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Mitochondria and Arrhythmias

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Abstract

Mitochondria are essential to providing ATP thereby satisfying the energy demand of the incessant electrical activity and contractile action of cardiac muscle. Emerging evidence indicates that mitochondrial dysfunction can adversely impact cardiac electrical functioning by impairing the intracellular ion homeostasis and membrane excitability through reduced ATP production and excessive reactive oxidative species (ROS) generation, resulting in increased propensity to cardiac arrhythmias. In this review, the molecular mechanisms linking mitochondrial dysfunction to cardiac arrhythmias are discussed with an emphasis on the impact of increased mitochondrial ROS on the cardiac ion channels and transporters that are critical to maintaining normal electromechanical functioning of the cardiomyocytes. The potential of using mitochondria-targeted antioxidants as a novel anti-arrhythmia therapy is highlighted.

Introduction

The normal functioning heart requires coordinated, rhythmic electrical activity and contractile action. At rest, the heart pumps about 280 liters of blood throughout the human body per hour, and the energy demand to meet this unceasing action consumes nearly 10% of the total body O_2 uptake [1]. Over 90% of the cellular ATP consumed in the heart is produced by the mitochondria through oxidative phosphorylation (OXPHOS) [2]. As the predominant energy generator in the heart, mitochondria account for ~30% of the volume of cardiac cells, forming a network surrounding sarcoplasmic reticulum (SR), myofilaments

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Conflict of Interest:
Dr. Dudley is an inventor of 13/551,790 A Method for Ameliorating or Preventing Arrhythmic Risk Associated with Cardiomyopathy by Improving Conduction Velocity and 13/507,319 A Method for Modulating or Controlling Connexin43 (Cx43) Level of a Cell and Reducing Arrhythmic Risk

and t-tubules [3]. It is estimated that one third of the cardiac ATP generated by mitochondria is used for sarcolemmal and SR ion channels and transporters, which are required for the electrical activity of the cardiac cells [4]. Therefore, mitochondrial dysfunction readily disrupts the cardiac rhythm through depleting energy supply to these channels and transporters [5, 6].

In addition to producing ATP, mitochondria also generate reactive oxygen species (ROS) as a by-product of OXPHOS. It is now widely accepted that in addition to their critical bioenergetic function, mitochondria function as signaling hubs in large part by regulating redox signaling in the cell [7, 8]. Under physiological conditions, trace amount of ROS establish a network of mitochondria-driven signals that integrate metabolism with gene transcription and enzymatic activity [9, 10]. Short term increases in ROS signals trigger adaptive responses and facilitate preconditioning, increasing cellular and tissue resistance against insult [11, 12]. On the other hand, persistently elevated ROS levels can trigger maladaptive responses and persistent abnormalities that compromise function at the molecular, cellular and tissue levels [13–15]; In this regard, excessive production of ROS elicits pathologic changes by altering cellular function and increasing cell death [16]. Emerging evidence has shown that excessive mitochondrial ROS production can impair cardiac excitability by affecting the function of various channels and transporters through direct interaction such as post-translational redox modification of cysteine (S-glutathionylation, sulfhydration and S-nitrosation) or tyrosine (nitration) residues [17–19]. Excessive mitochondrial ROS can also modulate ion channel/transporter function indirectly via associated signaling molecules, such as ROS-sensitive kinases including calcium-calmodulin-dependent protein kinase (CaMKII), cSrc and protein kinase C (PKC), or via redeox-sensitive transcription factors, such as NFκB [20–22].

Mitochondria are also critically involved in the homeostatic regulation of cellular cations such as Ca^{2+}, Na^{+} and K^{+}, disturbance of which can has important consequences for cardiac contractility, energetics and electrical activity [23–25]. There is a complex interrelationship between sarcolemmal and mitochondrial cation regulation. Mitochondria can uptake and extrude Ca^{2+}, for example, modulating cardiomyocyte function by serving as a dynamic buffer for sarcolemmal Ca^{2+} [26, 27]. Changes in sarcolemmal cation concentration, on the other hand, can influence mitochondrial structure [28, 29], energetics [30, 31] and mitochondria-dependent cell death [32]. Much of the mitochondria-sarcolemma cation interdependence is mediated by the ion channels or transporters located on the inner membrane of mitochondria (see below).

Many central metabolic systems operate totally or partially within the mitochondria. These systems dynamically regulate cellular energetic status and sarcolemmal ATP-sensitive potassium ($sarcK_{ATP}$) currents through oscillating mitochondrial membrane potential ($\Delta\Psi_m$) in response to the changes in the supply of fuel substrates and O_2 [33–35]. In the presence of metabolic stress such as myocardial ischemia, depolarization of $\Delta\Psi_m$ diminishes mitochondrial ATP production, resulting in the opening of the $sarcK_{ATP}$ channels, which creates a “current sink” in the myocardium, capable of slowing or blocking cardiac electrical propagation, thereby fomenting arrhythmias (see below) [33, 36].

After a brief review on the ionic basis of cardiac excitability, mitochondrial energetics/ROS production, and mitochondrial/sarcolemmal cation homeostasis, the role of mitochondrial dysfunction in influencing myocyte excitability and cardiac arrhythmogenesis will be discussed, with an emphasis on the impact of mitochondrial ROS on sarcolemmal and sarcoplasmic channel/transporter functioning. In addition, the potential antiarrhythmic therapies targeting mitochondrial dysfunction in cardiac diseases will be highlighted.

Ionic basis of cardiac excitability and contractile function

The normal contractile function of the mammalian heart depends on proper myocardial electrical activity, including the sequential activation of cells in specialized conducting system, the normal propagation of electrical activity through the myocardium, and the generation of action potentials in individual cardiomyocytes [37, 38]. The normal cardiac cycle begins with the action potential originating in the sinoatrial node, propagating through the atria to the atrioventriular node. The electrical activity then spreads through the His bundle and Purkinje fibers to the cardiac apex, exciting the working ventricular myocardium [39]. The propagation of myocardial electrical activity depends on electrical coupling mediated by gap junctions, ensuring the coordination of the electromechanical functioning of the working myocardium [40]. Myocardial action potentials are generated by the sequential activation and inactivation of ion channels conducting depolarizing, Na^+ and Ca^{2+}, and repolarizing, K^+, currents [37, 38]. During the action potential, Ca^{2+} influx through voltage-gated Ca^{2+} channels triggers the release of Ca^{2+} ions into the cytosol from the sarcoplasmic reticulum (SR) via ryanodine receptor 2 (RyR2). Ca^{2+} binds to the protein troponin-C of the troponin-tropomyosin complex, leading to cardiomyocyte longitudinal shortening. The synchronous shortening of the ventricular myocytes results in the contraction of the heart and the systolic ejection of blood [41]. The subsequent diastolic relaxation of the myocytes depends on the repolarization of membrane potential and the removal of Ca^{2+} from the sarcomere [41]. Myocardial action potential repolarization is determined by multiple outward K^+ currents through voltage-gated K^+ (Kv) and inwardly rectifying K^+ (Kir) channels, whereas removal of Ca^{2+} from sarcomere depends on sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), which retrieves cytosolic Ca^{2+} into SR, as well as Na^+/Ca^{2+} exchanger (NCX), an antiporter membrane protein extruding Ca^{2+} from the cell. Factors that interfere with the aforementioned channel functioning may impair cardiac excitability and lead to cardiac arrhythmias.

Mitochondrial energetics and ROS production

The mitochondria are organelles containing double-membrane structure (inner and outer membranes) that create separate compartments, the intermembrane space and mitochondrial matrix. Mitochondria utilize glucose and fatty acids, the primary metabolic substrates for the myocardium, to generate ATP through OXPHOS. Glucose and fatty acids are sequentially oxidized to produce acetyl-CoA, the metabolic intermediate allowing the production of reducing equivalents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) through the tricarboxylic acid (TCA) cycle. These reducing equivalents feed electrons to the electron-transport chain (ETC) along the mitochondrial inner membrane, where the electrons flow through the complexes (I, II, III and IV) of ETC,

and finally to molecular oxygen to produce H_2O. As electrons flow through ETC, redox reaction occurs at complex I, III and IV, which drives proton (H^+) across the inner membrane, from mitochondrial matrix into intermembrane space, establishing the proton gradient and the strongly negative mitochondrial membrane potential, $\Delta\Psi_m$ (~−180 to −240 mV). The energy stored in $\Delta\Psi_m$ and proton gradient drives H^+ flow through mitochondrial ATP synthase (complex V), the final complex of the ETC, back into the matrix, converting ADP to ATP (Figure 1).

As an inevitable byproduct of OXPHOS, ROS are produced as a result of incomplete reduction or a surplus of electrons in the ETC. The relationship of OXPHOS to ROS production is not entirely clear and is probably not always an inverse proportion [42], but it has been estimated that 0.1–1% of the electrons flowing through the ETC prematurely leak to O_2 at complexes I, II or III, causing the formation of superoxide ($O_2^{\bullet-}$), one of the major ROS in cardiac cells (Figure 1) [43]. The rate of ROS production in mitochondrial matrix depends on the proton motive force, the NADH/NAD^+ ratio, the reduced coenzyme Q10 (CoQH2)/coenzyme Q10 (CoQ) ratio, and the local O_2 concentration. Under conditions of high proton motive force, high CoQH2/CoQ or increased NADH/NAD^+ ratio, mitochondrial ROS production is increased [44]. Manganese superoxide dismutase (MnSOD), the primary antioxidant enzyme locating in mitochondria, catalyzes dismutation of superoxide to hydrogen peroxide (H_2O_2) and O_2 [45]; complementary systems aimed at scavenging resulting H_2O_2 such as peroxisomal catalase, cytosolic and mitochondrial glutathione peroxidases and mitochondrial and cytosolic peroxiredoxins then convert H_2O_2 to H_2O (and O_2 in the case of catalase). Although other cellular origins of ROS, including NADPH oxidase, xanthine oxidase and uncoupled NO synthase may contribute to the production of ROS, mitochondria are viewed as the major source of ROS in cardiomyocytes.

Under pathological conditions such as diabetes mellitus [46, 47], pathological cardiac hypertrophy [48], myocardial ischemia/reperfusion [49, 50] or heart failure [51, 52], the efficiency of respiratory chain is impaired, leading to increased electron leak from the ETC and, hence, increased mitochondrial ROS production. Accumulating ROS levels can trigger the opening of mitochondrial channels, mitochondrial permeability transition pore (PTP) [53] and inner membrane anion channel (IMAC) [35], leading to simultaneous depolarization of $\Delta\Psi_m$ in the mitochondrial network and further increases in ROS generation from ETC, a phenomenon known as mitochondrial ROS-induced ROS release [54, 55].

An excessive amount of ROS, including superoxide, H_2O_2, hydroxyl radicals ($^{\bullet}OH$), and peroxynitrite ($ONOO^-$/ONOOH), can lead to detrimental reactions with cellular lipids and proteins, resulting in cardiomyocyte damage, dysfunction and death. Impaired mitochondrial function also leads to the accumulation of deleterious metabolites (NADH, ADP, lactate and H^+), and the depletion of redox-defense antioxidant scavengers glutathione (GSH) [56], both of which can aggravate cellular damage caused by increased oxidative stress.

Increased mitochondrial ROS also reduce ATP production. It has been shown that superoxide can activate mitochondrial uncoupling proteins, leading to increased proton leak and uncoupling of mitochondrial ATP production from oxygen consumption [57, 58]. In addition, excessive mitochondrial ROS can cause oxidative damage to components of ETC,

including complex I, II [59], IV [60], ATP synthase [59], and cytochrome c oxidase [61], leading to impaired ATP production and increased ETC electron leak that favors ROS generation. Under pathological conditions like tissue hypoxia, decreased O_2 tension favors ROS generation while limiting ATP production [62]. Increased ROS can further impair ATP synthesis by inhibiting ETC. Increased mitochondrial ROS, therefore, can impair cellular electrical function directly by ROS-mediated signaling and oxidative damage (as discussed below), as well as indirectly by reducing ATP production that is essential for ion channel/transporters to function [5, 6].

Interdependent regulation of mitochondrial and sarcolemmal cation homeostasis

As mentioned above, sarcolemmal cation concentration is tightly controlled in cardiomyocytes by ion channels and transporters located on plasma membrane and SR. Mitochondria also harbor ion channels and transporters. Mitochondrial cation influx and efflux not only contribute to the dynamic regulation of cytoplasmic ionic homeostasis but also play a critical role in modulating mitochondrial function.

Mitochondrial Ca^{2+} is crucial for the regulation of energy production, mitochondrial morphology and cell death [63–65]. Under physiological conditions, increased mitochondrial Ca^{2+} activates tricarboxylic acid dehydrogenases [63, 66] and ATP synthase [67], promoting OXPHOS and ATP production. Elevated Ca^{2+} levels also increase mitochondrial fragmentation by regulating the mitochondrial fission factor DLP1 [65, 68]. Excessive mitochondrial Ca^{2+}, however, can increase ROS production [69–71] and induce apoptotic cell death by activating the mitochondrial permeability transition pore (PTP) [64]. Mitochondrial Ca^{2+} uptake is mediated mainly by the mitochondrial Ca^{2+} uniporter (MCU) driven by mitochondrial membrane potential $\Delta\Psi_m$. Recently, a coiled-coil domain-containing protein 109A (CCDC109A) has been identified to encode MCU [72, 73]. In addition to MCU, several other mechanisms have been reported to mediate mitochondrial Ca^{2+} uptake, including the rapid mode of uptake (RaM) [74, 75], ryanodine receptor 1 (Ryr1) [76, 77] and Ca^{2+}-selective conductance (mCa1 and mCa2) [78]. Tight interactions exist between endoplasmic/sarcoplasmic reticulum (ER/SR) and mitochondria, where Ca^{2+} is concentrated at the hundred micromolar range in microdomains containing inositol 1,4,5-triphosphate (IP3)/ryanodine (RyR2) receptors that permit Ca^{2+} transport from ER/SR into mitochondria [79–81]. These functional microdomains allow the cross-talk between mitochondria and SR, modulating Ca^{2+} handling and matching energy supply and demand by regulating mitochondrial respiration [82, 83]. SR-mitochondria communication has been implicated in ischemia-reperfusion injury [84] and cardiac arrhythmias [85]. Mitochondrial Ca^{2+} efflux is primarily mediated by the mitochondrial Na^+-Ca^{2+} exchanger (mNCX)[86] [26], although the mitochondrial Ca^{2+}/H^+ antiporter [87] and PTP [88, 89] have also been implicated in mitochondrial Ca^{2+} efflux mechanisms. With the capacity of taking up or extruding Ca^{2+} through multiple mechanisms, mitochondria have been viewed as an efficient Ca^{2+} buffer, shaping Ca^{2+} dynamics in multiple cell types [26, 27, 90, 91]. To what extent mitochondria contribute to cellular Ca^{2+} dynamics under physiological and pathological conditions remains under debate [92]. A recent review on the available

quantitative data suggests that mitochondria do not act as a significant buffer of cytosolic Ca^{2+} under physiological conditions. With prolonged elevation of cytosolic Ca^{2+} levels, however, mitochondrial Ca^{2+} uptake can increase 10- to 1000-fold and begin to impact cellular Ca^{2+} dynamics significantly [25].

Mitochondrial Na^+ is regulated by Na^+/H^+ exchanger (NHE)-mediated Na^+ uptake [93] and mNCX-mediated Na^+ extrusion [94]. Under physiological conditions, energized mitochondria extrude protons, and the resulting pH gradient drives the Na^+ gradient between mitochondrial matrix (lower $[Na^+]$) and cytosol (higher $[Na^+]$)[93, 95]. Sarcolemmal Na^+ levels increase significantly in pathological conditions such as heart failure [96, 97]. The rise in cytosolic $[Na^+]$ during heart failure widens the Na^+ gradient across mitochondria, leading to greater driving force for mNCX to extrude Ca^{2+} from mitochondria, thereby resulting in decreased mitochondrial $[Ca^{2+}]$ and altered mitochondrial energetics [82].

Potassium transport also plays important roles in mitochondrial structure and function. Mitochondrial matrix volume is controlled by K^+ fluxes: K^+ influx is mediated by Ca^{2+}-dependent (K_{Ca}) [98, 99] and ATP-dependent (mitoK_{ATP}) [100] K+ channels, whereas K+ efflux is conducted through a K^+/H^+ exchanger (KHE) [28]. KHE is activated with the expansion of mitochondrial volume, preventing excess matrix swelling [28, 101]. The activation of K_{Ca} and mitoK_{ATP} channels, on the other hand, increases mitochondrial matrix volume [28, 29]. Under pathological conditions, sarcolemmal and mitochondrial Ca^{2+} can become overloaded, triggering the activation of K_{Ca} [28, 29]. Mitochondrial Ca2+ overload can also activate mitoK_{ATP} and suppress the activity of KHE through depolarizing $\Delta\Psi_m$, loss of proton gradient and decreased ATP synthesis [29]. Mitochondrial Ca^{2+} overload, therefore, can result in mitochondrial swelling through the activation of K_{Ca}/mitoK_{ATP} and the inhibition of KHE. In addition, K^+ influx mediated by K_{Ca} [102] and mitoK_{ATP} channels [103, 104] have been implicated in mediating the beneficial effects of ischemic preconditioning, which will be discussed later in this review.

Mitochondrial ROS and cardiac sodium channels

Cardiac voltage-gated Na^+ (Nav) channels consist of heteromeric assembly of a pore-forming α subunit and auxiliary β subunits that modulate channel functions. Nav1.5 (*SCN5A*) is the major Nav α subunit expressed in the mammalian myocardium, whereas multiple Nav β subunits (Navβ1, β2, β3, β4.1 and β4.2) have been described in the cardiomyocytes [39]. Voltage-gated Na^+ channels play a critical role in the membrane excitability of cardiomyocytes by generating the rapid upstroke (phase 0) of the action potential. In addition, Nav channels, along with cardiac gap junctions, govern the impulse conduction velocity in the myocardium.

Abnormal cardiac Na^+ channel function has been described in hereditary cardiac diseases such as long QT syndrome (LQTS), Brugada syndrome and progressive cardiac conduction defect (PCCD) [105, 106] and in acquired cardiac conditions including myocardial ischemia [107, 108] and heart failure [109, 110]. Upon increased oxidative stress, the slowly inactivating component of sodium current (late I_{Na}) is shown to be increased in cardiomyocytes, leading to prolongation of action potential duration (APD), early after

depolarizations (EAD), increased Na^+/Ca^{2+} exchange and subsequent cellular Ca^{2+} overload, all of which are arrhythmogenic [111, 112]. Using a heterologous expression system, we have demonstrated that elevated intracellular NADH level leads to reduction of peak I_{Na} through a protein kinase C (PKC)-mediated increase in mitochondrial ROS production; NADH-induced I_{Na} reduction can be reversed by a mitochondrial-specific antioxidant, mito-TEMPO, or by inhibiting the mitochondrial respiratory chain [113]. Inhibition of other cellular source of ROS, including the NADPH oxidase, xanthine oxidase or NO synthase [113] did not alter the reduction in I_{Na} or the arrhythmic risk resulted from the loss of I_{Na}.

Cytosolic NADH and mitochondrial ROS are increased in a mouse model of nonischemic cardiomyopathy, resulting in cardiac I_{Na} reduction without altering membrane Na^+ channel protein expression levels; the reduced I_{Na} can be restored by NAD^+ or mito-TEMPO treatment, both mitochondrial antioxidants [52]. Consistent with these findings, reduced conduction velocity in human failing myocardium, which is associated with I_{Na} reduction, can be improved by NAD^+ treatment [52]. Interestingly, the A280V mutation in glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) protein, a mutation known to cause Brugada syndrome [114], reduces I_{Na} through increasing intracellular NADH levels and mitochondrial ROS [113, 115]; the reduction in I_{Na} by A280V GPD1-L can be reversed also by the treatment of NAD^+ or mito-TEMPO [113]. These observations highlight the critical role of mitochondrial ROS as a mediator to transduce altered cardiac metabolism (reflected in $NADH/NAD^+$ ratio) to the modulation of cardiac sodium channel function under pathological conditions such as myocardial ischemia or heart failure.

Cellular redox state, mitochondria, and Ca^{2+} homeostasis

Calcium ions are important intracellular signaling molecules, responsible for the regulation of numerous cellular processes in cardiomyocytes including excitation-contraction coupling, enzyme activity, transcription regulation and cell death [116]. The intracellular Ca^{2+} levels ($[Ca^{2+}]_i$) fluctuate markedly between systole and diastole, yet the changes in $[Ca2+]_i$ are highly regulated. Abnormal Ca^{2+} handling has been implicated in the mechanical dysfunction and arrhythmogenesis observed in cardiac diseases such as cardiac hypertrophy [117, 118], heart failure [119, 120] and myocardial ischemia [121, 122].

In cardiomyocytes, the cycling of $[Ca^{2+}]_i$ begins with the entry of Ca^{2+} into the cells through voltage-gated Ca^{2+} channels, including the L- (low threshold) and T- (transient) type channels. The L-type Ca^{2+} channel is the predominant Ca^{2+} channel isoform in ventricular cardiomyocytes, whereas T-type Ca^{2+} channel is expressed mainly in pacemaker, atrial and Purkinje cells [123]. The Ca^{2+} entry via Ca^{2+} channels triggers SR Ca^{2+} release via RyR2, resulting in the sarcomere contraction. Ca^{2+} uptake into SR by SERCA and extrusion by NCX lower $[Ca^{2+}]_i$ to baseline, allowing sarcomere relaxation. Multiple signaling pathways, including CaMKII, β-adrenergic receptors (β-AR), protein kinase A (PKA) and PKC, are involved in the modulation of the activities of these Ca^{2+} handling proteins (see reviews by Bers [116]). All these Ca^{2+} handling proteins contain thiol groups or methionines that are susceptible to the direct regulation by ROS or reducing agents.

Increased cellular ROS are known to cause a net increase in $[Ca^{2+}]_i$ in cardiomyocytes [124]. The effects of ROS on L-type Ca^{2+} channel current (I_{CaL}) in cardiomyocytes, however, are controversial. It has been shown that direct H_2O_2 application or increased mitochondrial ROS increases I_{CaL} and the sensitivity of I_{CaL} to isoproterenol in guinea pig ventricular myocytes [125] and that oxidized LDL enhances I_{CaL} through lysophosphatidylcholine-induced mitochondrial ROS [126]. In contrast to these observations, others report a decrease in I_{CaL} in ventricular cardiomyocytes with increased ROS [127, 128]. The discrepancies observed among the studies may be attributed to the differences in the animal species and type of ROS. It is critical to note that although grouped under the acronym of "ROS", different reactive species containing molecular oxygen varying greatly in reactivity, diffusion coefficient, and oxidization potential.

The effects of ROS on other Ca^{2+} handling proteins, on the contrary, are more consistent. Increased oxidative stress enhances the open probability of RyR2 and increases the efflux of Ca^{2+} from SR [18]. Photoactivated or antimycin A-induced mitochondrial ROS production triggers a transient increase in Ca^{2+} sparks from RyR2 [129]. The activities of SERCA, in contrast to RyR2, are inhibited upon increased oxidative stress [130–132]. This effect can be, at least partially, attributed to decreased mitochondrial ATP supply for SERCA pump secondary to mitochondrial dysfunction [17].

CaMKII has been shown to play an important role in modulating RyR2 and SERCA function in response to increased oxidative stress in cardiomyocytes (See reviews by Maier et al [133] and by Rokita et al [134]). The activity of NCX, an antiporter that removes one Ca^{2+} ion from cytosol in exchange for the import of 3 Na^+ ions, has been shown to be enhanced by ROS [135, 136]. The net effects of ROS on these Ca^{2+} handling proteins result in cytosolic Ca^{2+} overload and depletion of the SR Ca^{2+} store, leading to multiple detrimental effects including a prolonged action potential, delayed afterdepolarizations (DADs), contractile dysfunction and the activation of Ca^{2+}-dependent signaling (e.g., CaMKII, calcineurin and NFAT) [17, 137].

As was indicated earlier, mitochondria also play an important role in cytosolic Ca^{2+} regulation by taking up and releasing Ca^{2+}. The capacity of mitochondria to take up or release Ca^{2+} can have substantial impact on the spaciotemporal dynamics of Ca^{2+} signaling in cardiomyocytes [25, 27]. It has been demonstrated recently that impaired mitochondrial function, with depolarized mitochondrial membrane potential and ATP depletion, can lead to calcium transient alternans by affecting the capacity of the mitochondrial network to handle Ca^{2+} on a beat-to-beat basis. This change predisposes to the development of cardiac arrhythmias [138]. Pharmacological inhibition of MCU with Ru360 has been reported to reduce the incidence of ventricular arrhythmias induced by ischemia-reperfusion in the rat heart [139]. Increased oxidative stress has also been shown to alter mitochondrial $[Ca^{2+}]$ through modulating mitochondrial NCX function or cytosolic Ca^{2+} levels, contributing to the perturbation of intracellular Ca^{2+} homeostatsis [129, 140, 141]. For instance, increased oxidative stress during ischemia can depolarize $\Delta\Psi_m$ [142] and increase cytosolic Ca^{2+} levels [121, 122], which can force mitochondrial NCX into reverse transport mode and transport Ca^{2+} into cytosol [94, 143].

As discussed earlier, mitochondrial Ca^{2+} is a positive effector of OXPHOS under physiological conditions, yet Ca^{2+} overload can lead to mitochondrial dysfunction, at least partially, by increasing ROS production [69–71]. Multiple mechanisms have been proposed to explain Ca^{2+}-induced mitochondrial ROS production: (1) Enhanced ROS output from increased respiratory chain activity: Increased Ca^{2+} stimulates TCA cycle and OXPHOS, and enhanced metabolic rate simply results in more respiratory chain electron leakage and ROS as by-products [144, 145]. (2) Stimulation of nitric oxide synthase (NOS): Ca^{2+} is known to activate NOS and generate $NO^{\bullet}$, which has been shown to inhibit complex IV and enhance ROS generation from the Q cycle at complex III [146]. (3)Cytochrome c-mediated ETC inhibition: increased Ca^{2+} can enhance cytochrome c dislocation from mitochondrial inner membrane, either by competing cardiolipin binding sites or by increasing PTP opening, which can result in complex III inhibition and enhanced ROS generation [147, 148]. (4) Cross-talk with K^+ influx: as discussed earlier, mitochondrial Ca^{2+} overload can activate K_{Ca}/mitoK_{ATP}, leading to increased K+ influx and enhanced ROS production [102, 149].

Taken together, current evidence suggests a reciprocal interaction between Ca^{2+}-induced ROS production and ROS-induced Ca^{2+}-overload. The cross-talk between Ca^{2+} and ROS regulatory systems is normally under tight control to maintain normal physiological functions. With pathological stimuli such as myocardial ischemia and pressure/volume overload, multiple signaling and ionic mechanisms can lead to increased cellular and mitochondrial Ca^{2+} levels, resulting in increased ROS generation. Overt ROS production triggered by increased mitochondrial Ca^{2+} signals can lead to further increase in mitochondrial Ca^{2+} and ROS levels. This positive feed-forward loop consisting of Ca^{2+}-induced ROS production, ROS-induced ROS release and ROS-induced Ca^{2+} overload can exceed cellular capacity of ROS scavenging and Ca^{2+} clearance, resulting in cellular damage and death [141].

ROS, mitochondria and cardiac potassium channels

Multiple voltage-gated K^+ (Kv) channels and non-voltage-gated inwardly rectifying (Kir) channels contribute to myocardial action potential repolarization [38, 39]. Functional K^+ channels are integral membrane protein complexes consisting of pore-forming (α) subunits, multiple accessory (β) subunits and regulatory proteins [38, 39]. The α subunits of Kv channels are six-transmembrane-spanning domain (S1-S6) proteins, and functional Kv channels are composed of four α-subunits; In addition, a number of different types of Kv channel accessory subunits have been identified and shown to interact with Kv α subunits to modulate channel biophysical properties and cell surface expression [39, 150].

Based on differences in time- and voltage-dependent properties and pharmacological sensitivities, two main types of Kv channels have been distinguished: transient outward Kv (I_{to}) and delayed rectifier Kv (I_K) currents. Currents classified as I_{to} activate and inactivate rapidly upon membrane depolarization and underlie early (phase 1) repolarization, whereas I_K currents activate on depolarization with variable kinetics and underlie late (phase 2 & 3) repolarization [39]. The heterogeneities in the biophysical properties and expression levels

of various K^+ currents contribute to the inter-species and inter-regional differences in action potential waveforms [39, 151].

Similar to the Kv channels, multiple functionally distinct types of Kir channel pore-forming α-subunits (Kir1-6) have been identified. The Kir α-subunits, like Kv channels, assemble as tetramers to form functional Kir channels [39, 152, 153], although Kir α-subunits have only two, instead of six, transmembrane domains. It has been shown that cardiac I_{K1} channels reflect the heteromeric assembly of the Kir α-subunits, Kir 2.1 and Kir 2.2 [154–158] and that the predominant form of K_{ATP} channels in cardiac sarcolemma reflects the assembly of Kir6.2 and SUR2A [159]. While Kv currents contribute importantly to the repolarization of action potentials in mammalian ventricular myocardium, the Kir currents also contribute to shaping the resting and active membrane properties of cardiomyocytes. Among several types of Kir currents expressed in mammalian heart, I_{K1} contributes to the terminal phase of repolarization and the maintenance of resting membrane potentials in mammalian ventricular myocytes [39, 152, 153], whereas current conducted by sarcK_{ATP} channels (IK_{ATP}), gated by intracellular ATP/ADP levels, plays an important role in regulating cellular metabolism and electrophysiological responses to metabolic stresses such as myocardial ischemia [160, 161].

Increased ROS have been shown to reduce the expression of Kv currents, including I_{to} and multiple delayed rectifier I_K (including I_{Kr}, I_{Ks} and I_{Kur}) currents in ventricular cardiomyocytes [162–164], which can be reversed by increasing intracellular redox buffer reduced glutathione (GSH) [165, 166]. Decreased repolarizing Kv currents in cardiac ventricles can lead to delayed repolarization and prolonged action potential duration (APD), predisposing to the development of ventricular arrhythmias [39]. It has been shown that increased oxidative stress can impact the repolarizing Kv currents by modulating the expression levels of the mRNA and protein encoding these K^+ channels [164] or by altering the phosphorylation status of these K^+ channels through modulating the activities of PKC, PKA or protein tyrosine phosphatases [167–169]. It is not clear whether increased ROS can modulate Kv channel activities through direct oxidation of thiol groups.

Mitochondria also regulate myocyte membrane excitability through modulating sarcK_{ATP} channels. The sarcK_{ATP} channels, gated by ATP and thereby sensing the cellular energy status, are present at high density in the sarcolemmal membrane. SarcK_{ATP} channels are inhibited by ATP and activated by ADP, Mg or low pH, conditions that are associated with inadequate fuel supply, ischemia, and increased oxidative stress [104]. Upon ATP depletion and increased oxidative stress (e.g., during myocardial ischemia), sarcK_{ATP} channels are triggered to open, producing an inwardly rectifying repolarizing current. Because of the high cell surface expression density of sarcK_{ATP} channels, myocardial APD can be significantly shortened even with the opening of only 1% of the sarcK_{ATP} channels [170]. The opening of sarcK_{ATP} channels may be intrinsically protective against ATP depletion: shortened APD can reduce inward Ca^{2+} transient, thereby decreasing Ca^{2+}-mediated cardiac energy consumption and preventing Ca^{2+} overload-induced cell death. Nevertheless, with adequate numbers of sarcK_{ATP} channels in the open state, cardiomyocytes can become hyperpolarized and rendered unexcitable [171]. This creates a current sink capable of slowing or blocking electrical propagation in the myocardium, promoting the development

of cardiac arrhythmia [36, 172]. Indeed, it has been demonstrated that pharmacological inhibition of sarcK_{ATP} channels can reduce the incidence of ventricular arrhythmias in animal models [173–175] and in human [176–178].

Upon substrate deprivation or increased oxidative stress, sarcK_{ATP} currents and APD oscillate [179, 180]. The oscillations are synchronized with the fluctuations in mitochondrial membrane potential, $\Delta\Psi_m$ [35]. Under conditions of increased oxidative stress, $\Delta\Psi_m$ depolarizes, diminishing the amount of free energy available for ATP production [35]. There is evidence suggesting that $\Delta\Psi_m$ depolarization of mitochondrial network is mediated by cell-wide ROS production induced by focal increases in mitochondrial ROS, a process known as “ROS-induced ROS release” [54, 181]. The inner membrane anion channel (IMAC) has been shown to play an important role in influencing $\Delta\Psi_m$. The use of IMAC inhibitors can prevent mitochondrial depolarization of $\Delta\Psi_m$, preventing the oscillation in K_{ATP} currents and APDs upon increased oxidative stress [35]. In addition, pharmacological inhibition of IMAC was shown to prevent ventricular arrhythmias in intact mammalian hearts upon increased oxidative stress or ischemia [182, 183].

Another group of K_{ATP} channels are located on the inner membrane of the mitochondria (mitoK_{ATP} channels), which have been shown to play an important role in mediating the protective effects of ischemic preconditioning [103, 104]. In the resting heart, mitoK_{ATP} channel opening increases mitochondrial ROS production, which in turn triggers downstream signaling leading to gene transcription and cell growth [184]. The opening of mitoK_{ATP} channels before the onset of ischemia allows K^+ influx in mitochondria, partially dissipating $\Delta\Psi_m$ (“partial uncoupling”), which results in a compensatory increase in proton pumping and cellular respiration to maintain $\Delta\Psi_m$ and oxidative phosphorylation [103]. In addition, as $\Delta\Psi_m$ is depolarized during ischemia, mitoK_{ATP} opening provides additional K^+ influx to complensate for the lower driving force and to maintain mitochondrial volume, which is essential for maintaining a functioning ETC system [184]. Blocking mitoK_{ATP} channels abolishes the anti-arrhythmic effects of ischemic preconditioning [185], although some, but not all, pharmacological openers of mitoK_{ATP} channels were shown to be protective against ischemia-induced arrhythmias [175, 186, 187]. It is important to point out that many of the reports on mitoK_{ATP} channel function were based on results using pharmacological agents like diazoxide (mitoK_{ATP} channel opener) or hydroxydeconate (5-HD, a mitoK_{ATP} channel inhibitor), which are known to have other effects on mitochondrial function [184]. Recently, ROMK (Kcnj1) has been identified to encode a mitoK_{ATP} channel [188]. Targeting the molecular identity of mitoK_{ATP} channel may circumvent the caveats of a pharmacological approach and provide direct evidence of mitoK_{ATP} function.

Mitochondrial ROS and cardiac gap junction remodeling

Gap junctions, the membrane channels formed by the assembly of a pair of hemichannels consist of six connexin proteins, mediate the cell-to-cell communication of small metabolites and ions and play a critical role in cardiac impulse conduction [189]. There are three major connexin isoforms expressed in the heart: connexin (Cx) 40, Cx43 and Cx45. While Cx43 is extensively expressed in both the atrial and ventricular cardiomyocytes, Cx40 is predominantly expressed in the atria and specialized conduction system. Cx45 expression

is restricted to the sinoatrial node, atrioventricular node and adjoining His bundles [190]. Cx43 expression is known to be downregulated in various cardiac diseases, including cardiac hypertrophy [191], heart failure [192, 193], myocardial ischemia [194, 195] and cardiomyopathy [195]. Reduction in Cx43 can lead to slow conduction velocity, increased heterogeneity and exaggerated anisotropic properties of the ventricles [196, 197], all of which are arrhythmogenic and may facilitate the initiation and maintenance of ventricular arrhythmias [198, 199].

The activation of renin-angiotensin system (RAS), a hallmark of cardiomyopathy and heart failure [200, 201], is known to increased myocardial oxidative stress and downregulate ventricular Cx43 [202–204]. Transgenic mouse models with increased cardiac RAS activity [204, 205] have been shown to have high incidence of conduction block, ventricular arrhythmias and sudden death because of reduced cardiac Cx43 and impaired gap junction function [204, 205]. Using a gene targeted, cardiac-specific angiotensin converting enzyme overexpression mouse model (ACE8/8) [204], we have demonstrated that enhanced RAS signaling results in increased expression of the activated form of cSrc (p-cSrc at Tyr^{416}), a redox-sensitive tyrosine kinase, in ventricular myocardium. This activation leads to Cx43 reduction, impaired gap junction function, and subsequent increase in the propensity for ventricular arrhythmias and sudden cardiac death [13, 206]. The downregulation of Cx43 and increased arrhythmia risk in ACE8/8 mice can be ameliorated by pharmacologic inhibition of RAS [207] and cSrc [206]. It is known that increased myocardial p-cSrc results in the downregulation of Cx43 via the competition between p-cSrc and Cx43 for a binding site at zonula occludens-1, an intercalated disk scaffolding protein, leading to Cx43 destabilization and degradation [208]. Increased p-cSrc levels can also impair gap junction function through tyrosine phosphorylation of Cx43 [209]. Using the same ACE8/8 mouse model, we have recently demonstrated that cardiac ROS, specifically mitochondrial ROS, were markedly increased with enhanced RAS signaling [13, 206]. Treatment with mitochondria-targeted antioxidant, MitoTEMPO, but not the other types of antioxidants, reduces cSrc phosphorylation, restores the Cx43 expression, normalizes gap junction conduction, as well as ameliorates ventricular arrhythmias and sudden cardiac death in ACE8/8 mice [13]. These data suggest that mitochondrial oxidative stress plays a critical role in AngII–induced gap junction remodeling and arrhythmia. As mitochondrial ROS are increased in cardiac diseases such as cardiac hypertrophy [48], myocardial ischemia [50, 210] and heart failure [51, 52], conditions that are known to be associated with RAS activation, ventricular Cx43 downregulation and increased risk of arrhythmias, it would be of great interest to test if the treatment with mitochondria-targeted antioxidant can normalize Cx43 expression and prevent life-threatening arrhythmias in these pathological conditions.

Conclusion

In summary, mitochondrial dysfunction is prevalent in arrhythmogenic cardiac diseases including cardiac hypertrophy, heart failure and myocardial ischemia. Reduced ATP synthesis and increased ROS production associated with mitochondrial dysfunction can lead to malfunction of various cellular mechanisms that are required to maintain normal electrical functioning and intracellular ionic homeostasis in cardiomyocytes. As summarized in Figure 2 and Table 1, mitochondrial dysfunction can lead to reduced peak I_{Na} and downregulation

of Cx43, resulting in abnormal conduction and increased propensity for re-entrant type cardiac arrhythmias. Increased cellular ROS also increases late I_{Na} and reduces repolarizing Kv currents, leading to impaired repolarization, prolonged APD, EADs, increased electrical heterogeneity in the myocardium, and increased arrhythmia susceptibility. Mitochondrial dysfunction also leads to disrupted intracellular Ca^{2+} homeostasis in cardiomyocytes, resulting in cytosolic Ca^{2+} overload and proarrhythmic DADs. Finally, mitochondrial dysfunction also causes the depolarization of $\Delta\Psi_m$ and the opening of sarcoK_{ATP} channels, creating a current sink for the propagating depolarization wave, potentiating conduction block and arrhythmia. These observations suggest that mitochondria-targeted antioxidants may prove a more efficacious alternative to traditional ion channel blocking drugs to address arrhythmia in associated with cardiac diseases.

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Highlights

- We review the mechanisms by which mitochondrial dysfunction causes arrhythmias
- Mitochondrial dysfunction leads to increased reactive oxidative species production
- Mitochondrial dysfunction impairs sarcolemmal and sarcoplasmic channel functions
- Mitochondrial dysfunction results in impaired intracellular cation homeostasis
- The use of mitochondria-targeted antioxidants might be a novel antiarrhythmic therapy

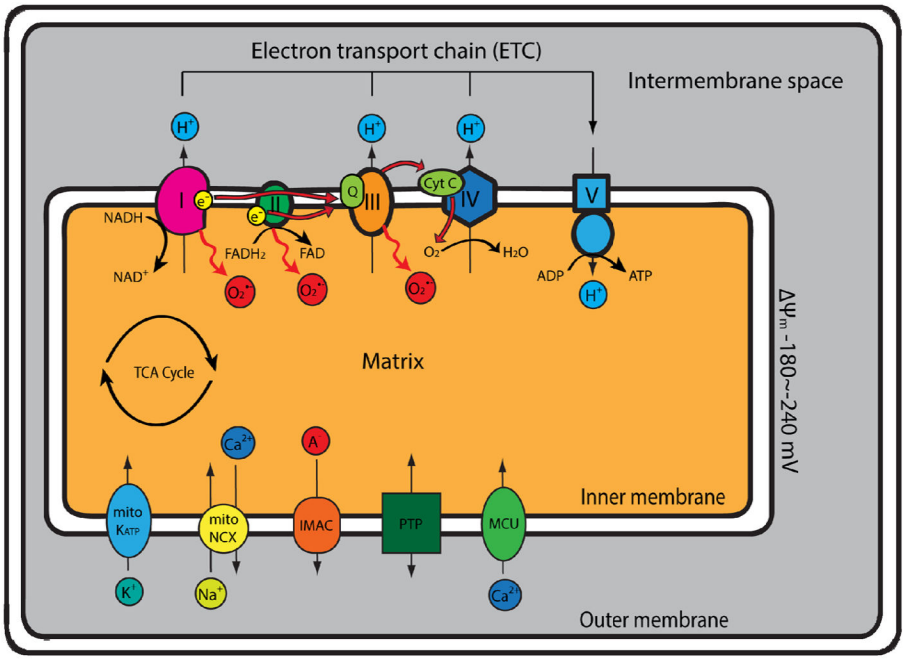

Figure 1. Schematic overview of oxidative phosphorylation and superoxide production in mitochondria

Reducing equivalents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) generated from the tricarboxylic acid (TCA) cycle donate electrons to the electron transport chain (ETC) on the mitochondrial inner membrane. The electrons pass through the ETC (complex I & II → coenzyme Q [Q] → complex III → cytochrome C [Cyt C] → complex IV → molecular O_2), where coupled redox reactions drives proton (H+) from the matrix, across the inner membrane, into the intermembrane space, forming the proton gradient and the negative mitochondrial membrane potential, $\Delta\Psi_m$ (~−180 to −240 mV). The proton-motive force then drives H^+ flow through mitochondrial ATP synthase (complex V) and generates ATP. An estimated 1–5% of the electrons prematurely leak to O_2 at complexes I, II or III, leading to the formation of superoxide ($O_2^{\bullet-}$). Several important mitochondrial channels are also located on the inner membrane: the mitochondrial K_{ATP} channels (mitoK_{ATP}), the mitochondrial Na/Ca exchanger (mitoNCX), the inner membrane anion channel (IMAC), the mitochondrial permeability transition pore (PTP) and the mitochondrial calcium uniporter (MCU).

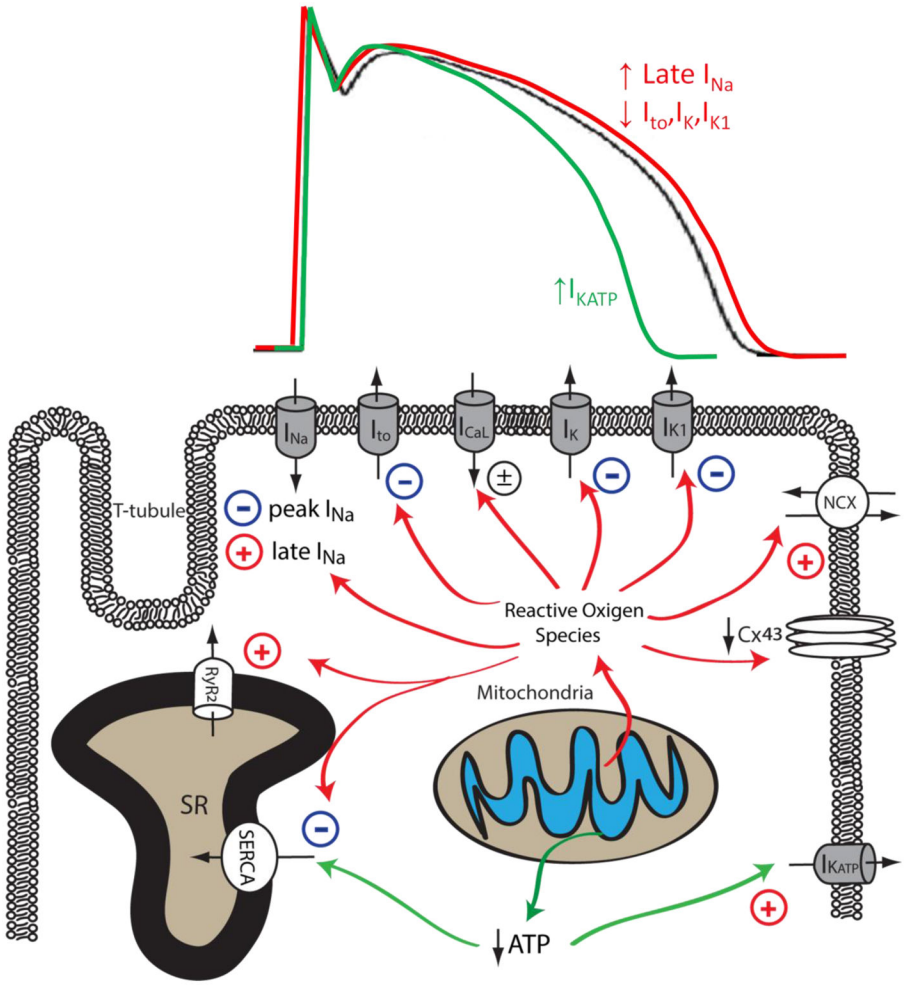

Figure 2. Effects of mitochondrial dysfunction on myocardial ion channels and calcium handling proteins

Mitochondrial dysfunction upon increased pathological or metabolic stress can lead to increased ROS production and reduced ATP synthesis. Increased cellular ROS can lead to the inhibition of peak I_{Na}, I_{to}, I_K, I_{K1}, SERCA and the downregulation of Cx43, whereas the activity of late I_{Na}, NCX and RyR are enhanced by increased oxidative stress. Reduced ATP production secondary to mitochondrial dysfunction can inhibit the activity of SERCA and increase the activity of sarcolemmal K_{ATP} channels. The impact of mitochondrial dysfunction on AP waveforms is illustrated on top: increased mitochondrial ROS production can prolong AP duration by increasing late I_{Na} and reducing repolarizing K^+ currents (Red). Under conditions such as acute ischemia, mitochondrial ATP production is reduced, leading to opening of sarcolemmal K_{ATP} channel and AP shortening (Green). The Baseline AP waveform is shown in black.

Table 1

Impact of mitochondrial dysfunction on cardiac arrhythmogenicity

Target Channel/Transporter	Impact of Mitochondrial Dysfunction	Impact on electrical/ionic homeostasis	Pro-arrhythmic mechanism
Peak I_{Na}	↓	↓ Na^+ influx	Slow conduction
Late I_{Na}	↑	↑ Na^+ influx, prolonged APD	EAD
I_{to}	↓	↓ K^+ influx, prolonged APD	EAD
I_{CaL}	±		
I_K	↓	↓ K^+ influx, prolonged APD	EAD
I_{K1}	↓	↓ K^+ influx, prolonged APD	EAD
I_{KATP}	↑	↑ K^+ influx, shortened APD	Current sink, slow conduction
NCX	↑	Cytosolic Ca^{2+} overload	DAD
Cx43	↓	Impaired gap junction function	Slow conduction
SERCA	↓	Cytosolic Ca^{2+} overload	DAD
RyR2	↑	Cytosolic Ca^{2+} overload	DAD
mitoNCX	Reverse mode	Cytosolic Ca^{2+} overload	DAD
$mitoK_{ATP}$/$mitoK_{Ca}$	↑	↑Mitochondrial K^+ influx	Protective, mechanism of ischemic-preconditioning

Peak I_{Na}: peak Na^+ current; Late I_{Na}: late Na^+ current; I_{to}: transient outward K^+ current; I_{CaL}: L-type Ca^{2+} current; I_K: delayed rectifier K^+ current; I_{K1}: inwardly rectifying K^+ current; I_{KATP}: ATP-sensitive K^+ current; NCX: Na^+/Ca^{2+} exchanger; Cx43: connexin 43; SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase; RyR2: ryanodine receptor 2; mitoNCX: mitochondrial Na^+/Ca^{2+} exchanger; $mitoK_{ATP}$: mitochondrial ATP-sensitive K^+ current; $mitoK_{Ca}$: mitochondrial Ca^{2+}-sensitive K^+ current; APD: action potential duration; EAD: early after-depolarization; DAD: delayed after-depolarization.