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Exploring Acute High-Altitude Hypoxic Myocardial Injury from the Perspective of Mitochondrial Quality Control

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Abstract: ***Acute high-altitude hypoxic exposure-induced myocardial injury poses a serious threat to the health of populations in high-altitude areas. Clinically, it primarily manifests as chest tightness, palpitations, shortness of breath, arrhythmias, and abnormal myocardial enzyme profiles. In severe cases, it can present as congestive heart failure. The main cause lies in the disruption of the mitochondrial quality control system under hypoxic conditions, leading to damage to mitochondrial structure and function. Therefore, this paper aims to systematically introduce the mitochondrial quality control system, elucidate the mechanisms of mitochondrial quality control imbalance during acute high-altitude hypoxia and its correlation with myocardial injury, and explore related treatment interventions in both traditional Chinese medicine and Western medicine.***

Keywords: High-altitude hypoxia, Myocardial injury, Mitochondrial quality control**.**

1. Introduction

Acute high-altitude hypoxic myocardial injury refers to a high-altitude disease characterized by pathophysiological changes such as degeneration and necrosis of myocardial cells caused by the characteristic hypoxic environment of high altitudes when people from low-altitude areas enter high-altitude regions [1]. In recent years, with the development of high-altitude areas, an increasing number of people from plain areas have been traveling to high altitudes, leading to a gradual rise in the incidence of acute high-altitude hypoxic myocardial injury [2]. The myocardium, as one of the most metabolically active organs in the body, is extremely sensitive to ischemia and hypoxia [3]. When humans rapidly enter high altitudes and experience acute hypoxia, hypoxia activates the adrenergic regulatory system, causing an increase in heart rate, while blood oxygen saturation significantly decreases, and respiratory rate and heart rate increase compensatorily [4]. These changes can exacerbate myocardial load, induce acute myocardial injury, and manifest as clinical symptoms such as chest tightness, palpitations, abnormal heart rate, and blood pressure [5]. Studies have shown that at altitudes above 3000 m, acute high-altitude exposure can lead to severe congestive heart failure, causing significant myocardial damage [6]. As altitude increases, the degree of hypoxia worsens, and the risk of myocardial injury also increases. Meanwhile, acute high-altitude hypoxic myocardial injury is highly prone to coexist with other high-altitude diseases, and mortality is high after disease progression [7]. Currently, physical treatment options for acute high-altitude hypoxic myocardial injury are often limited by factors such as resources and terrain [8], while drug treatments primarily target high-altitude cerebral edema and high-altitude pulmonary edema [9], lacking targeted drug therapies for myocardial injury. In recent years, although numerous domestic and international studies on protective factors and related signaling pathways in acute high-altitude hypoxic myocardial injury have been completed, the molecular mechanisms underlying acute high-altitude hypoxic myocardial injury remain unclear. Most studies suggest that it is mainly associated with oxidative stress, energy disturbance, apoptosis, inflammatory response, and disruption of mitochondrial structure and function [10,11]. The heart, as the blood-pumping organ for the entire body, requires mitochondria to provide substantial energy to maintain its continuous pumping function. Mitochondria are not only the primary source of ATP in myocardial cells but also involved in processes such as calcium homeostasis maintenance, ROS regulation, and apoptosis [12]. The stability of mitochondrial structure and function is closely related to acute high-altitude hypoxic myocardial injury. Current research has found that mitochondrial quality control, as a multi-level, dynamic cellular monitoring and maintenance system, can maintain mitochondrial structural integrity, normal function, and stable quantity. By coordinating multiple mechanisms, it maintains cellular energy metabolism and internal environment stability, serving as a crucial guarantee for the healthy, efficient, and sustainable operation of the cellular energy factory. Therefore, this article will systematically elaborate on how acute high-altitude hypoxic conditions disrupt mitochondrial quality control and explore its role as an integrated mechanism in myocardial injury and therapeutic implications.

2. Mitochondrial Quality Control

2.1 Overview of Mitochondrial Quality Control

Mitochondrial quality control is an intracellular system that ensures the health and efficiency of the energy factories, mitochondria. It is not a single process but is synergistically constituted by three interconnected and mutually regulating mechanisms: mitochondrial biogenesis, mitochondrial dynamics (fission and fusion), and mitophagy [13]. The core goal of mitochondrial quality control is to dynamically maintain the quantity, structure, function, and overall health of the mitochondrial network in response to changing cellular energy demands and internal/external environmental stresses. These three mechanisms do not operate in isolation; instead, they form a precise, cyclical “production - maintenance -

disposal" quality management system. These three processes are tightly coupled, forming a self-regulating feedback loop [14]. Among them, the mitochondrial dynamics process is the link for dynamic control and repair of mitochondrial quality, while mitophagy and mitochondrial biogenesis can control the degradation and renewal of mitochondria, thereby achieving dual regulation of mitochondrial quantity and quality.

2.2 Mitochondrial Biogenesis

Mitochondrial biogenesis refers to the biological process by which cells increase mitochondrial quantity and enhance mitochondrial function through related regulatory mechanisms. Its core purpose is to improve the overall metabolic efficiency of mitochondria by increasing mitochondrial DNA (mtDNA) copy number and the synthesis of metabolism-related proteins (such as oxidative phosphorylation enzyme complex subunits), thereby providing sufficient ATP for cells to adapt to changes in energy demand. Mitochondrial biogenesis is regulated by a complex molecular network, and its core pathway involves the following key factors: SIRT1, by deacetylating and activating downstream core regulatory factors, coordinates the transcription of nuclear-encoded mitochondrial genes; within mitochondria, SIRT1 also possesses antioxidant and anti-apoptotic functions, which are crucial for maintaining cardiomyocyte health [15]. Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is widely recognized as the master regulator of mitochondrial biogenesis. Its activity is regulated by phosphorylation, acetylation, etc., in response to changes in energy demand. Furthermore, PGC-1α can activate downstream nuclear transcription factors to jointly drive the expression of mitochondrial-related genes in the nuclear genome. Nuclear respiratory factor 1 (NRF1), upon activation by PGC-1α, directly regulates the expression of genes such as mitochondrial transcription factor A (TFAM), thereby transmitting signals to the mitochondrial genome [16]. Nuclear respiratory factor 2 (NRF2) primarily participates in regulating the expression of nuclear-encoded oxidative phosphorylation protein genes. Simultaneously, it is a key regulator of the antioxidant response, enhancing the cell's ability to scavenge oxygen free radicals and protecting mitochondria from oxidative damage. TFAM plays a dual role: firstly, as a packaging protein for mtDNA, it helps maintain its structural stability; secondly, as a transcription factor, it specifically binds to mtDNA promoters to initiate mtDNA transcription and replication [17]. Mitochondrial biogenesis is of great significance for maintaining cellular energy homeostasis and organ function, especially in the heart.

2.3 Mitochondrial Dynamics

Mitochondria can alter their morphology and maintain structural and functional stability through frequent fusion and fission, a process known as mitochondrial dynamics [18]. Mitochondrial fusion is primarily mediated by Mfn1/2 and OPA1, while mitochondrial fission is regulated by Drp1 and Fis1. Under normal conditions, fusion enables functional complementation between damaged mitochondria, and fission helps remove structurally impaired mitochondria, thereby preserving the function of healthy mitochondria and maintaining mitochondrial homeostasis [19].

Mitochondrial fission can be regulated by various proteins. Current research indicates that it primarily involves proteins that regulate mitochondrial fission, including Drp1 and Fis1. Among them, Drp1 is the main regulator of mitochondrial fission. As a GTPase, its hydrolytic activity is finely regulated to ensure strict control of mitochondrial volume according to cellular needs [20]. Aishwarya et al. found that when the activity of the Drp1 protein was inhibited by using the mitochondrial fission inhibitor mdivi-1, mitochondrial function in cardiomyocytes was significantly impaired [21]. Moreover, whether through repeated application of mdivi-1 or global gene knockout to achieve sustained attenuation of Drp1 activity, tissue damage is exacerbated [22]. Drp1 exerts its key role in controlling mitochondrial fission through phosphorylation at serine 616 (Ser616) [23]. Phosphorylation at Ser616 rapidly activates Drp1, promoting its assembly into ring-like structures around the outer mitochondrial membrane (OMM). These ring structures are recruited to the OMM and bind to receptors, including Fis1, mitochondrial fission factor (MFF), and mitochondrial dynamic proteins 49 and 51 (MiD49 and MiD51), thereby stimulating its GTPase activity at mitochondrial fission sites and ultimately inducing mitochondrial fission [24]. Furthermore, the expression of the Fis1 protein is also crucial. Its deficiency significantly inhibits the mitochondrial fission process, while its overexpression leads to the production of small, fragmented mitochondria [25]. Therefore, Fis1 is also an important protein involved in regulating the mitochondrial fission process.

Mitochondria, as organelles with a double-membrane structure, have independent fusion processes for their inner and outer membranes, yet these processes are highly coordinated [26]. This highly coordinated regulatory mechanism for mitochondrial inner and outer membrane fusion may be closely related to the interaction between OPA1 and Mfn1/2 during mitochondrial fusion. Mitochondrial fusion is primarily regulated by three related proteins: fusion of the outer mitochondrial membrane (OMM) is regulated by Mfn1/2, while fusion of the inner mitochondrial membrane (IMM) is mainly regulated by OPA1 [27]. The first step in OMM fusion is tethering mediated by Mfn1/2. Mfn1/2 proteins are anchored to the OMM via their transmembrane domains and utilize their guanosine triphosphatase (GTPase) activity to regulate membrane interactions. After tethering, mitochondria are brought into closer proximity through trans-interactions between MFN proteins, aiming to bring the outer membranes of two mitochondria into tighter contact. This step requires GTP binding and hydrolysis, ultimately leading to the merging of the outer membranes [28]. IMM fusion mainly involves OPA1, which can induce the formation of membrane protrusions. These protrusions play a key role in mitochondrial fusion. The completion of inner membrane fusion is marked by the contact and fusion of protrusions from the inner membranes of two mitochondria [29]. Furthermore, OPA1 is also involved in the formation and shaping of mitochondrial cristae, which is crucial for maintaining the structural integrity and function of the mitochondrial interior [30]. Studies have shown that mutations in the mitochondrial fusion gene OPA1 can disrupt the mitochondrial reticulum structure, leading to extensive mitochondrial fragmentation and a significant reduction in ATP production [31].

2.4 Mitophagy

Mitophagy is a selective autophagy process that specifically recognizes and removes damaged or excess mitochondria, thereby maintaining mitochondrial quality, cellular metabolic homeostasis, and energy balance. As an important cellular quality control mechanism, it is primarily activated under stress conditions such as reactive oxygen species (ROS) accumulation and loss of mitochondrial membrane potential. The process can be divided into four stages. Damaged Mitochondrion Recognition and Depolarization: Dysfunctional mitochondria experience a decrease in membrane potential, initiating the autophagic signal. Autophagosome Engulfment: A double-membrane phagophore engulfs the mitochondrion, forming a mitophagosome. Fusion with Lysosome: The mitophagosome fuses with a lysosome to form an autolysosome. Degradation and Recycling: Lysosomal enzymes degrade mitochondrial components, enabling nutrient recycling [32]. Mitophagy mainly involves two molecular mechanisms. Ubiquitin - dependent pathway: Represented by the PINK1/Parkin pathway. Under normal conditions, PINK1 is degraded by mitochondrial proteases; when mitochondria are damaged, PINK1 accumulates and is activated on the outer mitochondrial membrane, recruiting and activating the E3 ubiquitin ligase Parkin, which promotes ubiquitination of outer mitochondrial membrane proteins. The ubiquitin chains are phosphorylated by PINK1 and then recognized by autophagy adaptor proteins (such as p62, NDP52, OPTN), initiating autophagy. This pathway can also be Parkin-independent, with PINK1 directly phosphorylating ubiquitin and recruiting autophagy proteins [33]. Ubiquitin-independent pathway: Mediated by mitophagy receptors (such as NIX, BNIP3, FUNDC1). These receptors contain an LC3-interacting region (LIR) and can directly bind to the autophagy-related protein LC3, guiding the autophagosome to engulf the mitochondrion [34].

3. Disruption of Mitochondrial Quality Control

Acute high-altitude hypoxia initiates a core injury axis of "energy crisis–calcium overload–mROS burst," leading to rapid and specific disruption of the core components of myocardial mitochondrial quality control—biogenesis, dynamics, and mitophagy—ultimately driving cardiomyocyte death due to the inability to maintain functional mitochondria.

3.1 Mitochondrial Biogenesis

Hypoxia disrupts mitochondrial biogenesis through multi-layered mechanisms, with the core being the inhibition of the central regulatory pathway and the initiation of a vicious cycle of energy and quality control. At the molecular level, hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), which directly or indirectly inhibits the expression and activity of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α). PGC-1α is a key regulator of mitochondrial biogenesis, and its decreased activity leads to reduced expression of downstream critical transcription factors, such as nuclear respiratory factors 1/2 (NRF1/2) and mitochondrial transcription factor A (TFAM). NRF1/2 regulate nuclear-encoded mitochondrial protein genes, while TFAM is crucial for mitochondrial DNA (mtDNA) transcription, replication, and maintenance [35]. Consequently, inhibition of this pathway reduces the synthesis of new mitochondria. At the functional and structural levels, the aforementioned molecular changes result in an insufficient number of newly generated mitochondria, failing to replenish those damaged and cleared due to hypoxic stress. Simultaneously, acute hypoxia itself triggers a decrease in mitochondrial membrane potential, a burst of reactive oxygen species (ROS), and the opening of the mitochondrial permeability transition pore, exacerbating mitochondrial damage [36]. Thus, hypoxia disrupts mitochondrial structure and function, ultimately causing severe myocardial injury, through a coherent mechanism of inhibiting biogenesis signaling, reducing mitochondrial neogenesis, and aggravating the imbalance between energy and oxidative stress.

3.2 Mitochondrial Dynamics

Under normal conditions, mitochondrial fusion not only maintains the stability of its own reticular structure but also positively influences mitochondria-endoplasmic reticulum coupling, promoting the distribution of proteins and mitochondrial DNA, thereby maintaining normal oxidative phosphorylation function. Mitochondrial fission can promote cell proliferation, enabling the specific clearance of damaged mitochondria or fragments through the mitophagy pathway, preventing the diffusion of reactive oxygen species and the release of apoptotic factors [37]. The dynamic balance between mitochondrial fission and fusion is a crucial mechanism for maintaining the structural and functional stability of cardiomyocytes [38]. Mitochondrial dynamics is a core mechanism for maintaining mitochondrial quality and function, and its imbalance is involved in the pathological processes of various cardiovascular diseases [39,40]. Acute high-altitude hypoxia rapidly activates several kinases, promoting the phosphorylation of Drp1 at the serine 616 site [41], which subsequently affects calcium pump function, leading to an increase in cytoplasmic calcium concentration [42]. Calcium signaling can directly or indirectly promote Drp1 activation via calcium/calmodulin-dependent protein kinase (CaMK) [43], thereby inducing excessive mitochondrial fission. Through disrupting energy metabolism structures, amplifying oxidative damage, and directly initiating cell death programs, and interacting with autophagy dysfunction and biogenesis inhibition, it propels cardiomyocytes toward death [44]. Fis1, as a receptor on the OMM, binds to Drp1 recruited around the OMM during hypoxia, participating in mitochondrial fission [45]. Studies have found that mitochondrial fission is inhibited by knocking down Fis1 [46]. Both forms of OPA1 are essential for fusion. During hypoxia, long-form OPA1 is rapidly converted to short-form. The accumulation of short-form OPA1 can inhibit mitochondrial fusion and potentially accelerate mitochondrial fission [47]. Furthermore, endoplasmic reticulum stress and increased ROS during hypoxia may activate the ubiquitin-proteasome system, leading to Mfn2 degradation and inhibiting mitochondrial fusion [48]. Therefore, during acute high-altitude hypoxia, mitochondrial fusion is suppressed, and excessive mitochondrial fission ultimately leads to myocardial injury.

3.3 Mitophagy

First, in the early stages of hypoxia, mitochondrial electron transport chain function is impaired, electron leakage increases, and a large amount of reactive oxygen species (ROS) is generated and accumulates. This excess ROS inhibits the activity and expression of mitophagy-related proteins. Although hypoxia can upregulate the expression of its downstream target gene BNIP3 by activating HIF-1α, thereby promoting Beclin-1 release and LC3-II conversion to initiate mitophagy for clearing damaged mitochondria, this protective pathway gradually becomes imbalanced under sustained or severe hypoxic conditions. As hypoxia persists, ATP synthesis is severely insufficient, plunging cells into an energy crisis, which hinders the energy-dependent processes of autophagosome formation, engulfment, and fusion with lysosomes [49]. Concurrently, intracellular Ca^{2+} overload activates calcium-dependent proteases, disrupts the structure of autophagy-related proteins, and induces the opening of the mitochondrial permeability transition pore, exacerbating mitochondrial damage. Therefore, during acute high-altitude hypoxia, impairment of mitophagy contributes to myocardial injury.

4. Mitochondrial Quality Control Imbalance and Acute High-Altitude Hypoxic Myocardial Injury

The survival and efficient contraction of cardiomyocytes are highly dependent on a continuous, substantial supply of adenosine triphosphate (ATP) from mitochondria. Mitochondrial quality control (MQC) is a precise and dynamic regulatory system that maintains the homeostasis of the mitochondrial network in terms of quantity, morphology, function, and structure through the coordinated operation of its three core components: biogenesis, dynamics, and mitophagy. However, during acute myocardial hypoxia, this system experiences comprehensive and severe imbalance, leading to irreversible cardiomyocyte damage. The direct consequences triggered by MQC imbalance lead to cardiomyocyte injury and death through three primary pathways: (1) Energy Collapse: A sharp reduction in mitochondrial quantity and structural fragmentation directly weaken ATP synthesis capacity, diminishing the energy source for cardiomyocytes, impairing cardiac function, and causing myocardial cell damage [50]. (2) Oxidative Stress Storm and Apoptosis: Dysfunctional mitochondria not only fail as energy producers but also become major sources of reactive oxygen species (ROS). Accumulated ROS attack lipids, proteins, and DNA, causing oxidative damage. Simultaneously, fragmented and dysfunctional mitochondria experience a severe drop in membrane potential, and sustained opening of the mitochondrial permeability transition pore (mPTP) leads to the release of pro-apoptotic factors like cytochrome c into the cytosol. This activates proteases such as caspase-3, irreversibly initiating the mitochondrial pathway of apoptosis [51]. (3) Exacerbated Inflammatory Response: Damaged mitochondria release damage-associated molecular patterns (DAMPs) like mitochondrial DNA and formyl peptides. Recognized by pattern recognition receptors, these activate pathways such as the NLRP3 inflammasome, triggering intense local and systemic inflammatory responses that further attack cardiomyocytes and hinder tissue repair [52].

In summary, the imbalance in mitochondrial quality control manifests as fission/fusion imbalance, excessive autophagy, and inhibited biogenesis, ultimately leading to pathological reactions including energy failure, oxidative stress, apoptosis, and amplified inflammation. These pathological reactions constitute important mechanisms of myocardial injury during acute high-altitude hypoxia.

5. Intervention Strategies Targeting Mitochondrial Quality Control and Future Perspectives

Mitochondrial quality control has become a core target for the prevention and treatment of myocardial injury in recent years, with both Western and traditional Chinese medicine (TCM) showing significant potential in this field. Western medicine primarily employs targeted interventions, improving mitochondrial function by regulating specific molecular pathways. For instance, inhibiting the FOXO1-ROCK1 axis can help maintain mitochondrial homeostasis and alleviate hypoxic myocardial injury; antioxidants such as melatonin and N-acetylcysteine can scavenge reactive oxygen species and protect mitochondrial structure and function. Furthermore, modernized TCM components like astragaloside IV regulate mitochondrial quality control by modulating related pathways, offering new insights for acute high-altitude hypoxic myocardial injury. Although there is no specific record of “high-altitude disease” in TCM theory, based on its clinical manifestations such as chest tightness, chest pain, palpitations, dyspnea, and cyanosis of lips and nails, acute high-altitude hypoxic myocardial injury can be categorized under the scope of “chest impediment” in TCM. TCM treatment emphasizes holistic regulation and multi-target synergy. TCM compound formulas, such as Shuang Shen Ning Xin Capsule and Tongmai Formula, often intervene in mitophagy, dynamics, and biogenesis through multiple components and pathways. Additionally, bloodletting at the well points can boost qi, activate blood, and invigorate yang qi, thereby improving qi and blood circulation as well as mitochondrial energy metabolism and mitophagy [53]. Currently, the integration of traditional Chinese and Western medicine is gradually forming treatment strategies with a systematic perspective. In summary, based on mitochondrial quality control, the integration of traditional Chinese and Western medicine demonstrates synergistic advantages from microscopic mechanisms to holistic regulation, providing a more systematic approach for the prevention and treatment of acute high-altitude hypoxic myocardial injury.

6. Conclusion

The essence of acute high-altitude hypoxic myocardial injury is the systemic, decompensated collapse of the cardiomyocyte mitochondrial quality control system. In the acute hypobaric-hypoxic environment, the mitochondrial quality control network, upon which cardiomyocytes rely to maintain energy supply and structural integrity, suffers comprehensive disruption. Unable to restore homeostasis through self-regulation, this ultimately leads to the loss of cardiomyocyte function and even cell death.

Biogenesis inhibition, dynamics imbalance (excessive fission/insufficient fusion), and autophagy impairment are three key pathological links, and they form a vicious cycle with each other. Biogenesis inhibition: Hypoxia stabilizes HIF-1α to suppress PGC-1α and its downstream key factors such as NRF1/2 and TFAM, hindering the generation of new mitochondria and leading to insufficient mitochondrial production. Dynamics imbalance: Abnormal ROS and calcium signaling activate Drp1 and inhibit Mfn2 and OPA1, triggering excessive mitochondrial fission and impaired fusion, resulting in fragmentation and functional loss of the mitochondrial network. Autophagy impairment: Autophagy can be activated in the early stages of hypoxia to clear damaged mitochondria, but sustained hypoxia leads to energy failure, Ca^{2+} overload, etc., which instead inhibit autophagosome formation and the degradation process, causing dysfunctional autophagy. These three processes influence each other, forming a vicious cycle of "energy crisis—oxidative stress—structural damage," exacerbating the collapse of the mitochondrial network.

Future prevention and treatment strategies should focus on restoring homeostasis of the entire mitochondrial quality control (MQC) network. Through multi-target, multi-pathway coordinated interventions aimed at promoting mitochondrial biogenesis, regulating dynamic balance, and modulating autophagy, acute high-altitude hypoxic myocardial injury can be alleviated. Comprehensive regulation targeting this network provides a highly promising theoretical basis and direction for developing novel drugs to prevent and treat acute high-altitude cardiac injury.

In summary, this article systematically reveals the underlying mechanisms of acute high-altitude hypoxic myocardial injury from the perspective of mitochondrial quality control and provides a new theoretical framework and research directions for its prevention and treatment.

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