *328*, H1089–H1112. [CrossRef]
33. Bekhite, M.; González-Delgado, A.; Hübner, S.; Haxhikadrija, P.; Kretzschmar, T.; Müller, T.; Wu, J.M.F.; Bekfani, T.; Franz, M.; Wartenberg, M.; et al. The role of ceramide accumulation in human induced pluripotent stem cell-derived cardiomyocytes on mitochondrial oxidative stress and mitophagy. *Free Radic. Biol. Med.* **2021**, *167*, 66–80. [CrossRef]
34. Bhatti, J.S.; Sehrawat, A.; Mishra, J.; Sidhu, I.S.; Navik, U.; Khullar, N.; Kumar, S.; Bhatti, G.K.; Reddy, P.H. Oxidative stress in the pathophysiology of type 2 diabetes and related complications: Current therapeutics strategies and future perspectives. *Free Radic. Biol. Med.* **2022**, *184*, 114–134. [CrossRef]
35. Berthiaume, J.M.; Kurdys, J.G.; Muntean, D.M.; Rosca, M.G. Mitochondrial NAD(+)/NADH Redox State and Diabetic Cardiomyopathy. *Antioxid. Redox Signal* **2019**, *30*, 375–398. [CrossRef]
36. Emelyanova, L.; Ashary, Z.; Cosic, M.; Negmadjanov, U.; Ross, G.; Rizvi, F.; Olet, S.; Kress, D.; Sra, J.; Tajik, A.J.; et al. Selective downregulation of mitochondrial electron transport chain activity and increased oxidative stress in human atrial fibrillation. *Am. J. Physiol. Heart Circ. Physiol.* **2016**, *311*, H54–H63. [CrossRef]
37. Xie, W.; Santulli, G.; Reiken, S.R.; Yuan, Q.; Osborne, B.W.; Chen, B.X.; Marks, A.R. Mitochondrial oxidative stress promotes atrial fibrillation. *Sci. Rep.* **2015**, *5*, 11427. [CrossRef]
38. Dong, Z.; Shanmughapriya, S.; Tomar, D.; Siddiqui, N.; Lynch, S.; Nemani, N.; Breves, S.L.; Zhang, X.; Tripathi, A.; Palaniappan, P.; et al. Mitochondrial Ca^{2+} Uniporter Is a Mitochondrial Luminal Redox Sensor that Augments MCU Channel Activity. *Mol. Cell* **2017**, *65*, 1014–1028.e1017. [CrossRef]
39. Ajoolabady, A.; Nattel, S.; Lip, G.Y.H.; Ren, J. Inflammasome Signaling in Atrial Fibrillation: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2022**, *79*, 2349–2366.
40. Crepin, L.; Dasari, A.; Mougenot, N.; Trenquier, E.; Lanthiez, F.; Abdou, I.; Mihoc, M.; de Raymon-Cahuzac, A.; Ponnaiah, M.; Karkeni, E.; et al. Epicardial Fat Drives Macrophage Response in Atrial Cardiomyopathy. *Circ. Res.* **2026**, *139*, e328051. [CrossRef]
41. Yao, C.; Veleva, T.; Scott, L., Jr.; Cao, S.; Li, L.; Chen, G.; Jeyabal, P.; Pan, X.; Alsina, K.M.; Abu-Taha, I.D.; et al. Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation. *Circulation* **2018**, *138*, 2227–2242. [CrossRef]
42. Florea, S.M.; Blatter, L.A. Regulation of cardiac alternans by β-adrenergic signaling pathways. *Am. J. Physiol. Heart Circ. Physiol.* **2012**, *303*, H1047–H1056. [CrossRef]
43. Shattock, M.J.; Ottolia, M.; Bers, D.M.; Blaustein, M.P.; Boguslavskyi, A.; Bossuyt, J.; Bridge, J.H.; Chen-Izu, Y.; Clancy, C.E.; Edwards, A.; et al. Na^+/Ca^{2+} exchange and Na^+/K^+-ATPase in the heart. *J. Physiol.* **2015**, *593*, 1361–1382. [CrossRef]
44. Voigt, N.; Li, N.; Wang, Q.; Wang, W.; Trafford, A.W.; Abu-Taha, I.; Sun, Q.; Wieland, T.; Ravens, U.; Nattel, S.; et al. Enhanced sarcoplasmic reticulum Ca^{2+} leak and increased Na^+-Ca^{2+} exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* **2012**, *125*, 2059–2070. [CrossRef]
45. Foster, M.N.; Coetzee, W.A. K_{ATP} Channels in the Cardiovascular System. *Physiol. Rev.* **2016**, *96*, 177–252.

46. Avula, U.M.R.; Abrams, J.; Katchman, A.; Zakharov, S.; Mironov, S.; Bayne, J.; Roybal, D.; Gorti, A.; Yang, L.; Iyer, V.; et al. Heterogeneity of the action potential duration is required for sustained atrial fibrillation. *JCI Insight* **2019**, *5*, e128765.
47. Murphy, M.P. How mitochondria produce reactive oxygen species. *Biochem J.* **2009**, *417*, 1–13. [CrossRef]
48. Pfenniger, A.; Yoo, S.; Arora, R. Oxidative stress and atrial fibrillation. *J. Mol. Cell Cardiol.* **2024**, *196*, 141–151. [CrossRef]
49. Lenski, M.; Schleider, G.; Kohlhaas, M.; Adrian, L.; Adam, O.; Tian, Q.; Kaestner, L.; Lipp, P.; Lehrke, M.; Maack, C.; et al. Arrhythmia causes lipid accumulation and reduced glucose uptake. *Basic Res. Cardiol.* **2015**, *110*, 40. [CrossRef]
50. Dong, J.; Zhao, J.; Zhang, M.; Liu, G.; Wang, X.; Liu, Y.; Yang, N.; Liu, Y.; Zhao, G.; Sun, J.; et al. B3-Adrenoceptor Impairs Mitochondrial Biogenesis and Energy Metabolism During Rapid Atrial Pacing-Induced Atrial Fibrillation. *J. Cardiovasc Pharmacol. Ther.* **2016**, *21*, 114–126. [CrossRef]
51. Carnes, C.A.; Chung, M.K.; Nakayama, T.; Nakayama, H.; Baliga, R.S.; Piao, S.; Kanderian, A.; Pavia, S.; Hamlin, R.L.; McCarthy, P.M.; et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circ. Res.* **2001**, *89*, E32-38. [CrossRef]
52. Schotten, U.; Goette, A.; Verheule, S. Translation of pathophysiological mechanisms of atrial fibrosis into new diagnostic and therapeutic approaches. *Nat. Rev. Cardiol.* **2025**, *22*, 225–240. [CrossRef]
53. Ravelli, F. Mechano-electric feedback and atrial fibrillation. *Prog. Biophys. Mol. Biol.* **2003**, *82*, 137–149. [CrossRef]
54. Honarbakhsh, S.; Roney, C.; Horrach, C.V.; Lambiase, P.D.; Hunter, R.J. Autonomic modulation impacts conduction velocity dynamics and wavefront propagation in the left atrium. *Europace* **2024**, *26*, euae219. [CrossRef]
55. Zhang, A.; Li, H.; Song, Q.; Cui, Y.; Zhang, Y.; Wang, X.; Li, Z.; Hou, Y. High-fat stimulation induces atrial neural remodeling by reducing NO production via the CRIF1/eNOS/P21 axi. *Lipids Health Dis.* **2023**, *22*, 189. [CrossRef]
56. Venteclef, N.; Guglielmi, V.; Balse, E.; Gaborit, B.; Cotillard, A.; Atassi, F.; Amour, J.; Leprince, P.; Dutour, A.; Clément, K.; et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. *Eur. Heart J.* **2015**, *36*, 795–805a. [CrossRef]
57. Nalliah, C.J.; Bell, J.R.; Raaijmakers, A.J.A.; Waddell, H.M.; Wells, S.P.; Bernasochi, G.B.; Montgomery, M.K.; Binny, S.; Watts, T.; Joshi, S.B.; et al. Epicardial Adipose Tissue Accumulation Confers Atrial Conduction Abnormality. *J. Am. Coll. Cardiol.* **2020**, *76*, 1197–1211. [CrossRef]
58. Zhang, D.; Hu, X.; Li, J.; Liu, J.; Baks-Te Bulte, L.; Wiersma, M.; Malik, N.U.; van Marion, D.M.S.; Tolouee, M.; Hoogstra-Berends, F.; et al. DNA damage-induced PARP1 activation confers cardiomyocyte dysfunction through NAD(+) depletion in experimental atrial fibrillation. *Nat. Commun.* **2019**, *10*, 1307. [CrossRef]
59. Chang, Y.; Zou, Q. Mitochondrial calcium homeostasis and atrial fibrillation: Mechanisms and therapeutic strategies review. *Curr. Probl. Cardiol.* **2025**, *50*, 102988. [CrossRef]
60. Mohsin, N.; Matsumura, M.E.; Ahmad, T.; Sahar, K.U.; Mohammed, L. Conventional and Emerging Biomarkers for Predicting Post-Ablation Atrial Fibrillation Recurrence: An Updated Systematic Review. *Cardiol. Res.* **2026**, *17*, 361–378. [CrossRef]
61. Takahashi, T.; Soeki, T.; Tezuka, K.; Matsuura, T.; Uematsu, E.; Aibara, H.; Bando, R.; Zheng, R.; Takahashi, T.; Saijo, Y.; et al. Circulating mitochondrial cell-free DNA levels are associated with the recurrence of atrial fibrillation after catheter ablation for atrial fibrillation. *Am. Heart J. Plus* **2025**, *60*, 100638. [CrossRef]
62. Khan, H.R.; Yakupoglu, H.Y.; Kralj-Hans, I.; Haldar, S.; Bahrami, T.; Clague, J.; De Souza, A.; Hussain, W.; Jarman, J.; Jones, D.G.; et al. Left Atrial Function Predicts Atrial Arrhythmia Recurrence Following Ablation of Long-Standing Persistent Atrial Fibrillation. *Circ. Cardiovasc Imaging* **2023**, *16*, e015352. [CrossRef]
63. Chen, P.; Shi, Y.; Ju, J.; Pan, D.; Miao, L.; Guo, X.; Chen, Z.; Du, J. Left atrial appendage flow velocity predicts recurrence of atrial fibrillation after catheter ablation: A systematic review and meta-analysis. *Front Cardiovasc Med.* **2022**, *9*, 971848. [CrossRef]
64. Fakuade, F.E.; Steckmeister, V.; Seibertz, F.; Gronwald, J.; Kestel, S.; Menzel, J.; Pronto, J.R.D.; Taha, K.; Haghighi, F.; Kensah, G.; et al. Altered atrial cytosolic calcium handling contributes to the development of postoperative atrial fibrillation. *Cardiovasc Res.* **2021**, *117*, 1790–1801. [CrossRef]
65. Kanaan, G.N.; Patten, D.A.; Redpath, C.J.; Harper, M.E. Atrial Fibrillation Is Associated with Impaired Atrial Mitochondrial Energetics and Supercomplex Formation in Adults with Type 2 Diabetes. *Can. J. Diabetes* **2019**, *43*, 67–75.e61. [CrossRef]
66. Neef, S.; Dybkova, N.; Sossalla, S.; Ort, K.R.; Fluschnik, N.; Neumann, K.; Seipelt, R.; Schöndube, F.A.; Hasenfuss, G.; Maier, L.S. CaMKII-dependent diastolic SR Ca^{2+} leak and elevated diastolic Ca^{2+} levels in right atrial myocardium of patients with atrial fibrillation. *Circ. Res.* **2010**, *106*, 1134–1144. [CrossRef]
67. Hove-Madsen, L.; Llach, A.; Bayes-Genís, A.; Roura, S.; Rodriguez Font, E.; Arís, A.; Cinca, J. Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. *Circulation* **2004**, *110*, 1358–1363. [CrossRef]
68. Llach, A.; Molina, C.E.; Prat-Vidal, C.; Fernandes, J.; Casadó, V.; Ciruela, F.; Lluís, C.; Franco, R.; Cinca, J.; Hove-Madsen, L. Abnormal calcium handling in atrial fibrillation is linked to up-regulation of adenosine A2A receptors. *Eur. Heart J.* **2011**, *32*, 721–729. [CrossRef]

69. Schotten, U.; Greiser, M.; Benke, D.; Buerkel, K.; Ehrenteidt, B.; Stellbrink, C.; Vazquez-Jimenez, J.F.; Schoendube, F.; Hanrath, P.; Allessie, M. Atrial fibrillation-induced atrial contractile dysfunction: A tachycardiomyopathy of a different sort. *Cardiovasc Res.* **2002**, *53*, 192–201. [CrossRef]
70. Sossalla, S.; Kallmeyer, B.; Wagner, S.; Mazur, M.; Maurer, U.; Toischer, K.; Schmitto, J.D.; Seipelt, R.; Schöndube, F.A.; Hasenfuss, G.; et al. Altered Na(+) currents in atrial fibrillation effects of ranolazine on arrhythmias and contractility in human atrial myocardium. *J. Am. Coll. Cardiol.* **2010**, *55*, 2330–2342.
71. Wu, L.; He, Y.; Peng, L.; Liu, L.; Tao, X. Predictive accuracy of left atrial strain parameters for risk of atrial fibrillation recurrence: A systematic review and meta-analysis. *Front Med.* **2026**, *13*, 1798092. [CrossRef]
72. Mirza, M.; Caracciolo, G.; Khan, U.; Mori, N.; Saha, S.K.; Srivathsan, K.; Altemose, G.; Scott, L.; Sengupta, P.; Jahangir, A. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: A two-dimensional speckle strain study. *J. Interv. Card. Electrophysiol.* **2011**, *31*, 197–206. [CrossRef]
73. Borlaug, B.A.; Sharma, K.; Shah, S.J.; Ho, J.E. Heart Failure with Preserved Ejection Fraction: JACC Scientific Statement. *J. Am. Coll. Cardiol.* **2023**, *81*, 1810–1834. [CrossRef]
74. Schiattarella, G.G.; Altamirano, F.; Tong, D.; French, K.M.; Villalobos, E.; Kim, S.Y.; Luo, X.; Jiang, N.; May, H.I.; Wang, Z.V.; et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature* **2019**, *568*, 351–356. [CrossRef]
75. Haykal, R.; Kassar, A.; Chamoun, N.; Akoum, N. The left atrium in heart failure with preserved ejection fraction: What we know and what we do not know. *Heart Rhythm O2* **2025**, *6*, 1028–1038. [CrossRef]
76. Velollari, O.; Rommel, K.-P.; Kresoja, K.-P.; Lurz, P.; Gori, T. Focusing on microvascular function in heart failure with preserved ejection fraction. *Heart Fail. Rev.* **2025**, *30*, 493–503. [CrossRef]
77. Omote, K.; Verbrugge, F.H.; Borlaug, B.A. Heart Failure with Preserved Ejection Fraction: Mechanisms and Treatment Strategies. *Annu Rev. Med.* **2022**, *73*, 321–337. [CrossRef]
78. Paulus, W.J.; Tschöpe, C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. *J. Am. Coll. Cardiol.* **2013**, *62*, 263–271.
79. Gorica, E.; Geiger, M.A.; Di Venanzio, L.; Atzemian, N.; Kleeberger, J.A.; Grigorian, D.; Mongelli, A.; Emini Veseli, B.; Mohammed, S.A.; Ruschitzka, F.; et al. Cardiometabolic heart failure with preserved ejection fraction: From molecular signatures to personalized treatment. *Cardiovasc. Diabetol.* **2025**, *24*, 265. [CrossRef]
80. Wang, Y.; Zhang, J.; Wang, Z.; Wang, C.; Ma, D. Endothelial-cell-mediated mechanism of coronary microvascular dysfunction leading to heart failure with preserved ejection fraction. *Heart Fail. Rev.* **2023**, *28*, 169–178. [CrossRef]
81. Newman, J.D.; O'Meara, E.; Böhm, M.; Savarese, G.; Kelly, P.R.; Vardeny, O.; Allen, L.A.; Lancellotti, P.; Gottlieb, S.S.; Samad, Z.; et al. Implications of Atrial Fibrillation for Guideline-Directed Therapy in Patients with Heart Failure. *JACC* **2024**, *83*, 932–950. [CrossRef]
82. Chieng, D.; Sugumar, H.; Segan, L.; Tan, C.; Vizi, D.; Nanayakkara, S.; Al-Kaisey, A.; Hawson, J.; Prabhu, S.; Voskoboinik, A.; et al. Atrial Fibrillation Ablation for Heart Failure with Preserved Ejection Fraction: A Randomized Controlled Trial. *JACC Heart Fail* **2023**, *11*, 646–658. [CrossRef]
83. Van Gelder, I.C.; Rienstra, M.; Bunting, K.V.; Casado-Arroyo, R.; Caso, V.; Crijns, H.; De Potter, T.J.R.; Dwight, J.; Guasti, L.; Hanke, T.; et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **2024**, *45*, 3314–3414. [CrossRef]
84. Pathak, R.K.; Middeldorp, M.E.; Meredith, M.; Mehta, A.B.; Mahajan, R.; Wong, C.X.; Twomey, D.; Elliott, A.D.; Kalman, J.M.; Abhayaratna, W.P.; et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J. Am. Coll. Cardiol.* **2015**, *65*, 2159–2169.
85. Pathak, R.K.; Elliott, A.D.; Lau, D.H.; Middeldorp, M.E.; Linz, D.; Fitzgerald, J.L.; Gupta, A.; Ariyaratnam, J.P.; Malik, V.; Noubiap, J.J.; et al. Aggressive Risk Factor Reduction Study for Atrial Fibrillation Implications for Ablation Outcomes: The ARREST-AF Randomized Clinical Trial. *JAMA Cardiol.* **2025**, *10*, 1295–1304.
86. Elliott, A.D.; Verdicchio, C.V.; Mahajan, R.; Middeldorp, M.E.; Gallagher, C.; Mishima, R.S.; Hendriks, J.M.L.; Pathak, R.K.; Thomas, G.; Lau, D.H.; et al. An Exercise and Physical Activity Program in Patients with Atrial Fibrillation: The ACTIVE-AF Randomized Controlled Trial. *JACC Clin. Electrophysiol.* **2023**, *9*, 455–465.
87. Mendham, A.E.; Goedecke, J.H.; Zeng, Y.; Larsen, S.; George, C.; Hauksson, J.; Fortuin-de Smidt, M.C.; Chibalin, A.V.; Olsson, T.; Chorell, E. Exercise training improves mitochondrial respiration and is associated with an altered intramuscular phospholipid signature in women with obesity. *Diabetologia* **2021**, *64*, 1642–1659. [CrossRef]
88. Robinson, M.M.; Dasari, S.; Konopka, A.R.; Johnson, M.L.; Manjunatha, S.; Esponda, R.R.; Carter, R.E.; Lanza, I.R.; Nair, K.S. Enhanced Protein Translation Underlies Improved Metabolic and Physical Adaptations to Different Exercise Training Modes in Young and Old Humans. *Cell Metab.* **2017**, *25*, 581–592. [CrossRef]
89. Usman, M.S.; Bhatt, D.L.; Hameed, I.; Anker, S.D.; Cheng, A.Y.Y.; Hernandez, A.F.; Jones, W.S.; Khan, M.S.; Petrie, M.C.; Udell, J.A.; et al. Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* **2024**, *12*, 447–461. [CrossRef]

90. Lincoff, A.M.; Brown-Frandsen, K.; Colhoun, H.M.; Deanfield, J.; Emerson, S.S.; Esbjerg, S.; Hardt-Lindberg, S.; Hovingh, G.K.; Kahn, S.E.; Kushner, R.F.; et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N. Engl. J. Med.* **2023**, *389*, 2221–2232. [CrossRef]
91. Saglietto, A.; Falasconi, G.; Penela, D.; Francia, P.; Sau, A.; Ng, F.S.; Dusi, V.; Castagno, D.; Gaita, F.; Berruezo, A.; et al. Glucagon-like peptide-1 receptor agonist semaglutide reduces atrial fibrillation incidence: A systematic review and meta-analysis. *Eur. J. Clin. Investig.* **2024**, *54*, e14292. [CrossRef]
92. Yang, Z.; Wang, J.; Jiang, C.; Guo, H.; Li, M.; Zhao, Z.; Zhao, M.; Li, S.; Lai, Y.; He, L.; et al. Association between the preprocedural serum potassium level and atrial fibrillation recurrence after catheter ablation. *Heart Rhythm* **2024**, *21*, 2429–2436. [CrossRef]
93. Benz, A.P.; Amit, G.; Connolly, S.J.; Singh, J.; Acosta-Vélez, J.G.; Conen, D.; Deif, B.; Divakaramenon, S.; McIntyre, W.F.; Mtwesi, V.; et al. Colchicine to Prevent Atrial Fibrillation Recurrence After Catheter Ablation: A Randomized, Placebo-Controlled Trial. *Circ. Arrhythm. Electrophysiol.* **2024**, *17*, e01238. [CrossRef]
94. Schweitzer, M.K.; Wilting, F.; Sedej, S.; Dreizehnter, L.; Dupper, N.J.; Tian, Q.; Moretti, A.; My, I.; Kwon, O.; Priori, S.G.; et al. Suppression of Arrhythmia by Enhancing Mitochondrial Ca^{2+} Uptake in Catecholaminergic Ventricular Tachycardia Models. *JACC Basic Transl. Sci.* **2017**, *2*, 737–747. [CrossRef]
95. Woods, J.J.; Nemani, N.; Shanmughapriya, S.; Kumar, A.; Zhang, M.; Nathan, S.R.; Thomas, M.; Carvalho, E.; Ramachandran, K.; Srikantan, S.; et al. A Selective and Cell-Permeable Mitochondrial Calcium Uniporter (MCU) Inhibitor Preserves Mitochondrial Bioenergetics after Hypoxia/Reoxygenation Injury. *ACS Cent. Sci.* **2019**, *5*, 153–166. [CrossRef]
96. Di Marco, G.; Vallese, F.; Jourde, B.; Bergsdorf, C.; Sturlese, M.; De Mario, A.; Techer-Etienne, V.; Haasen, D.; Oberhauser, B.; Schleeger, S.; et al. A High-Throughput Screening Identifies MICU1 Targeting Compounds. *Cell Rep.* **2020**, *30*, 2321–2331.e2326. [CrossRef]
97. Liu, T.; Takimoto, E.; Dimaano, V.L.; DeMazumder, D.; Kettlewell, S.; Smith, G.; Sidor, A.; Abraham, T.P.; O'Rourke, B. Inhibiting mitochondrial Na^+/Ca^{2+} exchange prevents sudden death in a Guinea pig model of heart failure. *Circ. Res.* **2014**, *115*, 44–54. [CrossRef]
98. Neumann, J.T.; Diaz-Sylvester, P.L.; Fleischer, S.; Copello, J.A. CGP-37157 inhibits the sarcoplasmic reticulum Ca^{2+} ATPase and activates ryanodine receptor channels in striated muscle. *Mol. Pharmacol.* **2011**, *79*, 141–147. [CrossRef]
99. Hunt, T.E.; Traaen, G.M.; Aakerøy, L.; Bendz, C.; Øverland, B.; Akre, H.; Steinshamn, S.; Loennechen, J.P.; Hegbom, F.; Broch, K.; et al. Effect of continuous positive airway pressure therapy on recurrence of atrial fibrillation after pulmonary vein isolation in patients with obstructive sleep apnea: A randomized controlled trial. *Heart Rhythm* **2022**, *19*, 1433–1441. [CrossRef]

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