The Part Mitochondrial Dysfunction Plays in Heart Disease

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Doi: **10.5281/zenodo.17505165**
Received: 25 August 2025
Accepted: 14 September 2025

Abstract

Cardiovascular diseases (CVDs) continue to be the world's largest cause of mortality, even with improvements in diagnosis and care. There is mounting evidence that mitochondrial dysfunction plays a key role in the onset and advancement of CVDs. Because they are involved in the oxidative phosphorylation (OXPHOS) process that produces ATP, mitochondria, also referred to as the powerhouses of the cell, are essential for heart function. Additionally, they control vital cellular functions such redox signaling, calcium balance, and programmed cell death. Heart disease and cellular damage result when mitochondria are unable to maintain these essential functions, which can be caused by oxidative stress, genetic abnormalities, or imbalances in mitochondrial dynamics. Excessive formation of reactive oxygen species (ROS), which lead to oxidative stress and harm cellular components, including mitochondrial DNA (mtDNA), is one of the most harmful effects of mitochondrial malfunction. These alterations impair mitochondrial energy production and set off a vicious cycle of increased ROS buildup and cellular damage. Furthermore, malfunctions in the mechanisms that regulate mitochondrial quality, including fission, fusion, and mitophagy, make it more difficult for damaged organelles to be eliminated, which results in energy shortages and cardiomyocyte mortality.

Increased oxidative damage and accelerated cardiac damage are caused by dysregulated ROS scavenging mechanisms, such as deficits in MnSOD, GPx1, or Trx2. Targeting mitochondrial pathways offers an interesting prospect for new treatment approaches as our knowledge of the heart's mitochondrial function grows. Restoring mitochondrial function, strengthening antioxidant defense, or adjusting mitochondrial dynamics are some interventions that may provide potential ways to lessen the burden of CVD.

Key words- Mytochondrial dysfunction, ROS, mtDNA.

Introduction

The primary cause of illness and mortality worldwide has been cardiovascular diseases (CVDs). The worldwide burden of CVD is still rising despite significant therapy improvements, highlighting the urgent need for new therapeutic targets (1).

The pathogenesis of cardiovascular disease is complicated. This illness is caused by a number of pathogenic processes and risk factors. The pathophysiology of CVD is influenced by a number of anomalies in cells, including metabolic disorders, excessive reactive species (ROS) formation, energy deficiency, autophagy dysregulation, endoplasmic reticulum (ER) stress, and apoptosis activation. Mitochondrial dysfunction or malfunction plays a key role in these cellular perturbations (2).

Cardiomyocyte contraction is fueled by ATP produced by mitochondria, which gives the heart the energy it needs to pump blood. Moreover, mitochondria have a variety of physiologic roles, including controlling calcium

and reactive oxygen species (ROS) signaling, and they are important modulators of the cardiomyocyte response to different stimuli such hypoxia, oxidative stress, and hyperglycemia. (3).

Crucial double-membrane organelles for aerobic respiration in living cells, mitochondria also control cell metabolism and produce the energy that cells need through OXPHOS. Mitochondrial dysfunction, including diminished OXPHOS capability and increased ROS generation, can result from mutations in the nuclear genome (nDNA) and mitochondrial genome (mtDNA), which collectively regulate mitochondrial function. Human heart myocytes (HCM) need mitochondria as a vital site for cell metabolism to produce ATP, which gives them enormous energy for contraction and relaxation. The buildup of defective mitochondria will result in CVDs (4).

Cardiomyocytes' rhythmic electrical activity depends on the maintenance of ion channels and transporters, which utilize one-third of the cardiac ATP produced by mitochondria. Mitochondrial dysfunction adversely affects aerobic respiration and energy production, leading to impairment in cardiac rhythm. In addition, dysfunctional mitochondria may generate excessive reactive oxygen species (ROS), another factor contributing to ion channel and transporter abnormalities and membrane excitability disturbances, which are all crucial players in the pathogenesis of arrhythmias (5).

Mechanisms of Mitochondrial Dysfunction

A growing body of research is establishing new connections between the pathophysiology of CVD and mitochondrial dysfunction. The primary paths of mitochondrial damage, which include genetic factors (mtDNA damage), improper respiratory chain function, and inhibition of mitochondrial turnover, should be outlined in order to have a better understanding of the processes responsible for this interaction. The circular genomes of mitochondria resemble bacterial chromosomes. The circular, double-stranded mtDNA is approximately 16.5 thousand nucleotides long and is preserved via the creation and repair of mitochondrial enzymes. Thirteen structural genes that encode oxidative phosphorylation complex subunits, twenty-two transport RNAs (tRNAs), and two ribosomal RNAs (rRNAs) are among the 37 genes encoded by the mitochondrial genome that are essential for energy generation in the mitochondrial respiratory chain. MtDNA is found in several copies within a single organelle, just like bacterial chromosomes. As a result, mtDNA mutations can be either homoplasmic, in which case all copies of the molecule are identical, or heteroplasmic, in which case only a subset of mtDNA copies have a particular mutation. Over a person's lifetime, mitochondrial mutations may accumulate and result in a carrier phenotype. Human illnesses have been linked to several mtDNA mutations. Numerous variables influence the distribution and effect of mitochondrial mutations, with heteroplasmy being a key one. Due to the release of apoptotic chemicals and caspase activation caused by mitochondrial damage and loss of mitochondrial membrane integrity, mitochondria are powerful regulators of apoptosis. Furthermore, mitochondria contribute to the preservation of Ca2+ homeostasis. When Ca2+ is transferred from the ER, the main cellular Ca2+ reserve, it can cause mitochondrial malfunction and organelle disintegration. The mitochondria's and the ER's functions are closely related within the cell. Changes in mitochondrial lipid metabolism can trigger ER stress and the unfolded protein response (UPR). Interestingly, established causes of mitochondrial dysfunction include exposure to modified LDL (oxLDL) and hyperlipidemia, two risk factors for CVD (6).

The main processes behind mitochondrial dysfunction in CVD are depicted in the accompanying image. These include oxidative stress, compromised biogenesis, changed dynamics, mtDNA mutations, and calcium-handling abnormalities.

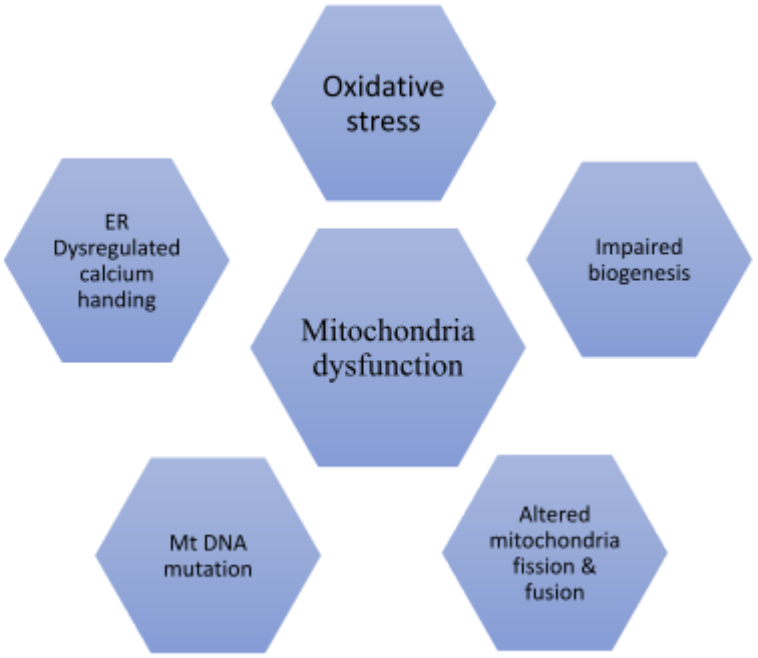

Figure-1 Schematic figure of mechanisms of mitochondrial dysfunction in CVDs

Cardiovascular disorders, namely ischemic heart disease, atherosclerosis, cardiomyopathy, and hypertension, are closely linked to mitochondrial dysfunctions. Reactive oxygen species (ROS) generation and associated signaling, decreased ATP, impaired mitochondrial regulatory responsibilities, cell growth and death, decreased mitochondrial electron transport chain activity, and an inflammatory response are all consequences of this altered mitochondrial function (7).

Overview of Reactive Oxygen Species Production

The sources of ROS production

Both positive and negative effects can be attributed to ROS. Whenever the generation of ROS exceeds the antioxidant capacity, oxidative stress results. ROS are produced by some enzymes or as a consequence of mitochondrial respiration or metabolism. Numerous environmental variables, including exposure to radiation and UV rays, smoking cigarettes, and excessive alcohol use, encourage the development of reactive oxygen species (ROS) and are linked to the emergence of several pathologies, including cardiovascular illnesses and cancer. Dioxygen (O2) is where ROS are first synthesized (8).

Despite being primarily produced by mitochondria, ROS can also come from a variety of intracellular sources, including as xanthine oxidase, uncoupled nitric oxide synthase, NAD(P)H oxidase, and ER stress (9).

Because the oxygen received by the submitochondrial particles oxidizing succinate or NADH was sensitive to catalase, some of this oxygen was converted to H2O2 (10).

Through oxidative phosphorylation, mitochondria produce ATP in conjunction with the electron transport chain (ETC). Superoxide dismutase 1 (SOD1) in the mitochondrial intermembrane space and SOD2 in the mitochondrial matrix convert superoxide, which is created when electrons from the ETC and other related enzymes leak out, to H2O2, a less reactive oxidant, and oxygen. Although mitochondria use most of the oxygen in the cell, just 1-2 percent of it seems to be converted to ROS (11).

The proximal mitochondrial ROS, superoxide (O−2) (O2−), is produced when electrons escape through the electron donors in complex I and complex III of the mitochondrial respiratory chain. Manganese superoxide dismutase (MnSODs) in the mitochondrial matrix catalytically converts superoxide into H2O2 due to its

instability and transiency; this form may readily traverse cellular membranes and oxidize a range of substrates. Another enzyme system known as the thioredoxin (Trx) system has acquired significance in relation to the scavenging of mitochondrial H2O2, despite the fact that catalase was the first enzyme to be identified that scavenges H2O2 and is not prevalent in mitochondria. Trx reductase delivers electrons from NADPH to Trx, which then sends them to Prx to convert H2O2 into H2O. Trx, NADPH-dependent Trx reductase, and peroxiredoxins (Prx) make up the Trx system. Above all, it has been demonstrated that Trx2 buffers mitochondrial H2O2 in cardiomyocytes. Recent research by Santulli et al. showed that in heart failure, the leaky Ryr2 causes mitochondrial calcium excess, which raises ROS generation in the mitochondria and oxidizes the Ryr2, increasing the SR/ER Ca2+ leak.

Heart contractility is totally paralyzed by this viscous loop of ROS production, calcium overload, and Ca2+ leakage. Notably, the signal for these phenomena comes upstream when the SR/ER has already started to exhibit calcium dysregulation, indicating that mitochondrial ROS are simply the consequence of compromised calcium release in these conditions (12).

Mitochondrial morphology in steady-state myocardium

The cytoplasm contains semiautonomous organelles known as mitochondria. Unlike other organelles, mitochondria have a double-layered membrane and double-stranded circular DNAs, or mtDNAs (13).

Abnormal cardiac physiological activity may arise from a failure to dynamically balance the competing processes of mitochondrial fusion and division. Steady-state mitochondrial dynamics refers to this. Mitochondrial fission is a crucial self-healing mechanism for regulating energy use and maintaining mitochondrial function. Studies have demonstrated that mitochondrial dynamics increase mitochondrial fission protein activity and decrease fusion protein activity in heart failure and cardiac hypertrophy (14).

The pathophysiology of cardiovascular diseases and mitochondrial dysfunction

The main cause of mitochondrial dysfunction

To identify mitochondrial heart disease, which is characterized as an impairment of the structure and/or function of the heart caused by mitochondrial pathology, coronary hypertension and valvular or congenital pathology must be ruled out. Two potential indicators of cardiac involvement include alterations in electrical activity and/or cardiomyopathy. It is estimated that 40% of individuals with mitochondrial dysfunction develop hypertrophic cardiomyopathy (HCM), the most prevalent kind of cardiomyopathy.

There is still uncertainty regarding the precise processes of cardiac damage in mitochondrial heart disease. According to certain theories, ventricular hypertrophy is an adaptive response to mitochondrial malfunction. Ultrastructural investigations, however, often revealed a considerable increase in the number and size of mitochondria, which causes the cardiomyocytes to grow, but they never detected evidence of expansion of the sarcomeric structures. Sarcomere disarray and mechanical inhibition of contractile activity are caused by abnormal mitochondria. Additionally, it's possible that these malfunctioning mitochondria generate a lot of ROS, which would lead to severe oxidative stress. Other potential effects of mitochondrial failure include oxidative stress, abnormalities in the usage of energy substrates, cytoplasmic calcium excess (which alters cardiomyocyte excitability), and an increased propensity for apoptosis. Hypokinesia, ventricular dilatation, the development of fibrotic regions, and anomalies in heart electrical activity would be the final results of these changes (15).

The pathophysiology of heart illness and the unique involvement of mitochondrial ROS

ROS participate in physiological processes, such as cell differentiation and proliferation and excitation-contraction coupling (ECC), at low concentrations. ROS's physiological or pathological function, however, varies according to their kind, concentration, and manufacturing location. ROS participate in physiological processes, such as cell differentiation and proliferation and excitation-contraction coupling (ECC), at low concentrations. Higher ROS levels, on the other hand, have the ability to alter the chemical makeup and functionality of intracellular molecules. For instance, ROS can modify intracellular lipids by lipid peroxidation,

create structural changes to proteins through enzymatic changes or deactivation, and impact the integrity of genomic DNA by causing mutations. (16).

ROS are produced by all vascular layers, including adventitia, smooth muscle, and endothelium. Vascular tone regulation, inflammation regulation, platelet aggregation and coagulation promotion or inhibition, and vascular growth are all critical functions of the endothelium. Vascular smooth muscle cell growth, relaxation, and contraction are regulated by ROS, which operate as signaling molecules in physiological contexts. Endothelial dysfunction and other cardiovascular disease problems are mostly caused by the imbalance between ROS (oxidants) and antioxidants that pathophysiological conditions create. The direct oxidative effects of ROS on macromolecules including proteins, lipids, and DNA have been connected to necrosis, cell damage, and cell death (17).

Several genetic models demonstrate the essential role of mitochondrial ROS and heart disease, showing that changes to either the pathways that produce ROS or the systems that scavenge them have a major effect on the physiology of the heart and the onset of heart disease. Replication of mtDNA is carried out by the mitochondrial polymerase DNA polymerase γ.

Genetic models that target p66shc, MAO, and NOX4 further indicate a specialized role for mitochondrial ROS in heart illness, as does the dysregulation of ROS caused by respiratory chain malfunction. As previously stated, p66shc, which is found in mitochondria, promotes the generation of hydrogen peroxide and takes part in the signaling of oxidative stress. The mitochondrial location of p66shc has been shown to be crucial for the cellular response to death stimuli as increased mitochondrial ROS can initiate apoptosis and MPTP-dependent death. In fact, cells without p66shc exhibit less reactive oxygen species (ROS) and are shielded from a range of proapoptotic triggers, including as staurosporine, hydrogen peroxide, and UV light. Some protective effects in the heart have been attributed to the protection provided by p66shc deletion in vitro. The diabetic cardiomyopathy streptozotocin model protects p66shc-knockout animals.

When p66shc is lost, diabetes-induced cardiac remodeling is reduced and heart function returns to baseline. Though the findings have been less clear in this context, p66shc has also been linked to the control of cardiomyocyte loss after cardiac IRI. Although p66shc deletion has been shown to provide cardioprotection in ex vivo IR investigations, in vivo IR studies have had the opposite result. These findings collectively imply that p66shc's effect on cardiac pathology may vary depending on the condition (18).

Role of mitochondrial dysfunction in cardiovascular disease

Atherosclerosis

The excessive generation of ROS due to mitochondrial malfunction oxidizes cellular proteins, lipids, and DNA. Due to its lack of histones and limited ability to repair itself, mitochondrial DNA is particularly vulnerable to oxidative damage. Additionally, as discussed in the previous section, Mitochondrial DNA Damage in Atherosclerosis, mutations in mitochondrial DNA produce a vicious cycle of ROS production (19).

Lipids, proteins, and mtDNA are all harmed by the mitochondria's increased generation of ROS. Of these, mtDNA is probably the most vulnerable to damage from physiologically significant ROS. Vascular smooth muscle cells (VSMCs) and endothelial cells exposed to ROS in cell cultures showed a preferential increase in mtDNA damage (in contrast to transcriptionally inactive nuclear β-globin gene), downregulation of steady-state levels of mtDNA-encoded mRNA transcripts, mitochondrial protein synthesis, membrane potential, and total cellular ATP pools. The pathophysiology of atherosclerosis is linked to hydroxynonenal, a byproduct of membrane lipid peroxidation that causes VSMC death by increasing ROS generation and causing mitochondrial dysfunction. In contrast, aconitase activity was decreased in both baseline and agonist-stimulated conditions, and VSMC proliferation was enhanced due to increased ROS generation caused by haploinsufficiency of SOD2 isoform (20).

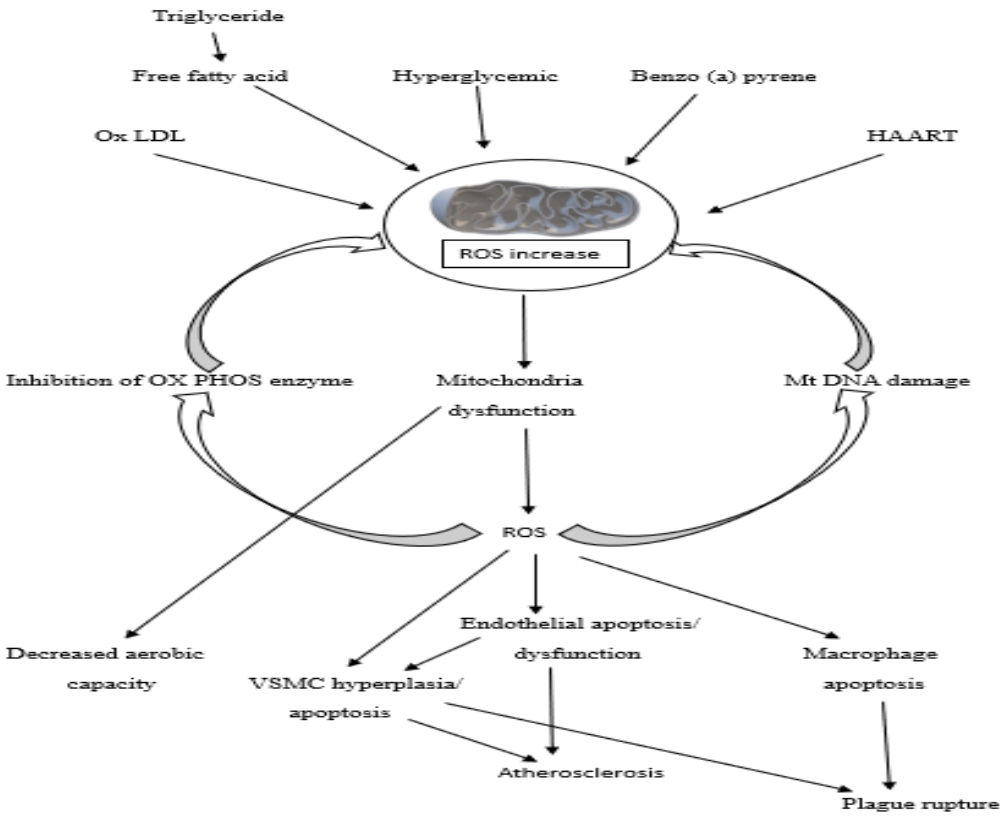

Figure-2 **Atherogenic mechanisms of mitochondrial dysfunction.**

The initial pathophysiological alteration in the early stages of atherosclerosis is endothelial dysfunction, which is typified by decreased NO production and secretion. The initial pathophysiological alteration in the early stages of atherosclerosis is endothelial dysfunction, which is typified by decreased NO production and secretion. Research has indicated that the primary reason of the reduced NO generation was eNOS breakdown, which was brought on by ROS-mediated oxidative stress as opposed to the suppression of eNOS gene expression. Additionally, the malfunction of eNOS decoupling will result in increased ROS production, which will further impair endothelial function and accelerate the onset of atherosclerosis. After anoxia, exogenous NO promotes the generation of excess NO, and reactive nitrogen species (RNS) are created when active oxygen and NO mix. ROS and RNS are involved in physiological regulation and disease pathogenesis, and they may play a significant role in endothelial function. The synthesis of nitric acid, apoptosis, and intracellular signaling are only a few of the events that are triggered by the mitochondria, which are essential to EC function. Overproduction of ROS caused atherosclerosis, apoptosis, and EC senescence (21).

The role of mitochondria in inflammation has been evaluated on a number of occasions. In addition, the phrase "inflammaging" has evolved to describe the age-related decline in mitochondrial function linked to the emergence of long-term age-related inflammatory diseases. This might improve our comprehension of the illness and enable us to develop more potent treatment plans, such as concentrating on mitochondrial oxidative stress. Two well-known pro-inflammatory features of mitochondrial dysfunction are increased oxidative stress and ROS generation in the mitochondria. It appears that mitochondrial malfunction has a major impact on the pro-inflammatory response and chronic inflammation in the arterial wall, which ultimately lead to the development of atherosclerosis (22).

"ROS-induced ROS" is the term for the process that happens when damaged mitochondria lead nearby mitochondria to create excessive amounts of ROS, changing the membrane potential. This ROS activity is typically countered by endogenous antioxidants. Oxidative stress and excessive ROS production, on the other hand, might worsen arterial wall oxidative damage and cause atherosclerotic plaque to develop (7).

Myocardial Infarction and ischemia/reperfusion injury

Mitochondrial dysfunction plays a major role in myocardial infarction (MI) and ischemia/reperfusion injury (IRI); in fact, factors that change mitochondrial behavior, including age, sex, statin use, and comorbidities like diabetes and metabolic syndrome, directly affect how effective cardioprotective measures are. The increasing intracellular proton concentration causes the cytoplasmic Na+ concentration to rise, which in turn triggers the activation of the Na+/H+ ion exchanger. As a result, the Na+/Ca+ ion exchanger, which regulates intracellular (later, mitochondrial) calcium excess, operates in reverse. The pH of the cardiomyocyte returns to normal when reperfusion begins, and rising oxygen levels trigger the mitochondrial machinery to generate more ROS and raise the calcium content of the mitochondria (mitochondrial re-energization). By increasing the mitochondria's calcium capacity and reducing the production of reactive oxygen species, it has been shown that a large conductance calcium-activated K+ channel (BKCa), which is expressed on the plasma membrane of most cell types but only on the inner mitochondrial membrane of adult cardiomyocytes (mitoBKCa), can prevent IRI. The mitoBKCa channel opens as a result of increased ROS generation during preconditioning, preventing MPTP opening, cardiomyocyte apoptosis, and calcium overload.

Certain cardioprotective methods have been shown to be directly dependent on the mitochondrial machinery; in particular, when the cardiomyocyte is ischemic preconditioned, the activation of mitochondrial ATP-sensitive K+ channels results in an increase in K+ influx due to the decrease in ATP production caused by ischemia. (23).

Cell/organ injury can be caused by a number of mechanisms, including decreased cellular energy status (low cellular ATP level, energy stress), increased production of reactive oxygen species (ROS), including hydrogen peroxide (H2O2), superoxide anions, hydroxyl radicals (OH.), and peroxynitrite, and the subsequent development of oxidative stress. Necrotic cell death, plasmalemma disintegration, and cardiomyocyte supercontracture are further effects of elevated Ca2+ and low cellular ATP brought on by compromised mitochondrial function. Low cellular ATP levels and elevated ROS and Ca2+ have a complicated interaction, making it difficult to pinpoint the exact molecular mechanisms and effects of these occurrences. Therefore, there is a complex link between mitochondrial damage and organ failure that surely extends beyond the inability to produce ATP. Because of possible variations in mitochondrial density and heterogeneity, early-stage HF studies of muscle homogenates or fibers might not detect impairments in mitochondrial function (24).

Heart failure

Because of possible variations in mitochondrial density and heterogeneity, early-stage HF studies of muscle homogenates or fibers might not detect impairments in mitochondrial function (25).

The disruption of Ca2+ homeostasis is a characteristic of heart failure. Reduced sarcoplasmic reticulum (SR) Ca2+ reuptake and increased Ca2+ leak through ryanodine receptors cause failing hearts to have higher baseline cytosolic Ca2+ but smaller transients after excitation. Because of their close proximity to the SR, it is thought that in pathological conditions, mitochondria serve as a Ca2+ sink, and that the excess Ca2+ that results causes mitochondrial dysfunction. α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and isocitrate dehydrogenase are among the several metabolic enzymes that are activated in the mitochondria by Ca2+. Ca2+ also controls other proteins that are involved in oxidative phosphorylation, ROS scavenging, or mPTP opening. Ca2+ is an essential regulator of mitochondrial activity due to these roles, and it may also play a role in the development of heart failure (26).

Cardiomyocyte aging and heart failure (HF) are brought on by deregulation of mitochondrial dynamics and mitophagy, which results in inflammation and is unable to eliminate damaged mitochondria. A malfunctioning mitochondrion may be able to expand to the cell level through interference with quality control mechanisms, which would ultimately lead to apoptosis and an excess of reactive oxygen species.

Abnormal mitochondria in the failing heart's component cardiomyocytes can lead to an excess of reactive oxygen species (ROS) and a reduction in the rate at which ATP synthesis occurs. ATP is the energy currency of living cells and the lifeblood of cardiomyocytes. Cardiomyocyte dysfunction results from decreased ATP synthesis rates, whereas abnormal mitochondria produce too many ROS, which damages and kills cardiomyocytes. The progressive decline in left ventricular (LV) function that characterizes heart failure is

ultimately caused by both of these mechanisms. The presence of elevated ROS generation and decreased ATP synthesis in the heart of patients with HF who have a lower ejection fraction (EF) is supported by a substantial body of research. (27).

Oxidative stress, proteotoxic insults, disruption of energy metabolism, Ca2+ dysregulation, and eventually cardiac myocyte death are all consequences of mitochondrial dysfunction. Heart failure is largely caused by cardiomyocyte loss, which also somewhat lessens ventricular systolic dysfunction. Cell death associated with mitochondrial dysfunction may be a target for heart failure therapy. Numerous microRNAs have been shown to improve heart function by regulating mitochondrial fusion and fission and inhibiting mitochondrion-mediated apoptosis.

Additionally, it has been shown that in DCM mice, reducing pyroptosis associated with mitochondrial dysfunction improves heart performance.

These early results, however, were mostly obtained from in vitro and preclinical animal models, and much more research is required to fully assess their potential for cardioprotection in humans (28).

Significant metabolic reprogramming and mitochondrial dysfunction can affect the heart, resulting in a rise in ROS generation and a decline in oxidative capability, oxidative phosphorylation, and ATP synthesis. Similar to cardiac hypertrophy and heart failure, decreased heart mitochondrial activity may lead to a disruption of the cellular bioenergetics of cardiomyocytes through increased glycolysis. Moreover, it has been demonstrated that the cardiomyocytes of people with coronary artery disease had 8–2000 times more mtDNA deletions than those of healthy individuals. This can drastically change mitochondrial function and raise the generation of ROS, resulting in cellular damage and dysregulated metabolism. Furthermore, mitochondrial malfunction can cause even a little increase in glucose metabolism, which might result in cardiomyocytes with metabolic inflexibility (29).

Cardiomyocyte physiology is influenced by mitochondria both directly and indirectly through the regulation of bioenegetics (cardiomyocytes have a high demand for oxygen consumption and ATP synthesis), redox signaling (physiological response), oxidative stress (pathological response), calcium handling, contractility properties, necrosis, and apoptosis. Maintaining the integrity and function of the heart's mitochondria is therefore essential for human health.

To preserve mitochondrial integrity, eukaryotic cells have evolved a number of monitoring systems.

1. A multilayer network of detoxifying systems that prevents excessive accumulation of oxygen- and aldehyde-mediated mitochondrial toxicity;

2. A protein quality control machinery that maintains mitochondrial proteostasis through the action of chaperones and protease; and

3. An interconnected network of mitochondria that regulates mitochondrial morphology and number through mitophagy, mitochondrial fusion, and fission. These are the three primary levels of surveillance (30).

Mitochondrial Dysfunction in Congenital Heart Disease

The frequency of proven birth abnormalities is from 5 to 10 per 1000 live births, making congenital cardiac deformities a likely source of birth problems (31).

Continuous fusion and fission cycles control the morphology and function of mitochondrial networks, which are essential for establishing the shape of organelles as well as for redistributing proteins and metabolites, delivering redox-sensitive signals, preserving the integrity of mtDNA, carrying out metabolic processes, and controlling QC and cell death pathways (32).

Reductions in cellular adenosine triphosphate (ATP) and phosphocreatine, altered substrate selectivity, elevated production of reactive oxygen species (ROS), and decreased expression in individual electron transport

complexes are all indicators of mitochondrial dysfunction and impaired cellular energy production in adult heart failure (HF), according to a substantial and expanding body of research (33).

Conclusion

All human cells, tissues, and organs have mitochondria, although the heart and other cells with greater energy needs need mitochondria more than others. The functioning of the ATP-producing apparatus and electron transport chain must be tightly controlled in mitochondria. Furthermore, mitochondria are malleable organelles that may dynamically alter their shape and number of cells in response to external stimuli. Additionally, the fission/fusion balance and mitochondrial biogenesis need to be carefully regulated. Deregulation of mitochondrial biogenesis may have negative effects in CVD. For instance, elevated oxidative stress and Ca2+ flow tip the scales in favor of fission in ischemic heart disease or ischemia/reperfusion damage, causing mitochondrial fragmentation and triggering apoptosis. In diabetic hyperglycemia and cardiac failure, fission overactivation can also be harmful. On the other hand, large mitochondria may arise in restrictive cardiomyopathy due to the predominance of mitochondrial fusion. Since the heart's primary energy source is its mitochondria, impairment of the respiratory chain and ATP synthesis may be regarded as a central component of mitochondrial dysfunction, which in turn causes oxidative stress, apoptosis, aberrant autophagy, and other pathophysiological abnormalities seen in cardiovascular disease. Thus, it may be proposed that the main treatment goal for improving mitochondrial dysfunction in different types of CVD is to restore the respiratory activity and ATP-producing ability of the mitochondria.

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