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ORIGINAL

MECHANISMS OF MYOCARDIAL HYPOXIA-INDUCED ENDOPLASMIC RETICULUM STRESS AND MITOCHONDRIAL AUTOPHAGY ON CARDIAC ARRHYTHMIAS IN FITNESS ENTHUSIASTS AND ATHLETES

Miao Hao[1], Guanlin Yang[2], Dongyu Min[3], Ping Hou[4*]

[1] First clinical college，Liaoning University of Traditional Chinese Medicine，Shenyang，110032，China.
[2] Key Laboratory of TCM Viscera Theory and Application of Ministry of Education, Liaoning University of Traditional Chinese Medicine，Liaoning University of Traditional Chinese Medicine，Shenyang，110032，China.
[3] Traditional Chinese medicine experimental center，Liaoning Traditional Chinese Medicine Rehabilitation Center，Shenyang，110083，China.
[4] Cardiology Department，the First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine，Shenyang，110033，China
E-mail: haomiao123asd@126.com

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ABSTRACT

Arrhythmias are a prevalent cardiovascular condition, frequently seen in athletes and fitness enthusiasts due to their high-intensity physical activities, which can complicate or be secondary to heart failure, myocardial hypoxia, ischemia, and in severe cases, lead to sudden death. In the context of athletic and fitness-oriented lifestyles, myocardial hypoxia—often a result of intense physical exertion—can significantly impact endoplasmic reticulum stress and mitochondrial autophagy. The endoplasmic reticulum (ER) plays a crucial role in cellular protein synthesis. Disruptions in ER homeostasis, due to various factors including strenuous physical activity, can lead to an accumulation of misfolded proteins in the ER, triggering ER stress. This stress has been identified in various diseases and is of particular interest in the athletic population, where the body's systems, including the heart, are often pushed to their limits. Furthermore, mitochondrial autophagy, a process vital for maintaining cellular health by degrading and recycling mitochondrial components, has been linked to arrhythmia. This connection is especially pertinent in athletes, as their hearts undergo considerable physiological stress and adaptation in response to ongoing physical demands. This study aims to

explore the mechanisms by which myocardial hypoxia induces ER stress and mitochondrial autophagy, and how these processes contribute to the development of cardiac arrhythmias in athletes and fitness enthusiasts. By focusing on this specific group, the research seeks to provide a deeper understanding of the cardiac risks associated with high levels of physical activity and to inform preventative and therapeutic strategies tailored to this population.

KEYWORDS: Myocardial hypoxia; Endoplasmic reticulum stress; Mitochondrial autophagy; Mrrhythmology

1. INTRODUCTION

Cardiac arrhythmias, characterized by irregular heartbeats, pose a significant health challenge, especially in the context of athletes and fitness enthusiasts. While physical activity is generally beneficial for cardiovascular health, intense and prolonged exercise can lead to adverse cardiac events, including arrhythmias(Bober, Ciriello, & Jones, 2018). This study delves into the mechanisms underlying myocardial hypoxia-induced endoplasmic reticulum (ER) stress and mitochondrial autophagy and their role in the development of cardiac arrhythmias in athletes(Takahashi et al., 2021).

Myocardial hypoxia, a condition where the heart muscle receives insufficient oxygen, is a common consequence of strenuous physical activity. In athletes, who frequently push their cardiovascular systems to the limits, this can lead to significant physiological changes. One such change is ER stress, which occurs when the protein-folding capacity of the ER is overwhelmed, leading to an accumulation of misfolded proteins. This condition is particularly relevant in the context of the heart, as it can disrupt normal cardiac function and potentially lead to arrhythmias(Busch, Van, & Roberts, 1999).

Another critical factor in this equation is mitochondrial autophagy, a process responsible for the degradation and recycling of damaged mitochondria. This process is vital for maintaining cellular health, especially in the heart, which has high energy demands. In the setting of myocardial hypoxia, mitochondrial autophagy can be dysregulated, contributing to cardiac dysfunction and the propensity for arrhythmias(Plant, Xiong, Romero, Dai, & Goldstein, 2020). Athletes, due to their high levels of physical exertion, are at a unique intersection where these two processes—ER stress and mitochondrial autophagy—can converge to impact heart health adversely. This study aims to explore these mechanisms in depth, providing insight into how the heightened physical demands placed on athletes' hearts can lead to the development of arrhythmias(Arturo et al., 2019; Morand, Arnaud, & Pepin, 2018). The goal is to enhance our understanding of the cardiac risks associated with high-intensity athletic activities and to inform strategies for monitoring, preventing, and

treating heart-related complications in this population. By focusing on these key aspects, we can contribute to safer athletic practices and better health outcomes for those engaged in regular, intense physical activity (Zhuan et al., 2020). The mechanism of ERS caused by myocardial hypoxia and mitochondrial autophagy on arrhythmia is still unclear. Therefore, this study reviews the mechanism of ERS caused by myocardial hypoxia and mitochondrial autophagy on arrhythmia (Cuadrado, Lim, Alcontin, Calang, & Jumawan, 2019).

2. The mechanism of endoplasmic reticulum stress induced by myocardial hypoxia on arrhythmia

2.1 Endoplasmic reticulum stress due to myocardial hypoxia

ERS is one of the mechanisms of cardiovascular disease. ERS is suborganelle stress. ER calcium homeostasis imbalance and misfolded protein aggregation can cause er stress. The endoplasmic reticulum is very active and susceptible to environmental factors. In oxygen, sugar, the depletion of atp deficiency, calcium overload, internal and external environmental stress factors such as cell all can cause homeostasis unbalance, did not fold proteins or misfolded proteins in the ER lumen accumulation, which in turn activated protein quality control system, adapting to protein synthesis and degradation, to restore its normal function (Xu et al., 2015).

Er stress can be classified into three types according to different causes: unfolded/misfolded triggered by protein unfolded protein response (UPR), overload response triggered by er transport of overexpressed proteins, and sterol deprivation activation cascade. Among them, UPR is most closely associated with cardiovascular disease. ERS is an adaptive response of cells, which is beneficial to the recovery of ER function and provides guarantee for cell survival. However, Persistent ERS and protein misfolding is not solved, inflammation and apoptosis can be further induced to clear the affected cells. Oxygen is a very important metabolic base in mammals. Maintaining oxygen stability is key to survival, especially normal respiratory, cardiovascular and hematopoietic systems. Changes in oxygen tension are regulated through a variety of oxygen sensitivity pathways. Hypoxia of cardiomyocytes has certain damage to cardiovascular system, and ERS caused by myocardial hypoxia may cause arrhythmias.

2.2 Mechanism of endoplasmic reticulum stress on arrhythmia

(Mennerich et al., 2022) showed that hypoxia mainly affects ER stress response by regulating the PERK pathway. (Niu et al., 2021) showed that down-regulated IRE1-JNK-Beclin1 signaling cascade inhibited ER stress-mediated autophagy and protected neonatal rats from hypoxic-ischemic brain injury. In addition, apolipoprotein A - L - 4 f I simulate peptide can improve obesity rat

myocardial infarction cardiac systolic function and diastolic function, reduce inflammatory reaction, restricted area of myocardial infarction (mi) and myocardial fibrosis cells, reduce the cell necrosis, and through the inhibition of ERS can protect the heart of obese rats with myocardial infarction (D. Wang et al., 2022). ERS induced apoptosis is related to the pathogenesis of myocardial injury caused by hypoxia and ischemia. Studies have shown (Liu et al., 2021) that ERS response is strong in rats with myocardial injury, the expression of apoptoses-related molecule Bcl-2 is significantly decreased, while the pro-apoptotic protein Bax is significantly increased, and the oxygen reduction status of ER is unbalanced. CHOP siRNA transfection in H9c2 cells treated with high glucose and hypoxia can successfully knock down the gene expression of low CHOP. The gene expression of CHOP can effectively reverse the pro-apoptotic effects of cell cycle arrest and hypoxia and promote the up-regulation of Bcl-2 and down-regulation of Bax. In H9c2 cells treated with high glucose and hypoxia, knockdown of low CHOP gene expression can effectively restore the level of ERS-related proteins and improve cardiac function. Interference with CHOP pathway can regulate apoptosis by regulating Bcl-2 and Ero1. Inhibition of ERS can alleviate apoptosis and myocardial injury caused by hypoxia and ischemia. (Zou & Liu, 2021) also suggested that inhibition of er stress by activating MAPK/ERK signaling routing alleviates hypoxia-mediated myocardial cell damage.

ER aggregates abnormally under oxidative stress, viral infection, hypoxia and ischemia and other environmental conditions, resulting in er stress and the production of more partner proteins. Current studies have shown that when exposed to external stimuli, cells will first produce an ERpressure, which is a cellular self-protection response (Tao et al., 2022). Er stress is a signaling passageway involved in the expression and regulation of various genes. Er stress response can be classified into three categories: overload response, sterol cascade response, and UPR. In ERS response, UPR is the main signal transduction pathway, which is the main marker of ERS response, there are three highly correlated signaling pathways in er stress: (1) PERK; ② Activated transcription factor 6 (ATF6); ③ Inositol demand enzyme 1 (IRE1) (Yu et al., 2021). Under normal physiological conditions, these three-star protein molecules bind to the chaperone protein, Glucose regulatedprotein 78 (GRP78), in an inactive state. GRP78 can form complex GRP78/Bip with immunoglobulin-binding protein (Bip), GRP78/Bip is the main regulator of UPR. The expression GRP78/Bip was correlated with ER function, er pressure and cell injury. The isolation of GRP78/Bip from three pressure-sensing protein molecules, PERK, IRE1, and ATF6, combined with unfolded proteins, improved the folding ability of er proteins, reduced the accumulation of misfolded proteins, and thus ensured correct folding of proteins and prevented protein aggregation. As the years passed, multiple studies confirm that ERS can cause cardiovascular diseases, such as myocardial ischemia/reperfusion, dilated cardiomyopathy, hypertension and heart failure (Jin et al., 2017).

In recent years, the ER dysfunction | on the apoptosis of more and more attention. There are three widely recognized ER apoptosis pathways: CHOP gene activation transcriptional pathway, C-Jun amino-terminal kinase (JNKs) activation pathway, and caspase-12 activation pathway. The activated transcription pathway of CHOP gene is a member of the CCAAT enhancer binding protein clan. This pathway leads to cell apoptosis by down-regulating bcl-2 expression, depleting glutathione, and promoting reactive oxygen species production to eliminate damaged cells that cannot restore normal function. The activation pathway of C-Jun amino-terminal kinase (JNKs) refers to that IRE1 is activated under stress and is mediated by Tumornecrosis factor receptor-associated factor 2(TRAF2) and apoptotic signal-regulated kinase 1(ASK1), resulting in the formation of ire1-JNK-TrAF2-ASK1 intricate, which leads to the activation of ASK1 kinase and the activation of JNK pro-apoptotic signal transduction pathway, which transmits signals to components in the nucleus and ultimately regulates cell expression through nuclear transcription factors. Cysteine aspartase 12(Caspase-12) is a unique marker of ERS cell apoptosis. Caspase-12 is a proteolytic enzyme that exists only in the ER and is activated by er stress. Activated Caspase-12 activate caspase-9 by shearing, leading to cleavage and activation of downstream caspase-3 with degraded cell structure and inducing apoptosis by triggering a series of cascade reactions (J. Wang, Hu, & Jiang, 2016). IRE1 is a transmembrane protein located in the ER with dual activities of protein kinase and endonuclides. The activated IRE1 endonuclides generate XBP1 (XBP1s) with transcriptional activity by catalyzing the irregular splicting of XBP1 transcription factor mRNA, thus driving a major UPR gene expression program. IRE1 endonuclease can also degrade specific mRNA substrates, thus participating in the regulation of cell survival and function. In mammals, the IRE1 signaling pathway is involved in regulating a wide range of biological processes, including cellular destiny, metabolic homeostasis, and immune responses. IRE1 activation is initiated by homotypic interactions of pressure-sensing cavity domains that favor trans-autophosphorylation of the nuclease domain extended by kinases on the cytoplasmic side of the ER membrane.

At the onset of er stress, GRP78/Bip has an anti-apoptotic effect due to its induced expression. To reduce the burden of er, UPR mainly increases protein mRNA degradation through the PERK and IRE1 pathways, inhibits protein translation, and accelerates protein degradation. PERK is an ERS sensor that relieves ERS damage and by means of inhibits myocardial apoptosis, which plays a main role in slowing down the happen of heart failure. Platelet reactive protein 4 is an effector molecule of er stress response, which can activate ATF6a to improve the expression of quality control protein in er and contribute to its production of complex protective molecular chaperone, which plays a protective role in myocardial cells. In ERS response, PERK, as a type 1 trans-er protein, senses ERS and transmits stress signals to the cytoplasm and nucleus. Activation after PEAK phosphorylation leads to reduced

translation, reduced protein synthesis, and relieved ER stress. Activation of PERK signaling pathway occurs in the primeval phase of ERS, which inhibits protein synthesis and promotes cell survival. With persistent er stress, PERK promotes CHOP expression levels, which in turn promotes apoptosis. PERK specific phosphatase dephosphorylation inhibits PERK and regulates in the central nervous system, hypoxia, ischemia-reperfusion injury, and metabolic abnormalities. Another er stress response pathway is mediated by ATF6. ATF6 is an ER transmembrane protein, it is a member of the Leucine zipper transcription divisor family. Under normal conditions, there are two configurations in the ERS, namely ATF6u and ATF6β, both of which are members of the cyclic adenosine effector element binding protein transcription factor family, and their amino terminal cytoplasmic region has a essential leucine zipper DNA transcription stimulation environment. ATF6 exists in the ER, and its domain in the ER entocoele unite to GRP78. When ERS occurs, ATF6 dissociates from GRP78, and free ATF6 is activated to produce active ATF6x fragment, which is transferred to the nucleus to regulate UPR gene transcription. The transcriptional expression of Bip, XBP1, CHOP and other proteins was induced.ERS is closely related to electrical remodeling of cardiomyocytes and cardiomyopathy. In recent years, UPR has been reported to regulate a variety of cardiac ion channels, for example, activation of UPR leads to posttranslational modification of Na1.5 and related auxiliary subunits, and the PERK signaling pathway down-regulates the expression of NA.1.5 and Kv4.3. HERG plasma channels lead to cardiac arrhythmias (Liao et al., 2021). All channel proteins are packaged and change the structure in the ER, and ion channels can operate normally only in the stable state of the ER (Zhou & Li, 2019).There are many passageways relevanted to ERS induced arrhythmias(FIG.1).

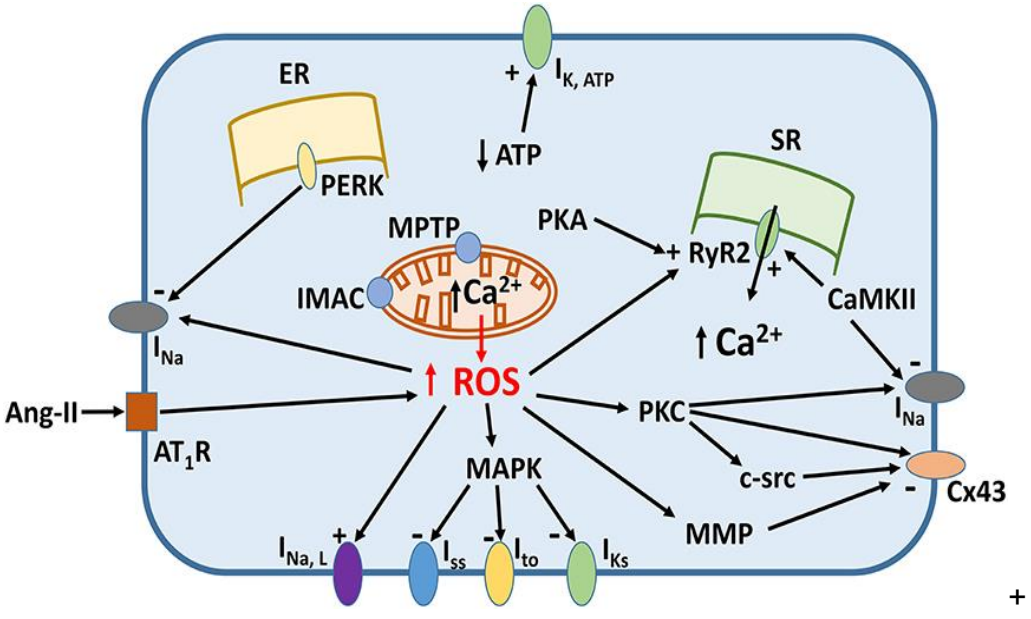

Figure 1: Signal passageways relevanted to ERS leading to arrhythmia (Tse, Yan, Chan, Tian, & Huang, 2016).

3. Effect of mitochondrial autophagy induced by myocardial hypoxia on arrhythmia

3.1 Mitochondrial autophagy due to myocardial hypoxia

Eukaryotic cells deal with genetic disturbances, nutritional deficiencies, senescence, oxidative stress and toxic environmental damage through a highly self-regulated "self-feeding" process known as autophagy. Autophagy can remove abnormal mitochondria in time, and thus keep the cell's energy supply normal. The regulation of mitochondrial autophagy is related to cell senescence, genome stability, tumor formation and hypoxic-ischemic lesions (Yang et al., 2020). Mitochondria is the center of cell energy metabolism and life sustaining activities and is one of the main targets of hypoxia injury. When hypoxia occurs, the metabolic mode of cells changes from oxidative phosphorylation to anaerobic glycolysis, resulting in insufficient energy supply and lack of oxygen molecules as electron acceptors, resulting in the production of large amounts of reactive oxygen species in electron transport chain complexes. These reactive oxygen species can destroy proteins, lipid membrane molecules and nucleic acids, resulting in mitochondrial damage and dysfunction. The contents of damaged mitochondria are released into the cytoplasm and trigger mitochondria-related apoptosis by activating the downstream Caspase cascade, thereby causing cell damage. Stable mitochondrial function and structure are key factors for cell survival under hypoxia. In addition to inducing apoptosis, mitochondrial injury sometimes induces mitochondrial autophagy. Mitochondrial autophagy, which selectively isolates and degrades damaged or incomplete mitochondria, plays an important role in many biological processes. Under normal circumstances, autophagy of mitochondria plays a certain role in clearing mitochondrial dysfunction and plays a certain protective role in cells by reducing the excessive generation of reactive oxygen species. However, sustained or severe injury may induce excessive mitochondrial autophagy, resulting in excessive mitochondrial destruction, thus aggravating injury and accelerating cell death (H. Wu et al., 2019). The interaction between ERS and mitochondrial autophagy is one of the mechanisms leading to cell proliferation. Mitochondrial autophagy is a common and necessary mechanism to protect human mitochondria and highly unsaturated mitochondrial membranes. Dysfunction of mitochondrial autophagy will produce pathogenic effects (Fu & Huang, 2020).

3.2 Mechanism of mitochondrial autophagy induced by myocardial hypoxia

Mitochondrial autophagy is an evolutionarily conserved cellular process. There are many pathways related to mitochondrial autophagy in mammals, among which PINK1 / Parkin, Nix/Bnip3 and FUNDC1 have been confirmed. Studies have shown that regulating the PI3K-Akt pathway can induce

mitochondrial autophagy to reduce myocardial cell apoptosis (Chen, 2021). In addition, previous studies have found that regulating the MTORC1-ULK1-FundC1 pathway can reduce mitochondrial autophagy and reduce myocardial injury (Xiao, 2020). Multiple studies (Ren, 2020; Zhu et al., 2019) have shown that regulation of PINK1/Parkin pathway can regulate mitochondrial autophagy to alleviate myocardial ischemia-reperfusion injury. Mitochondrial outer membrane protein BNIP3L/NIX mediates mitochondrial autophagy during ischemia/reperfusion by interacting with autophagic protein LC3. After cerebral hypoxia and ischemia, BNIP3L dimer degrades through the ubiquitin proteasome pathway, resulting in mitochondrial autophagy loss. Inhibition of BNIP3L loss reverses mitochondrial autophagy loss and plays a neuroprotective role (X. Wu). The inhibition of mitochondrial autophagy in HL-1 cells can increase mitochondria-derived ROS, thereby increasing RyR2 overactivity, and the reduction of mitochondrial autophagy contributes to the changes of arrhythmia in aging cardiomyocytes. Well-controlled mitochondrial homeostasis, including mitochondrial autophagy, is critical for maintaining cardiac function. Mitochondrial autophagy in the heart was temporarily activated in response to Pressure overload (PO) but was observed after conventional autophagy was down-regulated. In PO process, the loss of mitochondrial autophagy is the main factor affecting mitochondrial dysfunction and heart failure (Fabrizio & Alessandro, 2018). The TAC-induced mitochondrial autophagy is mediated through the ULK1-dependent mechanism, and Ulk1 plays a key role in the protection of myocardial cells during the mediation of PO. In addition, there are many potential pathways of mitochondrial autophagy affecting arrhythmia(FIG.2).

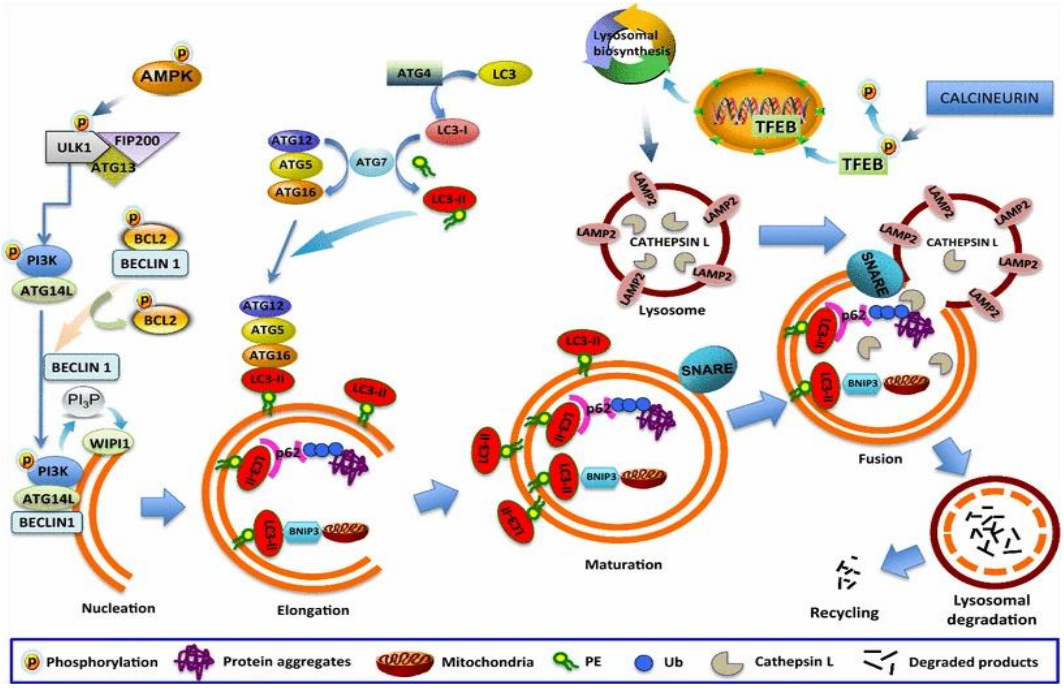

Figure 2: Potential signaling pathways related to arrhythmias caused by mitochondrial autophagy (Lee et al., 2017)

4. Cause of ERS and mitochondrial autophagy on arrhythmia induced by myocardial hypoxia

Cardiomyocyte apoptosis is a major pathological process of cardiovascular diseases, mainly caused by hypoxia. In addition, hypoxic damage is not only a common cardiovascular disease, but can also appear after different treatments. Oxidative stress is an important cause of hypoxia injury. The quercetin pretreatment inhibits H/ R-mediated reactive oxygen species （ROS） production overload and oxidative stress-induced damage and increases mitochondrial autophagy. Regulating the mRNA expression and protein expression level of transmembrane BAX inhibitor motif-containing 6 (TMBIM6), regulating ERS, and increase the susceptibility of cardiomyocytes to H/R. Regulation of SIRT1/TMBIM6 can regulate mitochondrial autophagy and ERS.

Mitochondrial injury may be one of the important mechanisms leading to pulmonary artery smooth muscle injury. In addition, the inhibitory effect of MdiVI-1 on mitochondrial fracture can reduce mitochondrial destruction of hypoxic PASMC, reduce ER stress, and improve the function of pulmonary artery smooth muscle in hypoxic rats. In addition, by inhibiting mitochondrial autophagy and alleviating ERS, the expression level of apoptosis-related proteins in cardiomyocytes can be reduced significantly, and the myocardial injury induced by hypoxia and reoxygenation can be significantly reduced, and the cardiac function can be improved in rats. When the neurotransmitter acetylcholine is combined with it, parasympathetic M2AChR will cause parasympathetic excitation, which is a potential target for treating hypoxia and reoxygenation injury. In addition, M2AChR can regulate mitochondrial functional status through the PINK/Parkin pathway to reduce the damage caused by hypoxia and reoxygenation of cardiomyocytes, including improving mitochondrial autophagy, fusion division and mitochondrial function. In addition, the reduction of ERS in I/R injury through pharmacologic intervention is also closely related to M2AChR.

5. Conclusion

This study highlights the intricate relationship between myocardial hypoxia-induced endoplasmic reticulum stress and mitochondrial autophagy and the development of cardiac arrhythmias, particularly in athletes and fitness enthusiasts. The findings underscore that intense physical exertion, characteristic of athletic activities, can precipitate myocardial hypoxia, leading to significant ER stress and altered mitochondrial autophagy. These physiological responses, while part of the body's adaptive mechanism to increased physical demands, can increase the risk of arrhythmias in this population. For athletes, understanding these mechanisms is crucial, as it underscores the importance of monitoring heart health, especially for those

engaged in high-intensity sports. The study provides valuable insights into the need for tailored cardiac care and preventive strategies for athletes, balancing the benefits of their training regimes with the potential cardiac risks involved. Moreover, the research points to the potential for developing targeted therapies and intervention strategies that address the unique cardiac stressors faced by athletes. This could involve innovative approaches to training, recovery, and medical interventions that specifically mitigate the risks of ER stress and mitochondrial autophagy-related arrhythmias. In conclusion, while athletic pursuits offer numerous health benefits, this study serves as a reminder of the critical need to be cognizant of the cardiac risks associated with high-level physical activity. It calls for a collaborative approach involving athletes, coaches, and medical professionals to ensure heart health is given paramount importance in the pursuit of athletic excellence.

Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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