STRUCTURAL AND FUNCTIONAL MITOCHONDRIAL CHANGES IN CHRONIC HEART FAILURE

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Abstract

Chronic heart failure remains one of the most severe cardiovascular syndromes associated with high morbidity and mortality worldwide. Increasing evidence indicates that mitochondrial dysfunction plays a central role in the progression of heart failure by disrupting energy production, redox balance, and calcium homeostasis in cardiomyocytes. Impaired mitochondrial dynamics, including altered fusion, fission, and mitophagy, lead to the accumulation of damaged organelles and progressive cellular injury. Structural and functional mitochondrial alterations are closely associated with myocardial remodeling, fibrosis, and contractile dysfunction. This review summarizes current data on the role of mitochondrial dysfunction in chronic heart failure, highlighting its contribution to disease progression and its potential as a therapeutic target for restoring myocardial energy homeostasis.

Keywords: mitochondrial dysfunction, heart failure, oxidative stress, apoptosis, energy deficit, cardiomyocytes, mitophagy, calcium homeostasis, fibrosis, myocardial remodeling.

Heart failure (HF) is a complex clinical and pathophysiological syndrome characterized by the inability of the heart to provide adequate tissue perfusion with normal or increased venous filling [1]. Despite advances in pharmacotherapy and interventional technologies, mortality and disability in HF remain high, necessitating clarification of the molecular mechanisms underlying disease progression [2]. One of the key pathogenetic links in the modern understanding of HF is considered to be impaired mitochondrial function of cardiomyocytes, leading to energy deficiency, increased oxidative stress, and activation of cell death pathways [3, 4].

Cardiomyocyte mitochondria provide the bulk of ATP synthesis through oxidative phosphorylation, maintain ion homeostasis, and participate in the regulation of intracellular calcium, control of apoptosis, and stress signaling [5]. Under conditions of chronic stress or injury, mitochondrial adaptive mechanisms (mitophagy, biogenesis, fusion/fission dynamics) are aimed at maintaining the cellular energy status [6]. When these processes are disrupted, damaged organelles accumulate and bioenergetic potential decreases, making mitochondria the cornerstone of heart failure pathogenesis [7].

The key mechanisms of mitochondrial dysfunction in heart failure are decreased ATP synthesis and energy deficit. Disruption of the respiratory chain complexes and loss of mitochondrial membrane potential lead to a decrease in ATP production [8]. Cardiomyocytes, which have a high energy demand, lose the ability to maintain normal ionic activity (Na^+/K^+-ATPase, Ca^{2+}-ATPase) even with moderate ATP deficiency, leading to calcium imbalance, the development of diastolic dysfunction, and decreased contractility [9]. Increased production of reactive oxygen species (ROS). Dysfunction of complexes I and III of the respiratory chain increases electron leakage and the formation of superoxide anion and other ROS [10]. Chronic oxidative stress damages mitochondrial phospholipids, proteins, and DNA, initiates membrane lipid peroxidation, and provokes an inflammatory response that promotes myocardial remodeling [11, 12].

Impaired mitochondrial dynamics: fusion/fission and mitophagy. Biomechanical balance between mitochondrial fusion (mediated by OPA1, Mfn1/2) and fission (Drp1) is necessary to maintain mitochondrial population quality [13]. Excessive fission and/or insufficient mitophagy lead to the accumulation of low-functioning mitochondria, which exacerbates energy deficiency and oxidative stress [14]. Impaired mitophagy complicates the removal of damaged organelles and the formation of a healthy mitochondrial pool [15].

Mitochondria are involved in buffering intracellular calcium, and their dysfunction leads to pathological calcium overload [16]. Excess mitochondrial calcium initiates the mitochondrial membrane permeability transition (mPTP), which causes a loss of membrane potential, the release of proapoptotic factors, and rapid energy collapse [17, 18].

When mitochondria are damaged, cytochrome c and other proapoptotic proteins are released, initiating caspase-dependent and caspase-independent programmed cell death pathways [19]. Furthermore, severe energy depletion leads to necrotic, uncontrolled cell destruction, promoting inflammatory cell infiltration and fibrosis [20]. Numerous experimental models (cardiac pressure overload, myocardial infarction, chronic ischemia, toxic models) demonstrate early mitochondrial changes before the onset of pronounced contractile dysfunction: a decrease in ATP and creatine phosphate levels, electron leakage, structural changes in mitochondria (swelling, loss of cristae), and a decrease in the activity of respiratory chain complexes [21].

Clinically, patients with heart failure exhibit signs of mitochondrial dysfunction: decreased mitochondrial respiratory reserve potential in myocardial biopsies, elevated markers of oxidative damage, and a correlation between the degree of mitochondrial dysfunction and the severity of symptoms and prognosis [22, 23]. Multi-omics studies indicate changes in the expression of genes regulating mitochondrial biogenesis (PGC-

1α, NRF1) and mitochondrial dynamics, reflecting systemic disruption of the mitochondrial network in heart failure [24, 25].

Mitochondrial dysfunction promotes the activation of profibrotic pathways, induces cardiomyocyte apoptosis, and attracts inflammatory cells—all of which contribute to the development of intermuscular fibrosis, altered myocardial mechanics and conductivity, which clinically manifests as heart failure progression, the development of arrhythmias, and a decrease in prognostic potential [26, 27].

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