IJC Heart & Vasculature 52 (2024) 101414

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

The role of iron overload and ferroptosis in arrhythmia pathogenesis

Jingsong Shen [a], Hengsong Fu [a], Yanling Ding [a], Ziyang Yuan [a], Zeming Xiang [a], Miao Ding [a], Min Huang [a], Yongquan Peng [a], Tao Li [a,b], Kelan Zha [a], Qiang Ye [a,*]

[a] Department of Cardiology, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China
[b] Key Laboratory of Medical Electrophysiology of Ministry of Education and Medical Electrophysiological Key Laboratory of Sichuan Province, Collaborative Innovation Center for Prevention and Treatment of Cardiovascular Disease, Institute of Cardiovascular Research, Southwest Medical University, Luzhou 646000, China

ARTICLE INFO

Keywords:
Ferroptosis
Molecular mechanism
Arrhythmia
Oxidative stress
Iron overload

ABSTRACT

Ferroptosis is a newly discovered form of programmed cell death triggered by intracellular iron overload, which leads to the accumulation of lipid peroxides in various cells. It has been implicated in the pathogenesis and progression of various diseases, including tumors, neurological disorders, and cardiovascular diseases. The intricate mechanism underlying ferroptosis involves an imbalance between the oxidation and antioxidant systems, disturbances in iron metabolism, membrane lipid peroxidation, and dysregulation of amino acid metabolism. We highlight the key molecular mechanisms governing iron overload and ferroptosis, and discuss potential molecular pathways linking ferroptosis with arrhythmias.

1. Introduction

Arrhythmia is a prevalent cardiovascular disease (CVD) generally associated with various heart diseases. Epidemiological data have revealed that approximately 3 million individuals worldwide succumbed to sudden cardiac death (SCD) annually, with arrhythmic sudden death accounting for 80 % of these cases [1]. The main pathophysiological mechanisms of arrhythmia include cardiac electrical remodeling, cardiac structural remodeling and oxidative stress. The advent of pacemakers has significantly benefited patients with bradyarrhythmia. Although catheter ablation and implantable cardioverter defibrillator (ICDs) have proven effective in ameliorating tachyarrhythmias such as atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation (VF), their widespread application remains limited owing to exorbitant treatment costs, substantial recurrence rates and overall outcomes [2]. Despite remarkable advancements in non-pharmacological therapies for arrhythmia, anti-arrhythmic drugs remain the most effective treatment in certein types of arrhythmias. Notably, anti-arrhythmic drugs themselves may induce arrhythmias [3]. Consequently, elucidation of the novel pathogenic mechanisms underlying arrhythmia and identification of efficacious therapeutic targets are urgently required.

Ferroptosis, a recently discovered form of cell death, is characterized by the accumulation of Fe^{2+} within cells, which triggers the generation of numerous reactive oxygen species (ROS). Oxidative damage to the cell membrane ultimately leads to cell death [4]. Ferroptosis has been implicated in various cardiovascular diseases including atherosclerosis, ischemia–reperfusion injury, heart failure, myocardial infarction, and doxorubicin cardiomyopathy [4,5]. Emerging evidence suggests that ferroptosis is associated with arrhythmia.(Table 1) These findings highlight the potential involvement of ferroptosis in arrhythmia pathogenesis [6]. This review summarizes the current research progress on the relationship between arrhythmias and ferroptosis and elucidates the underlying interaction mechanisms.

2. Ferroptosis

Ferroptosis was first described by Dixon et al. in 2012. It has distinct morphological characteristics, biochemical attributes, and regulatory genes compared to other programmed cell death processes, such as apoptosis, autophagy, and necrosis. Morphologically, ferroptotic cells display augmented mitochondrial membrane density accompanied by reduced or absent mitochondrial cristae. They also exhibit diminished cellular volume while maintaining a normal nuclear volume without nuclear condensation. These morphological traits distinguish ferroptosis from other forms of cell death. Biochemically, the prominent hallmarks of ferroptosis include iron accumulation, excessive ROS generation, and lipid peroxidation within cellular membranes [4]. Mechanistically, ferroptosis primarily involves dysregulation of the glutathione antioxidant system, perturbations in iron metabolism homeostasis, lipid

* Corresponding author.
E-mail address: art006023@yeah.net (Q. Ye).

https://doi.org/10.1016/j.ijcha.2024.101414
Received 21 January 2024; Received in revised form 20 April 2024; Accepted 23 April 2024

Table 1
Summary of researches about ferroptosis-related arrhythmias.

1st Author	Ref	Sample	Type Of Arrhythmia	Findings
Chang Dai	[7]	Mouse	AF	The frequent and excessive consumption of alcohol triggers ferroptosis, thereby increasing the susceptibility rate to AF. Inhibiting ferroptosis can effectively counterbalance iron overload disorders and reduce the production of ROS, ultimately decreasing the vulnerability to AF.
Robert A Rose	[8]	Mouse	Bradycardia, AF	Chronic iron overload selectively reduces Ca(V) 1.3-mediated $I_{Ca\text{-}L}$, leading tobradycardia, slowing of electrical conduction, and AF as seen in patientswith iron overload.
Jin Fang	[9]	Rat	AF	Fpn-mediated ferroptosis is involved in the new-onset AF with LPS-inducedendotoxemia via worsening the calcium handling proteins dysregulation
Dishiwen Liu	[10]	Beagles and H9C2 cells	AF	CF-exos-miR-23a-3p may promote ferroptosis. The development of AF in a persistent direction could be prevented by intervening with exosomal miRNAs to reduce oxidative stress injury and ferroptosis.
Vincenzo Russo	[11]	Patients with beta-thalassemia major	AF	P-wave dispersion, as an independent risk factor for development of AF, is correlated to myocardial iron deposit, as assessed by CMR T2* imaging.
Hong-Jie Yang	[12]	Rat	AF	A traditional Chinese medicine called Shensong Yangxin reduced AF susceptibility, inhibited electrical remodeling and structural remodeling via up-regulating Fpn, decreasing intracellular iron overload and reducing ROS production.
Yuling Han	[6]	hamster model and human ESC (hESC)-derived SAN-like pacemaker cells		SARS-CoV-2 infections derange human sinoatrial node-like pacemaker cells, facilitating ferroptosis. Early deferoxamine and imatinib administration reduces viral infection in human embryonic stem cell cardiomyocytes. Suggests ferroptosis is involved in the arrhythmia progression in COVID-19 patients

peroxidation within cellular membranes and impairment of mitochondrial function.

2.1. Dysregulation in glutathione antioxidative system

The metabolism of glutathione (GSH) is closely linked to ferroptosis, as the depletion of GSH, deficiency of cysteine (Cys), and inactivation of glutathione peroxidase 4 (GPX4) can induce ferroptotic cell death [13]. The dimeric cystine-glutamate reverse transport system (System Xc^-) is composed mainly of solute carrier family 3 member 2 (SLC3A2) and solute carrier family 7 member 11 (SLC7A11). This system facilitates the uptake of Cys into cells while exporting an equal amount of glutamate outward. The cellular uptake of Cys leads to its reduction into two cysteine molecules, serving as the precursor for GSH synthesis. Under the catalysis of intracellular glutathione peroxidase, GSH can effectively mitigate intracellular ROS and lipid peroxidation, thereby maintaining the stability of the lipid bilayer membrane. Inhibition of System Xc^- activity results in reduced cystine absorption and impaired synthesis of reducing glutathione, ultimately elevating susceptibility to oxidative damage and ferroptosis [14]. Recent studies have demonstrated that P53 protein downregulates SLC7A11 to inhibit System Xc^- activity, consequently reducing cellular antioxidant capacity and making cells more vulnerable to ferroptosis [15].

GPXs is a family of eight human subtypes that exhibit tissue expression and substrate specificity. Among these subtypes, GPX4 plays a pivotal role in the regulation of ferroptosis by utilizing GSH to convert peroxide lipids into their corresponding alcohols. Depletion of GSH or inhibition of GPX4 increases the susceptibility to ferroptosis, including that induced by RSL3 (ferroptosis inducer) and its derivatives. Additionally, cells with GPX4 knockout or low expression display heightened sensitivity to ferroptosis [16]. Selenium plays a pivotal role in GPX4 activity. Supplementation with selenium can enhance resistance against ferroptosis, whereas selenium depletion can increase sensitivity to ferroptosis [17]. Superoxide is considered a crucial substance implicated in myocardial reperfusion injury, arrhythmia, and other pathological processes. Selenium-containing glutathione peroxidase (GSH-Px) within the body can effectively eliminate superoxide [18]. In cardiomyocyte metabolism, excess free radicals can oxidize unsaturated fatty acids, causing their degradation. However, the presence of selenium along with a series of glutathione peroxidases synthesized by GPX4 can prevent such degradation.

2.2. Abnormal iron metabolism

Iron is an essential trace element present in almost all life forms and is involved in many biological processes. Intracellular iron homeostasis can only be achieved when there is a balance among the absorption, export, and utilization of iron within cells. Numerous studies have demonstrated that iron deficiency can lead to disorders, whereas excessive iron accumulation can cause severe damage to the body through excessive ROS generation, resulting in cellular dysfunction, tissue and organ impairment, or death [19]. In the event of iron overload, elevated Fe^{2+} levels within the cell instigate a Fenton reaction with hydrogen peroxide, thereby catalyzing hydroxyl radical (OH·) formation and subsequently inducing lipid peroxidation on the cellular membrane, ultimately leading to ferroptosis. The iron chelator deferoxamine (DFO) can effectively inhibit intracellular iron overload-induced ferroptosis, highlighting the crucial role of iron metabolism in the initiation and progression of this process [19].

Absorption of iron ions into the small intestinal epithelium is facilitated by ferroportin1 (FPN1), which is located in the basal membrane of the small intestinal epithelium and allows its entry into the bloodstream [20]. Subsequently, Fe^{3+} in the blood forms a complex with transferrin (TF), upon binding to the transferrin receptor 1 (TFR1) on cell membranes, it undergoes endocytosis and is reduced to Fe^{2+} by prostate 6 transmembrane epithelial antigen 3 (STEAP3) [21,22]. Fe^{2+} can

participate in oxidation reactions. Disruption of iron homeostasis leads to the excessive production of Fe^{2+} through the Fenton reaction, resulting in the generation of hydroxyl radicals and ROS, which causes cellular and tissue damage [23]. Dixon et al. demonstrated that modulation of intracellular iron levels can influence cell sensitivity to ferroptosis, with increased expression of TF and TFR1 promoting ferroptosis susceptibility [4]. Ferroportin (FPN), the only known iron exporter protein in vertebrate cells, plays an essential role in maintaining intracellular iron homeostasis and normal cardiac function; its deficiency can lead to iron overload-induced ferroptosis. Compared to wild-type mice, FPN knockout mice (Fpn fl/fl Myh6. Cre +) exhibited elevated cardiac ferritin levels, enlarged left ventricle size, decreased left ventricular ejection fraction (LVEF), and increased intracellular iron concentration and oxidative stress and exaggerated the AF vulnerability, which was alleviated by ferroptosis inhibition. [24].

2.3. Lipid peroxidation

Accumulated ROS attack polyunsaturated fatty acid (PUFA) chains in cell membranes, generating large amounts of harmful lipid peroxide that ultimately triggers ferroptosis. PUFAs such as arachidonic acid (AA) and eicosapentaenoic acid contain easily extractable diallyl hydrogen atoms, which are prone to lipid peroxidation and play key roles in ferroptosis [25]. In ferroptotic cells, polyunsaturated fat AA is significantly depleted while AA-derived lipid fragments can be detected in the culture supernatant of GPX4-/- mouse embryonic fibroblasts [26]. Long-chain acyl-CoA synthetase 4 (ACSL4) and lysophosphatidylcholinesterase 3 (LPCAT3), which encode enzymes involved in the insertion of AA into membrane phospholipids, prevent ferroptosis induced by the GPX4 inhibitors RLS3 and ML162 upon deletion. This suggests that highly oxidative PUFAs, such as AA, present within membranes allow for direct or indirect GPX4 inhibition-induced GSH depletion before performing ferroptosis [14].. Using a newly developed molecular dynamics model of lipid membranes Agmon et al. hypothesized that during the ferroptosis of phospholipids containing oxidized PUFAs, membrane thinning and increased curvature drive increased oxidant accessibility, ultimately leading to micelle formation causing irreversible damage to membrane integrity [27].

2.4. Mitochondrial dysfunction

Mitochondria, the powerhouses of the cell, serves as the primary sites for oxidative phosphorylation, generating most of the adenosine triphosphate(ATP) in eukaryotic cells through the electron transport chain (ETC) [28,29]. However, mitochondria is also a major source of ROS. Recent studies have demonstrated that energy expenditure, such as during glucose deprivation, can activate AMP-activated protein kinase (AMPK), an energy-sensing enzyme. This activation effectively suppresses the synthesis of specific PUFAs and inhibits ferroptosis by phosphorylating and deactivating acetyl-CoA carboxylase (ACC), a pivotal enzyme involved in fatty acid biosynthesis. Conversely, AMPK inactivation promotes ferroptosis progression [30]. Inhibitors targeting ETC complexes or mitochondrial uncoupling agents significantly enhance drug-induced ferroptosis mediated by compounds, such as erastin and its analogues. These findings suggest that electron transport and proton pumping within mitochondria play crucial roles in triggering ferroptosis [31], potentially linked to ATP production and subsequent AMPK inhibition. Dihydroorotate dehydrogenase (DHODH), a lutein-dependent enzyme located on the inner mitochondrial membrane, catalyzes the oxidation of dihydroorotate to orotate, while providing electrons for CoQ reduction to CoQH2. This process hampers lipid peroxidation and consequently decelerates ferroptotic progression [32]. Using a rat model of cardiac ischemia/reperfusion injury, Luo et al. observed elevated levels of ROS within the mitochondria along with depolarization of the inner mitochondrial membrane, swelling of the mitochondria, and imbalanced dynamics during ischemia/reperfusion. Fer-1 treatment effectively mitigated these changes while reducing cardiac inflammation in rats subjected to ischemia/reperfusion injury [33]. Recent studies have shown that ferroptosis alters mitochondrial morphology and function. Ferroptotic cells exhibit morphological damage characterized by increased mitochondrial potential and membrane density, reduced volume, diminished or absent mitochondrial cristae, and disrupted outer mitochondrial membrane integrity [34] (Fig. 1).

3. Ferroptosis and arrhymias

The mechanism of arrhythmia includes abnormalities in impulse formation and conduction. Changes in the excitability of the autonomic nervous system or disorders affecting its function may result in inappropriate impulse release. Moreover, pathological conditions can induce abnormal automaticity in typically non-autonomous cardiomyocytes, such as atrial and ventricular myocytes. Triggered activity refers to the depolarization of the atrium, ventricle, or His-Purkinje tissue outside the normal activation sequence and is commonly due to early or delayed afterdepolarizations. When occurring repetitively, these afterdepolarizations can by themselves maintain tachyarrhythmias. Conduction block generally plays a pivotal role in the initiation of reentry, which represents the predominant mechanism underlying tachyarrhythmia.

Recent research has found that iron overload selectively diminishes the density of Cav1.3-mediated I_{CaL} in mouse atrial myocytes, resulting in bradycardia, impaired conduction velocity (CV), and susceptibility to AF [8,35], suggesting a link between ferroptosis and arrhythmias. Cardiac electrical remodeling, cardiac structural remodeling and oxdative stress play important roles in arrhythmia pathologies and ferroptosis can cause arrhythmias through all of these mechanisms.

3.1. Cardiac electrical remodeling and ferroptosis

Arrhythmia is closely related to cardiac electrical remodeling. Ion channel remodeling is the basis of cardiac electrical remodeling. Notably, intracellular Na^+ and Ca^{2+} overload, caused by the Na^+ and Ca^{2+} channel remodeling, and the disorder of K^+ currents, play important roles in the occurrence and maintenance of arrhythmias.

Transient outward K^+ current (I_{to}) channels are the main component of action potential phase 1 in cardiac myocytes, and plays a crucial role in action potential duration (APD) [36]. Yue et al. discovered that reduced I_{to} density was associated with alterations in cardiac electrophysiology and facilitated arrhythmia development in a canine model of AF [37]. In the early and middle stages of myocardial infarction, the glutathione metabolic pathway is significantly downregulated, especially GPX4, which protects cells from ferroptosis. Rozanski et al. demonstrated a significant reduction in endogenous GSH levels in rat hearts after myocardial infarction, resulting in oxidative stress-induced changes in the GSH redox status that promoted the remodeling of I_{to} channels and the subsequent downregulation of I_{to}. This downregulation was mitigated by supplementation with GSH [38]. Similarly, decreased GSH levels and subsequent I_{to} downregulation were observed in ventricular myocytes of diabetic rats [39].

Furthermore, the accumulation of ROS during ferroptosis can induce oxidative stress, leading to alterations in ion channels [40–42]. H_2O_2 and angiotensin II (AngII) downregulate a cardiac Na^+ channel (SCN5A) transcription in isolated ventricular myocytes through NF-κB binding to SCN5A promoter, resulting in arrhythmia by reducing the total sodium current and slowing the CV [42]. Additionally, H_2O_2 promotes late sodium current ($I_{Na\text{-}L}$), prolongs APD, induces early afterdepolarization (EADs), triggers activity, and initiates or maintains ventricular fibrillation in elderly rats [40]. Song et al. observed similar effects in guinea pig and rabbit models, in which H_2O_2 prolonged the APD by enhancing the late sodium current in ventricular myocytes. This leads to EADs and post-contraction events while inducing intracellular calcium overload

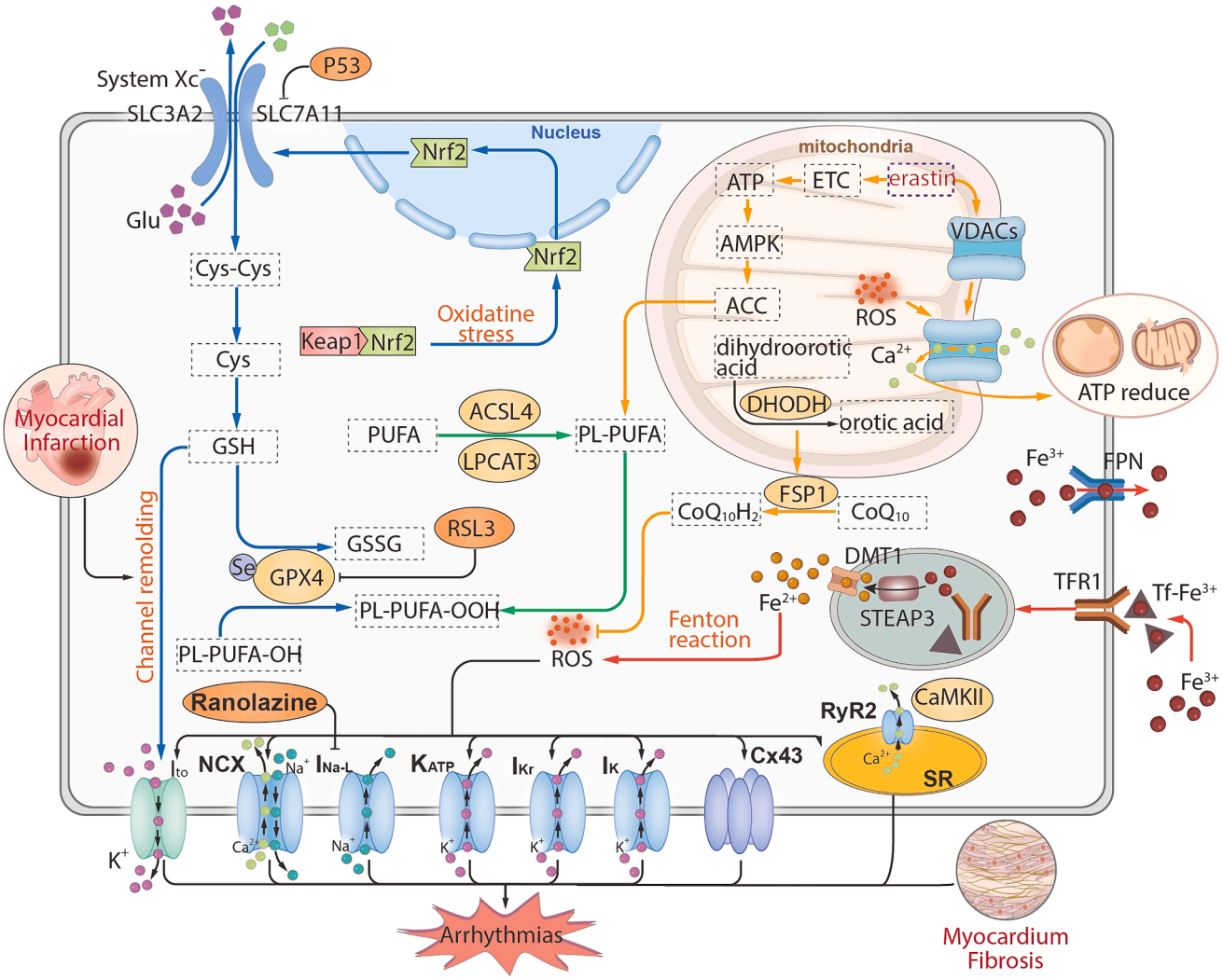

Fig. 1. Schematic diagram of the relationship of ferroptosis and arrhythmias in the cardiomyocyte. (1) Blue lines represent ferroptosis due to disruption of the glutathione antioxidative system and arrhythmias. The dysfunction of the System Xc^- leads to reduced glutathione(GSH) synthesis and decreased antioxidant capacity of the cell. Furthermore, the decrease in GSH leads to the remodeling of the transient outward K^+ current (I_{to}) channel. (2) Red lines represent ferroptosis due to abnormal iron metabolism and arrhythmias. Iron metabolism disorder, leading to intracellular iron accumulation and increased reactive oxygen species (ROS) produced through the Fenton reaction. (3) Green lines represent ferroptosis due to oxidative stress and lipid peroxidation and arrhythmias. Lipids in the cell membrane are oxidized in response to ROS, and GSH can reduce the oxidized lipids to alcohols. (4) Yellow lines represent ferroptosis due to mitochondrial dysfunction and arrhythmias. Mitochondrial dysfunction leads to the accumulation of ROS, ATP synthesis reduction, calcium overload, and ultimately causing the mitochondrial membranes to rupture. ROS accumulation leads to changes in ion channels, including increasing late sodium current ($I_{Na\text{-}L}$), RYR2 phosphorylation and CaMKII activity, inhibiting the delayed-rectifier K + current (I_K), the delayed rectifier potassium current (I_{kr}), and the ATPsensitive K + current (K_{ATP}), and I_{to}, decreasing Connexin43, and increasing the risk of arrhythmia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

via the Na^+/Ca^{2+} exchanger (NCX) mechanism [41]. Ranolazine, a known blocker of late sodium current, inhibits ROS-mediated effects mentioned above [40,41]. Moreover, an increased late sodium current leads to Na^+ accumulation within cardiomyocytes which enhances NCX activity. This results in an elevated cytoplasmic Ca^{2+} concentration, which causes calcium overload [43]. In addition to affecting sodium and calcium channels, ROS can also inhibit cardiac potassium channels, such as the delayed-rectifier K + currents (I_K), and the ATPsensitive K + current (K_{ATP}), resulting in reduced repolarization reserve and prolonged APD, while downregulating I_{to} [44]。.

3.2. *Inflammation, cardiac structural remodeling and ferroptosis*

Inflammation of the heart occurs mainly in myocardial infarction, heart failure, myocarditis, and is closely related to arrhythmia. If inflammation is not healed in a short time, it will cause pathological healing and lead to fibrosis. Myocardial fibrosis serves as an indicator of cardiac structural remodeling and constitutes the underlying mechanism for persistent arrhythmias.

Many studies have found that atrial structural remodeling plays an important role in the development of AF. Myocardial fibrosis is the main marker of atrial structural remodeling, which can disrupt the continuity of muscle bundles, interfere with the formation of tight junctions containing Connexin, and interfere with cardiac electrical conduction, resulting in slow conduction and conduction block [45]. In addition, coupling between cardiomyocytes and fibroblasts/myofibroblasts can change the electrical activity of cardiomyocytes, promote ectopic discharges, and promote the development of AF [46].

Previous studies have indicated that oxidative stress can induce myocardial fibrosis and increase the risk of arrhythmia [47,48]. In patients with chronic myocardial infarction complicated by persistent ventricular tachycardia, electrical conduction slows down in areas

where living cardiomyocytes and fibrous tissue bundles interweave, and in regions where cardiomyocytes are parallel and separated by connective tissue bundles, leading to the reentry phenomenon [48]. Furthermore, a study demonstrated that the administration of hydrogen peroxide to rat and rabbit hearts resulted in varying degrees of fibrosis, thereby eliciting EADs and triggering activity (TA) in ventricular myocytes. Consequently, this led to the development of ventricular tachycardia and ventricular fibrillation [48].

Furthermore, oxidative stress can also affect gap junction conduction between cardiomyocytes, thereby influencing arrhythmias. In a mouse model of cardiac renin-angiotensin system activation using ACE 8/8 mice overexpressing a cardiac-specific angiotensin-converting enzyme, decreased Connexin43 (Cx43) expression led to Cx43 dephosphorylation and reduced function. This weakens the gap junction function and disrupts the connections between cardiomyocytes, resulting in increased susceptibility to ventricular tachycardia and sudden death. However, the administration of angiotensin-converting enzyme inhibitor along with a c-Src inhibitor, which is a tyrosine kinase inhibitor competing for the binding site on Cx43, can reverse these changes [49,50].

3.3. Mitochondrial dysfunction, oxidative stress and ferroptosis

Mitochondrial dysfunction is also closely associated with arrhythmias. Mitochondria produce ATP through oxidative phosphorylation to provide energy for essential ion channels and transport proteins in the sarcoplasmic reticulum and the sarcoplasm of cardiomyocytes. However, mitochondrial dysfunction can deplete the energy required by these channels and proteins, leading to cardiac arrhythmias [51–53].

Abnormalities in the handling of Ca^{2+} ions are frequently observed in atrial cardiomyocytes of patients with AF. And oxidative stress has been linked to both Ca^{2+}-handling irregularities and an increased risk of AF. Calmodulin-dependent protein kinase II (CaMKII) is activated by oxidative stress through oxidation at Met281/282, which is found to be elevated in patients with AF. CaMKII seems to impact the electrophysiology of the atria, potentially through its phosphorylation of RyR2 and Nav1.5. Numerous studies have demonstrated an increase in CaMKII-phosphorylated RyR2, leading to enhanced afterdepolarizations in both ventricular and atrial myocytes due to an elevation in calcium leakage from RyR2 receptors [54,55]. AMPK can be activated by metabolic stress and AF, and it plays a crucial role in preserving the integrity of atrial $I_{Ca\text{-}L}$, Ca^{2+} handling, and cell contractility. Reduced expression of AMPK in the atria resulted in alterations in electrophysiological properties and increased atrial ectopic activity prior to the onset of spontaneous AF [56–58].

Changes in mitochondria morphology during ferroptosis may be closely associated with voltage-dependent anion channels (VDACs), which are channel-forming proteins located on the outer mitochondrial membrane and are responsible for regulating the passive diffusion of hydrophilic anions and respiratory substrates. Closure of VDACs helps inhibit mitochondrial metabolism and reduce mitochondrial membrane potential [59]. Conversely, opening of VDACs along with excessive ROS production leads to calcium overload within mitochondria, promoting the opening of the mitochondrial permeability transition pore (mPTP), exacerbating the reduction in transmembrane potential, and depletion of ATP within mitochondria [60].

Animal experiments conducted by Dai et al. revealed that excessive alcohol consumption led to a substantial increase in serum non-heme iron concentration, iron accumulation, and oxidative stress response within mouse atrial tissue. These changes result in shortened RR intervals, effective refractory periods (ERPs), 90 % action potential duration (APD90), prolonged QTc intervals, and increased risk of AF. However, most of these alterations could be partially or completely reversed using the ferric death inhibitor Fer-1 [7]. Furthermore, Shizukuda's analysis of data from 22 newly diagnosed C282Y homozygous patients with hereditary hemochromatosis revealed a correlation between plasma malondialdehyde (MDA) levels, a biomarker of oxidative stress, and supraventricular arrhythmia activity [61], suggesting that increased oxidative stress is associated with arrhythmias.

Animal experiments have demonstrated that mice lacking selenium exhibit myocardial fibrosis and systolic dysfunction accompanied by increased myocardial oxidative stress levels [62]. Rats fed selenium-rich feed display a reduced incidence and severity of arrhythmias, such as ventricular tachycardia and irreversible ventricular fibrillation prior to cardiac reperfusion injury, compared to rats on normal feeding regimens [63]. Further investigations revealed that this phenomenon was associated with increased mitochondrial and cytoplasmic GSH-Px activity in the cardiomyocytes. In animal models of myocardial infarction, researchers observed that intravenous administration of sodium selenite not only significantly augmented heart rate and aortic maximum flow rate, but also enhanced cardiac output and coronary blood flow. Additionally, it reduced peripheral vascular resistance while exhibiting antiarrhythmic properties. Specifically, it mitigated the occurrence of premature ventricular contractions(PVC) and ventricular flutter (VF), and eradicated ventricular late potentials (VLP) [64].

3.4. Iron overload

The accumulation of iron in cardiomyocytes induces oxidative stress and mitochondrial impairment, ultimately resulting in systolic/diastolic dysfunction and cardiac fibrosis. Multiple studies have demonstrated a correlation between myocardial iron overload and arrhythmias. Patients with chronic iron overload may develop iron overload cardiomyopathy, which is characterized by ventricular arrhythmias and heart failure, leading to increased mortality in individuals with severe β-thalassemia and reduced life expectancy in those with transfusion-dependent refractory anemia, hereditary hemochromatosis, and other iron overload disorders. Cardiac magnetic resonance imaging plays a crucial role in assessing cardiac structure and function for predicting cardiac complications in patients with severe β-thalassemia. The presence of iron deposition significantly reduced the T1, T2, and T2* values (relaxation parameters arising principally from local magnetic field inhomogeneities that are increased with iron deposition), with T2 being the most sensitive parameter for assessing tissue iron overload and providing a quantitative measure of its severity [65,66]. In a study on complications in 88 patients with severe β-thalassemia in Taiwan Lu et al. demonstrated that there was a positive correlation between the magnitude of T2 value on cardiac magnetic resonance imaging and the relative risk of arrhythmia, suggesting an augmented myocardial iron load and an increased incidence of arrhythmia [67]. In another study, Mancuso et al. observed that among 28 adult patients with thalassemia and heart failure, 79 % exhibited T-wave inversion, 46 % experienced supraventricular arrhythmias, 43 % displayed low voltage, 18 % showed a rightward shift of the QRS axis, and 15 % presented an S1Q3 pattern, all indicative of severe cardiac pathological changes [68].

In addition to clinical experiments, animal studies have confirmed that iron overload can result in arrhythmia [69–73]. A gerbil model of iron overload cardiomyopathy was established by subcutaneous injection of iron dextran. Electrocardiography and high-resolution optical imaging were performed on the anterior surface of gerbil hearts. The analysis revealed that gerbils treated with iron exhibited prolonged QRS and PR intervals on their electrocardiogram (ECG), and slowed the action potential CV and conduction block [70]. In another study, a gerbil model of iron overload cardiomyopathy was established using repeated injections of iron glucan. The whole-cell giga-seal technique was used to analyze the action potential of gerbil cardiomyocytes. The peak value of the action potential decreased, whereas the duration decreased in these cells. Additionally, sodium currents in ventricular myocytes from overloaded gerbils decreased, whereas transient outward potassium currents increased; however, inward rectifying potassium currents remained unchanged [72]. Subcutaneous injection of iron dextran in Mongolian gerbils resulted in the prolongation of the PR interval on ECGs along with bradycardia, prolonged QT interval, PVC, varying degrees of

atrioventricular blockage, ST segment changes, and late T-wave inversion. The iron chelator DFO significantly extended the survival period and prevented ECG alterations, but had minimal effect on total cardiac iron content [71]. Walker et al., found a higher incidence rate for PVC among gerbils treated with iron dextran (10/16 = 63 %) and a higher mortality rate before experimental completion (4/16, 25 %) [73]. Furthermore, iron overload selectively diminishes the density of Cav1.3-mediated $I_{Ca\text{-}L}$ in mouse atrial myocytes, resulting in bradycardia, impaired CV, and susceptibility to AF [8,35].

4. Conclusion

Ferroptosis is a recently discovered form of regulated cell death that differs from apoptosis, necrosis, and other modes of cell death. Its primary mechanisms involve iron overload, an imbalance between oxidation and antioxidants due to iron metabolism disorders, and membrane lipid peroxidation. Ferroptosis is associated with the onset and progression of various diseases. Recent studies have also demonstrated its association with arrhythmias. The key mechanisms underlying arrhythmia encompass disturbances in iron and metabolism, lipid metabolism, and mitochondrial dysfunction. However, further experimental research is required to uncover additional mechanisms that can serve as a foundation for anti-ferroptotic treatments targeting arrhythmias.

Funding

This study was supported by Medical Research project of Sichuan Province (S22091), Medical Research project of Sichuan Province (S21111) and Key Laboratory of Medical Electrophysiology of Ministry of Education (KeyME-2018-10).

CRediT authorship contribution statement

Jingsong Shen: Writing – review & editing, Writing – original draft, Conceptualization. **Hengsong Fu:** Writing – original draft. **Yanling Ding:** Writing – original draft. **Ziyang Yuan:** Writing – original draft. **Zeming Xiang:** Writing – original draft. **Miao Ding:** Writing – original draft. **Min Huang:** Writing – original draft. **Yongquan Peng:** Writing – review & editing, Writing – original draft. **Tao Li:** Writing – review & editing. **Kelan Zha:** Writing – review & editing, Visualization, Conceptualization. **Qiang Ye:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ye reports financial support was provided by Southwest Medical University Institute of Cardiovascular Research. Qiang Ye reports a relationship with Southwest Medical University Institute of Cardiovascular Research that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S. Mendis, S. Davis, B. Norrving, Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease, Stroke 46 (5) (May 2015) e121–e122, https://doi.org/10.1161/strokeaha.115.008097.
[2] A. Gheini, A. Pourya, A. Pooria, Atrial fibrillation and ventricular tachyarrhythmias: advancements for better outcomes, Cardiovasc. Hematol. Disord. Drug Targets 20 (4) (2020) 249–259, https://doi.org/10.2174/1871529x20666201001143907.
[3] J.E. Tisdale, M.K. Chung, K.B. Campbell, et al., Drug-induced arrhythmias: a scientific statement from the American heart association, Circulation 142 (15) (2020) e214–e233, https://doi.org/10.1161/cir.0000000000000905.
[4] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, et al., Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072, https://doi.org/10.1016/j.cell.2012.03.042.
[5] D.P. Del Re, D. Amgalan, A. Linkermann, Q. Liu, R.N. Kitsis, Fundamental mechanisms of regulated cell death and implications for heart disease, Physiol. Rev. 99 (4) (2019) 1765–1817, https://doi.org/10.1152/physrev.00022.2018.
[6] Y. Han, J. Zhu, L. Yang, et al., SARS-CoV-2 infection induces ferroptosis of sinoatrial node pacemaker cells, Circ. Res. 130 (7) (Apr 2022) 963–977, https://doi.org/10.1161/circresaha.121.320518.
[7] C. Dai, B. Kong, T. Qin, et al., Inhibition of ferroptosis reduces susceptibility to frequent excessive alcohol consumption-induced atrial fibrillation, Toxicology 465 (2022) 153055, https://doi.org/10.1016/j.tox.2021.153055.
[8] R.A. Rose, M. Sellan, J.A. Simpson, et al., Iron overload decreases CaV1.3-dependent L-type Ca2+ currents leading to bradycardia, altered electrical conduction, and atrial fibrillation, Circ. Arrhythm. Electrophysiol. 4 (5) (2011) 733–742, https://doi.org/10.1161/circep.110.960401.
[9] J. Fang, B. Kong, W. Shuai, et al., Ferroportin-mediated ferroptosis involved in new-onset atrial fibrillation with LPS-induced endotoxemia, Eur. J. Pharmacol. 913 (2021) 174622, https://doi.org/10.1016/j.ejphar.2021.174622.
[10] D. Liu, M. Yang, Y. Yao, et al., Cardiac fibroblasts promote ferroptosis in atrial fibrillation by secreting exo-miR-23a-3p targeting SLC7A11, Oxid. Med. Cell Longev. 2022 (2022) 3961495, https://doi.org/10.1155/2022/3961495.
[11] V. Russo, A. Rago, B. Pannone, et al., Early electrocardiographic evaluation of atrial fibrillation risk in beta-thalassemia major patients, Int. J. Hematol. 93 (4) (Apr 2011) 446–451, https://doi.org/10.1007/s12185-011-0801-3.
[12] H.J. Yang, B. Kong, W. Shuai, J.J. Zhang, H. Huang, Shensong Yangxin attenuates metabolic syndrome-induced atrial fibrillation via inhibition of ferroportin-mediated intracellular iron overload, Phytomedicine 101 (Jul 2022) 154086, https://doi.org/10.1016/j.phymed.2022.154086.
[13] B.R. Stockwell, J.P. Friedmann Angeli, H. Bayir, et al., Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2) (2017) 273–285, https://doi.org/10.1016/j.cell.2017.09.021.
[14] X. Jiang, B.R. Stockwell, M. Conrad, Ferroptosis: mechanisms, biology and role in disease, Nat. Rev. Mol. Cell Biol. 22 (4) (Apr 2021) 266–282, https://doi.org/10.1038/s41580-020-00324-8.
[15] L. Jiang, N. Kon, T. Li, et al., Ferroptosis as a p53-mediated activity during tumour suppression, Nature 520 (7545) (2015) 57–62, https://doi.org/10.1038/nature14344.
[16] W.S. Yang, R. SriRamaratnam, M.E. Welsch, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (1–2) (2014) 317–331, https://doi.org/10.1016/j.cell.2013.12.010.
[17] I. Ingold, C. Berndt, S. Schmitt, et al., Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis, Cell 172 (3) (2018) 409–422.e21, https://doi.org/10.1016/j.cell.2017.11.048.
[18] T.M. Seibt, B. Proneth, M. Conrad, Role of GPX4 in ferroptosis and its pharmacological implication, Free Radic Biol Med. 133 (Mar 2019) 144–152, https://doi.org/10.1016/j.freeradbiomed.2018.09.014.
[19] E. Corradini, E. Buzzetti, A. Pietrangelo, Genetic iron overload disorders, Mol Aspects Med. 75 (Oct 2020) 100896, https://doi.org/10.1016/j.mam.2020.100896.
[20] A. Donovan, C.A. Lima, J.L. Pinkus, et al., The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis, CellMetab. 1 (3) (Mar 2005) 191–200, https://doi.org/10.1016/j.cmet.2005.01.003.
[21] Y. Xie, W. Hou, X. Song, et al., Ferroptosis: process and function, Cell Death Differ. 23 (3) (Mar 2016) 369–379, https://doi.org/10.1038/cdd.2015.158.
[22] X. Wu, Y. Li, S. Zhang, X. Zhou, Ferroptosis as a novel therapeutic target for cardiovascular disease, Theranostics. 11 (7) (2021) 3052–3059, https://doi.org/10.7150/thno.54113.
[23] S. Swaminathan, Iron homeostasis pathways as therapeutic targets in acute kidney injury, Nephron 140 (2) (2018) 156–159, https://doi.org/10.1159/000490808.
[24] S. Lakhal-Littleton, M. Wolna, C.A. Carr, et al., Cardiac ferroportin regulates cellular iron homeostasis and is important for cardiac function, Proc. Natl. Acad. Sci. USA 112 (10) (2015) 3164–3169, https://doi.org/10.1073/pnas.1422373112.
[25] T. Müller, C. Dewitz, J. Schmitz, et al., Necroptosis and ferroptosis are alternative cell death pathways that operate in acute kidney failure, CellMol Life Sci. 74 (19) (Oct 2017) 3631–3645, https://doi.org/10.1007/s00018-017-2547-4.
[26] J.P. Friedmann Angeli, M. Schneider, B. Proneth, et al., Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice, Nat. Cell Biol. 16 (12) (Dec 2014) 1180–1191, https://doi.org/10.1038/ncb3064.
[27] E. Agmon, J. Solon, P. Bassereau, B.R. Stockwell, Modeling the effects of lipid peroxidation during ferroptosis on membrane properties, Sci. Rep. 8 (1) (2018) 5155, https://doi.org/10.1038/s41598-018-23408-0.
[28] J.R. Friedman, J. Nunnari, Mitochondrial form and function, Nature 505 (7483) (2014) 335–343, https://doi.org/10.1038/nature12985.
[29] P. Li, D. Nijhawan, X. Wang, Mitochondrial activation of apoptosis, Cell 116 (2 Suppl) (2004) S57–S59, https://doi.org/10.1016/s0092-8674(04)00031-5, 2 p following S59.
[30] H. Lee, F. Zandkarimi, Y. Zhang, et al., Energy-stress-mediated AMPK activation inhibits ferroptosis, Nat. Cell Biol. 22 (2) (Feb 2020) 225–234, https://doi.org/10.1038/s41556-020-0461-8.
[31] M. Gao, J. Yi, J. Zhu, et al., Role of mitochondria in ferroptosis, Mol. Cell 73 (2) (2019) 354–363.e3, https://doi.org/10.1016/j.molcel.2018.10.042.
[32] C. Mao, X. Liu, Y. Zhang, et al., DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer, Nature 593 (7860) (May 2021) 586–590, https://doi.org/10.1038/s41586-021-03539-7.

[33] Y. Luo, N. Apaijai, S. Liao, et al., Therapeutic potentials of cell death inhibitors in rats with cardiac ischaemia/reperfusion injury, J. Cell Mol. Med. 26 (8) (Apr 2022) 2462–2476, https://doi.org/10.1111/jcmm.17275.
[34] Y. Zhao, Y. Li, R. Zhang, F. Wang, T. Wang, Y. Jiao, The role of erastin in ferroptosis and its prospects in cancer therapy, Onco. Targets Ther. 13 (2020) 5429–5441, https://doi.org/10.2147/ott.S254995.
[35] C. Stewart, A.P. Shortland, The biomechanics of pathological gait - from muscle to movement, Acta Bioeng. Biomech. 12 (3) (2010) 3–12.
[36] T. Volk, T.H. Nguyen, J.H. Schultz, J. Faulhaber, H. Ehmke, Regional alterations of repolarizing K+ currents among the left ventricular free wall of rats with ascending aortic stenosis, J. Physiol. 530 (Pt 3) (2001) 443–455, https://doi.org/10.1111/j.1469-7793.2001.0443k.x.
[37] L. Yue, P. Melnyk, R. Gaspo, Z. Wang, S. Nattel, Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation, Circ. Res. 84 (7) (1999) 776–784, https://doi.org/10.1161/01.res.84.7.776.
[38] G.J. Rozanski, Z. Xu, Glutathione and K(+) channel remodeling in postinfarction rat heart, Am. J. Physiol. Heart Circ. Physiol. 282 (6) (Jun 2002) H2346–H2355, https://doi.org/10.1152/ajpheart.00894.2001.
[39] Z. Xu, K.P. Patel, M.F. Lou, G.J. Rozanski, Up-regulation of K(+) channels in diabetic rat ventricular myocytes by insulin and glutathione, Cardiovasc Res. 53 (1) (Jan 2002) 80–88, https://doi.org/10.1016/s0008-6363(01)00446-1.
[40] N. Morita, J.H. Lee, Y. Xie, et al., Suppression of re-entrant and multifocal ventricular fibrillation by the late sodium current blocker ranolazine, J. Am. Coll. Cardiol. 57 (3) (2011) 366–375, https://doi.org/10.1016/j.jacc.2010.07.045.
[41] Y. Song, J.C. Shryock, S. Wagner, L.S. Maier, L. Belardinelli, Blocking late sodium current reduces hydrogen peroxide-induced arrhythmogenic activity and contractile dysfunction, J. Pharmacol. Exp. Ther. 318 (1) (Jul 2006) 214–222, https://doi.org/10.1124/jpet.106.101832.
[42] L.L. Shang, S. Sanyal, A.E. Pfahnl, et al., NF-kappaB-dependent transcriptional regulation of the cardiac scn5a sodium channel by angiotensin II, Am. J. Physiol. Cell Physiol. 294 (1) (Jan 2008) C372–C379, https://doi.org/10.1152/ajpcell.00186.2007.
[43] E. Murphy, C. Steenbergen, Mechanisms underlying acute protection from cardiac ischemia-reperfusion injury, Physiol. Rev. 88 (2) (Apr 2008) 581–609, https://doi.org/10.1152/physrev.00024.2007.
[44] Y. Yang, W. Shi, N. Cui, Z. Wu, C. Jiang, Oxidative stress inhibits vascular K(ATP) channels by S-glutathionylation, J. Biol. Chem. 285 (49) (2010) 38641–38648, https://doi.org/10.1074/jbc.M110.162578.
[45] G.A. Begg, A.V. Holden, G.Y. Lip, S. Plein, M.H. Tayebjee, Assessment of atrial fibrosis for the rhythm control of atrial fibrillation, Int. J. Cardiol. 220 (2016) 155–161, https://doi.org/10.1016/j.ijcard.2016.06.144.
[46] S. Nattel, How does fibrosis promote atrial fibrillation persistence: in silico findings, clinical observations, and experimental data, Cardiovasc. Res. 110 (3) (2016) 295–297, https://doi.org/10.1093/cvr/cvw092.
[47] K. Koli, M. Myllärniemi, J. Keski-Oja, V.L. Kinnula, Transforming growth factor-beta activation in the lung: focus on fibrosis and reactive oxygen species, Antioxid. Redox Signal. 10 (2) (Feb 2008) 333–342, https://doi.org/10.1089/ars.2007.1914.
[48] N. Morita, A.A. Sovari, Y. Xie, et al., Increased susceptibility of aged hearts to ventricular fibrillation during oxidative stress, Am. J. Physiol. Heart Circ. Physiol. 297 (5) (Nov 2009) H1594–H1605, https://doi.org/10.1152/ajpheart.00579.2009.
[49] S. Iravanian, A.A. Sovari, H.A. Lardin, et al., Inhibition of renin-angiotensin system (RAS) reduces ventricular tachycardia risk by altering connexin43, J. Mol. Med. (Berl.) 89 (7) (Jul 2011) 677–687, https://doi.org/10.1007/s00109-011-0761-3.
[50] A.A. Sovari, S. Iravanian, E. Dolmatova, et al., Inhibition of c-Src tyrosine kinase prevents angiotensin II-mediated connexin-43 remodeling and sudden cardiac death, J. Am. Coll. Cardiol. 58 (22) (2011) 2332–2339, https://doi.org/10.1016/j.jacc.2011.07.048.
[51] M. Schramm, H.G. Klieber, J. Daut, The energy expenditure of actomyosin-ATPase, Ca(2+)-ATPase and Na+, K(+)-ATPase in guinea-pig cardiac ventricular muscle, J. Physiol. 481 (Pt 3) (1994) 647–662, https://doi.org/10.1113/jphysiol.1994.sp020471.
[52] C.L. Overend, D.A. Eisner, S.C. O'Neill, Altered cardiac sarcoplasmic reticulum function of intact myocytes of rat ventricle during metabolic inhibition, Circ Res. 88 (2) (2001) 181–187, https://doi.org/10.1161/01.res.88.2.181.
[53] H.S. Silverman, M.D. Stern, Ionic basis of ischaemic cardiac injury: insights from cellular studies, Cardiovasc Res. 28 (5) (May 1994) 581–597, https://doi.org/10.1093/cvr/28.5.581.
[54] S. Nattel, J. Heijman, L. Zhou, D. Dobrev, Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective, Circ Res. 127 (1) (2020) 51–72, https://doi.org/10.1161/circresaha.120.316363.
[55] S. Yoo, G. Aistrup, Y. Shiferaw, et al., Oxidative stress creates a unique, CaMKII-mediated substrate for atrial fibrillation in heart failure, JCI Insight 3 (21) (2018), https://doi.org/10.1172/jci.insight.120728.
[56] M. Harada, A. Tadevosyan, X. Qi, et al., Atrial fibrillation activates AMP-dependent protein kinase and its regulation of cellular calcium handling: potential role in metabolic adaptation and prevention of progression, J. Am. Coll. Cardiol. 66 (1) (2015) 47–58, https://doi.org/10.1016/j.jacc.2015.04.056.
[57] K.N. Su, Y. Ma, M. Cacheux, et al., Atrial AMP-activated protein kinase is critical for prevention of dysregulation of electrical excitability and atrial fibrillation, JCI Insight 7 (8) (2022), https://doi.org/10.1172/jci.insight.141213.
[58] D. Tong, G.G. Schiattarella, N. Jiang, et al., Impaired AMP-activated protein kinase signaling in heart failure with preserved ejection fraction-associated atrial fibrillation, Circulation 146 (1) (2022) 73–76, https://doi.org/10.1161/circulationaha.121.058301.
[59] D. Fang, E.N. Maldonado, VDAC regulation: a mitochondrial target to stop cell proliferation, Adv. Cancer Res. 138 (2018) 41–69, https://doi.org/10.1016/bs.acr.2018.02.002.
[60] D. De Stefani, A. Bononi, A. Romagnoli, et al., VDAC1 selectively transfers apoptotic Ca2+ signals to mitochondria, Cell Death Differ. 19 (2) (Feb 2012) 267–273, https://doi.org/10.1038/cdd.2011.92.
[61] Y. Shizukuda, D.J. Tripodi, D.R. Rosing, Iron overload or oxidative stress? Insight into a mechanism of early cardiac manifestations of asymptomatic hereditary hemochromatosis subjects with C282Y homozygosity, J. Cardiovasc. Transl. Res. 9 (4) (Aug 2016) 400–401, https://doi.org/10.1007/s12265-016-9704-2.
[62] N. Metes-Kosik, I. Luptak, P.M. Dibello, et al., Both selenium deficiency and modest selenium supplementation lead to myocardial fibrosis in mice via effects on redox-methylation balance, Mol. Nutr. Food Res. 56 (12) (Dec 2012) 1812–1824, https://doi.org/10.1002/mnfr.201200386.
[63] S. Tanguy, F. Boucher, S. Besse, V. Ducros, A. Favier, J. de Leiris, Trace elements and cardioprotection: increasing endogenous glutathione peroxidase activity by oral selenium supplementation in rats limits reperfusion-induced arrhythmias, J. Trace Elem. Med. Biol. 12 (1) (Mar 1998) 28–38, https://doi.org/10.1016/s0946-672x(98)80018-7.
[64] K. Keler, G. Diuk, B. Kuklinski, G. Peters, B. Pole, [Effect of sodium selenite on the course of acute experimental myocardial infarct]. *Kardiologiia.* Sep 1985;25(9):72-6. Vliianie selenita natriia na techenie ostrogo infarkta miokarda v éksperimente.
[65] L.J. Anderson, S. Holden, B. Davis, et al., Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload, Eur. Heart J. 22 (23) (Dec 2001) 2171–2179, https://doi.org/10.1053/euhj.2001.2822.
[66] P. Kirk, M. Roughton, J.B. Porter, et al., Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major, Circulation 120 (20) (2009) 1961–1968, https://doi.org/10.1161/circulationaha.109.874487.
[67] M.Y. Lu, S.S. Peng, H.H. Chang, et al., Cardiac iron measurement and iron chelation therapy in patients with β thalassaemia major: experience from Taiwan, Transfus Med. 23 (2) (Apr 2013) 100–107, https://doi.org/10.1111/tme.12014.
[68] L. Mancuso, A. Mancuso, E. Bevacqua, P. Rigano, Electrocardiographic abnormalities in thalassemia patients with heart failure, Cardiovasc. Hematol. Disord. Drug Targets. 9 (1) (Mar 2009) 29–35, https://doi.org/10.2174/187152909787581345.
[69] P. Carthew, B.M. Dorman, R.E. Edwards, J.E. Francis, A.G. Smith, A unique rodent model for both the cardiotoxic and hepatotoxic effects of prolonged iron overload, Lab. Invest. 69 (2) (Aug 1993) 217–222.
[70] K.R. Laurita, E.T. Chuck, T. Yang, et al., Optical mapping reveals conduction slowing and impulse block in iron-overload cardiomyopathy, J. Lab Clin. Med. 142 (2) (Aug 2003) 83–89, https://doi.org/10.1016/s0022-2143(03)00060-x.
[71] C.A. Obejero-Paz, T. Yang, W.Q. Dong, et al., Deferoxamine promotes survival and prevents electrocardiographic abnormalities in the gerbil model of iron-overload cardiomyopathy, J. Lab Clin. Med. 141 (2) (Feb 2003) 121–130, https://doi.org/10.1067/mlc.2003.18.
[72] Y.A. Kuryshev, G.M. Brittenham, H. Fujioka, et al., Decreased sodium and increased transient outward potassium currents in iron-loaded cardiac myocytes. Implications for the arrhythmogenesis of human siderotic heart disease, Circulation 100 (6) (1999) 675–683, https://doi.org/10.1161/01.cir.100.6.675.
[73] E.M. Walker Jr., R.G. Morrison, L. Dornon, et al., Acetaminophen combinations protect against iron-induced cardiac damage in gerbils, *Ann. Clin. Lab Sci.* Fall 39 (4) (2009) 378–385.