



Bioenergetics in Cardiovascular Disease

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ABSTRACT

Numerous conditions affecting the heart and blood vessels are referred to as “cardiovascular diseases” that include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, etc. It is important to keep in mind that, as we go closer to 2030, more people are expected to die globally from CVD than from all malignancies combined. The genesis and progression of numerous heart disorders are characterized by mitochondrial dysfunction. Myocardial infarction, different types of cardiomyopathies, arrhythmias, hypertension, and atherosclerosis are only a few of the cardiovascular illnesses that are influenced by mitochondrial dysfunction. Mitochondria have a critical part in bioenergetic and anabolic metabolism, and they also play a role in intracellular Ca²⁺ fluxes. In addition to this, mitochondrial dysfunction also promotes regulated cell death and the establishment of an inflammatory environment, which causes tissue loss. The myocardium requires a steady supply of cellular energy in the form of ATP to do work. The mitochondrion generates over 95% of the body's ATP. As a result, mitochondria are essential for proper cardiac function in terms of bioenergetics. Different approaches to ameliorate mitochondrial dysfunction include the drugs that target the mitochondria, technologies for genome editing and modification like TALENS (Transcription activator-like effector nucleases), zinc finger nuclease (ZFN), and more recently RNA guided endonucleases (RGENs). Emerging research areas include technologies that aim to preserve the viability of the proteasome and the recycling of the mitochondrial components. Recent therapies of bioenergetics in CVD include mitochondrial targeted drugs and probes like Citicoline, MitoQ, MitoB, and Idebenone; targeting AMPK (AMP-activated protein kinase), PGC-1 α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), etc.

Keywords: Cardiovascular Diseases, Bioenergetics, Mitochondria, Electron Transport Chain, mtDNA.

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INTRODUCTION

In the Western World, the leading cause of death and morbidity continues to be cardiovascular disease. Compared to the incidence of all cancers combined, it is responsible for more deaths¹. Numerous conditions affecting the heart and blood vessels are referred to as "cardiovascular diseases" (CVDs). These include coronary heart disease, which affects the blood arteries feeding the heart muscle, cerebrovascular disease, which affects the blood vessels supplying the brain, peripheral arterial disease, which affects the blood vessels supplying the arms and legs, rheumatic heart disease, which results in damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria, and congenital heart disease, which affects the normal growth and function of the heart from birth, blood clots in the leg veins, which can dislodge and move to the heart and lungs. Heart attacks and strokes are typically sudden, severe events that are mostly brought on by a blockage that stops the flow of

blood to the heart or brain. Estimates show that 17.9 million deaths, or 32% of all deaths, occurred as a result of CVDs in 2019. 85% of these deaths were caused by heart attacks and strokes. 17 million people died prematurely (before the age of 70) in 2019 as a result of non-communicable diseases, with cardiovascular diseases (CVDs) being responsible for 38% of those deaths². It is important to keep in mind that, as we go closer to 2030, more people are expected to die globally from CVD than from all malignancies combined³. In recent years, it is now obvious that the genesis and progression of numerous heart disorders (HDs) are characterized by mitochondrial dysfunction^{4,5}. Mitochondria are found in 3 different places among cardiac fibers and makeup 30% of the total volume of cardiomyocytes⁶. These structures exhibit continuous shifts in terms of both bioenergetics and biological science during cardiomyocyte differentiation and are very active throughout all stages of heart development⁷. Cardiovascular illnesses include ischemic and alcoholic cardiomyopathy, myocarditis, dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), cardiac conduction problems, and sudden mortality have all been linked to abnormalities in mitochondrial structure and function. Although abnormalities in the mitochondria's bioenergetic function are frequently linked to heart failure, this connection may not always be direct. To put it another way, the defect(s) causing the bioenergetic problem could be in a non-



bioenergetic pathway, such as the signaling between mitochondria and nuclei, or it could be in general biosynthesis of mitochondria or degradation pathways⁸.

A mother's 16 kb genome is passed on to mitochondria, which are intracellular organelles produced by bacteria¹. Possibly the top three roles that the mitochondria play in homeostasis are: They serve as the main ATP and ROS producers⁹. They control the homeostasis of calcium¹⁰. They regulate the intrinsic apoptotic cascade's functioning¹¹. The Inner Mitochondrial Membrane (IMM) is the location of the respiratory complexes (1–5). Complexes 1 and 2 work together to transport the Krebs cycle-generated electrons that NADH and FADH give to create a proton gradient. Complex 1, 3, and 4 pump protons across the IMM to maintain the gradient. The rotator mechanism of Complex V, which converts ADP to ATP at a ratio of 3:3 protons returned to the matrix per 1 ATP net synthesized, dissipates this potential imbalance between the low pH of the intermembrane gap and the alkali matrix¹². The cellular energy standard is ATP. It is necessary for all exergonic processes, including DNA repair, transcription, translation, and antioxidant production. Disease suffers greatly when this ability to produce energy is lost. For instance, it is anticipated that as cap VSMC age, they decrease the ability to produce collagen and promote the breakdown of the extracellular matrix, increasing the fragility of atherosclerotic plaque¹³.

The likelihood of rupture is anticipated to rise¹⁴ when these threats are coupled with micro vascularization and micro-calcification of the cap¹⁵. Apoptosis-inducing factors, cytochrome c, Smac/DIABLO, endonuclease G, and serine protease Omi/HtrA2 are just a few of the proapoptotic proteins that are released by mitochondria to indicate cell death in addition to their crucial role in energy metabolism. Cytochrome c has received the most research attention of these proteins¹⁶.

MITOCHONDRIAL BIOENERGETICS

Heart tissue, which needs a lot of energy, has many mitochondria, which make up 20% to 40% of the volume of each cell. The generation of mitochondrial energy requires both genetic factors encoded by nuclear and mitochondrial DNA that influence the typical functioning of the mitochondria, such as the activity of enzymes and accessibility of cofactors, in addition to environmental factors, which include the availability of substrate fuels (like carbohydrates, fats, and proteins) along with oxygen. The Krebs cycle, pyruvate oxidation, mitochondrial fatty acid oxidation, and the ultimate step, OXPHOS, are only a few of the interconnected bioenergetic mechanisms that contribute to mitochondrial energy metabolism. Adenosine triphosphate (ATP) synthase (complex V), the electron transport chain I–IV, and the adenine nucleotide translocator (ANT) are among the protein complexes that carry out OXPHOS at the mitochondrial inner membrane.

In cardiac muscle, the primary energy source for ATP generation is oxidative phosphorylation (also known as the electron transport chain). Fatty acids must be efficiently transported into the cardiomyocyte and then into the mitochondria to be used for bioenergetic production via mitochondrial FAO. This requires some transport proteins, including carnitine, two carnitine palmitoyl transferases, and fatty acid translocase. The Krebs cycle and FAO provide the majority of the intra-mitochondrial decreased NADH and FADH₂, that act as the primary source of electrons to the electron transport chain¹⁷. In healthy cardiac tissue, the availability of ATP from other sources (such as glycolytic metabolism) is constrained. The heart additionally keeps phosphates with high energy reserves in addition to these metabolic intermediates and bioenergetic pathways (e.g., ATP, phosphocreatine pools)⁸.

CONTRIBUTION OF MITOCHONDRIAL DYSFUNCTION TO CARDIOVASCULAR DISEASE

- Myocardial infarction, different types of cardiomyopathies, arrhythmias, hypertension, and atherosclerosis are only a few of the cardiovascular illnesses that are influenced by mitochondrial dysfunction.
- Mitochondria have a critical part in bioenergetic and anabolic metabolism, and they also play a central role in intracellular Ca²⁺ fluxes, which makes them necessary for the physiological function of the cardiovascular system.
- Inflammatory responses and waves of programmed cell death that are involved in the pathogenesis of the cardiovascular disease are actively encouraged by damaged mitochondria in addition to losing their physiological activities.

By ensuring proper catabolism and anabolic metabolism and managing intracellular Ca²⁺ trafficking, healthy mitochondria promote the functioning of practically every cell in the cardiovascular system during normal conditions. An undamaged mitochondrial network also contributes to the maintenance of inflammatory homeostasis and the integrity of tissues by preventing the start of the transduction of signal cascades that result in the production of pro-inflammatory substances and regulated cell death. In addition to altering intracellular Ca²⁺ fluxes and disrupting metabolism, mitochondrial dysfunction also promotes regulated cell death and the establishment of an inflammatory environment, which causes tissue loss. Mitophagy plays a key role in maintaining cardiovascular homeostasis by effectively removing defective mitochondria that develop as a result of natural cellular processes or accumulate in response to pathological signals⁴.



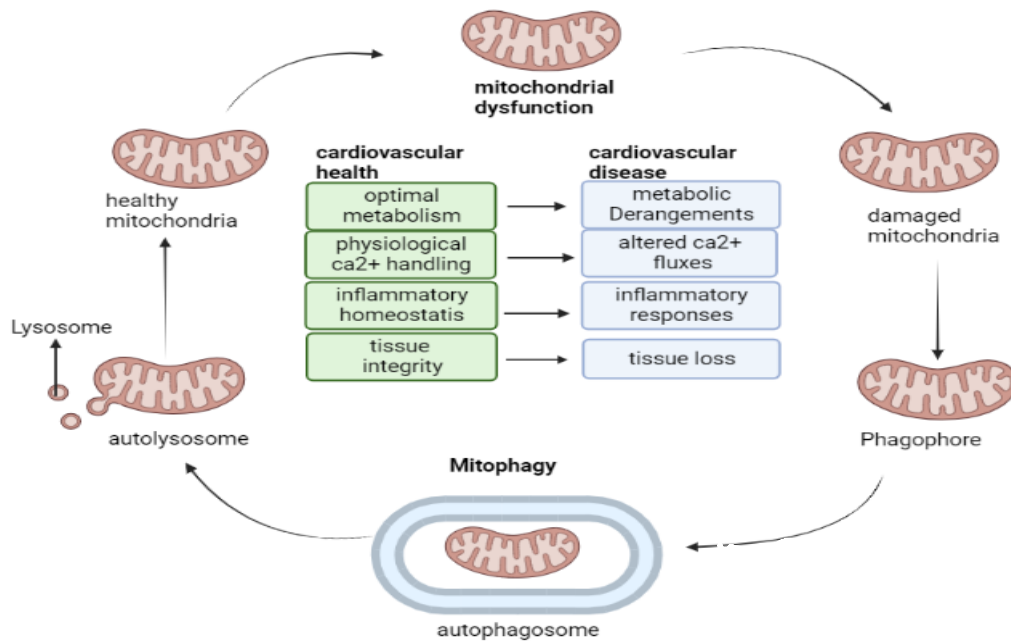


Figure 1: Contribution of mitochondrial dysfunction to cardiovascular disease

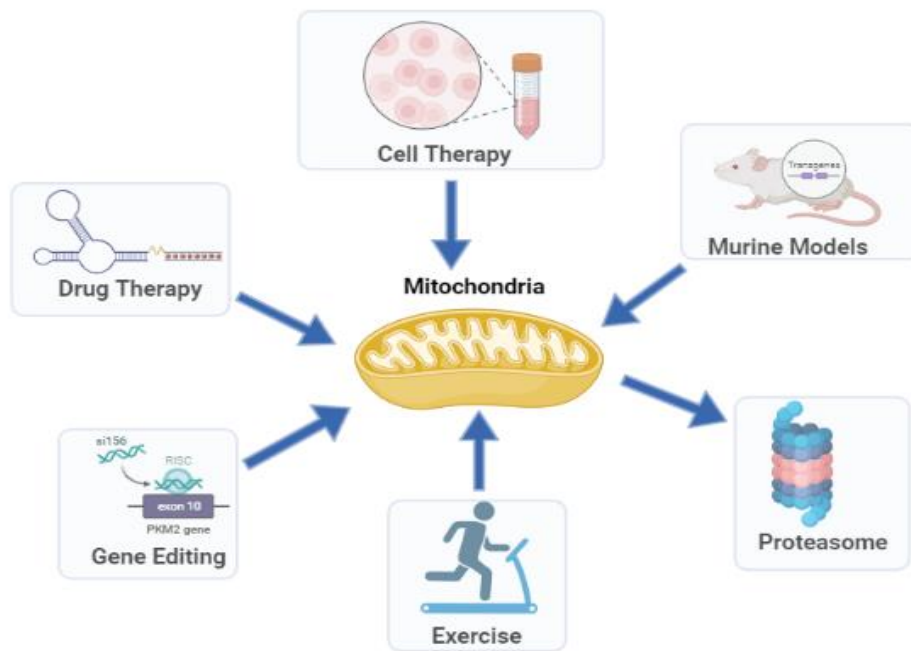


Figure 2: Different approaches to ameliorate mitochondrial dysfunction

DIFFERENT APPROACHES TO AMELIORATE MITOCHONDRIAL DYSFUNCTION

Drugs that target the mitochondria can be used to lower free radical levels and examine respiratory chain activity. Technologies for genome editing and modification like TALENs and zinc finger nucleases can be utilized to modify both mitochondrial and nuclear gene loci. The mtDNA genome pool can be improved by applying stem cell technologies and cell therapy to favorably change defective mtDNA copy numbers. Moreover, it has been demonstrated that exercise causes gene shuffling to increase the number of healthy mitochondrial genome copies. Last but not least, emerging research areas include technologies that aim to preserve the viability of the

proteasome and the recycling of mitochondrial components¹.

In the United States (U.S.), peripheral arterial disease (PAD), a symptom of systemic atherosclerosis, affects 8 to 12 million people, the majority of whom are older^{18,19}. Limping, rest discomfort, and loss of tissues are some indications and symptoms of PAD that are caused by impaired bioenergetics and oxidative tissue damage in the impaired lower extremities. Minimal blood flow via ruptured arteries and ineffective Adenosine Triphosphate (ATP) synthesis by damaged mitochondria are the two factors that contribute to the lower energy state²⁰.

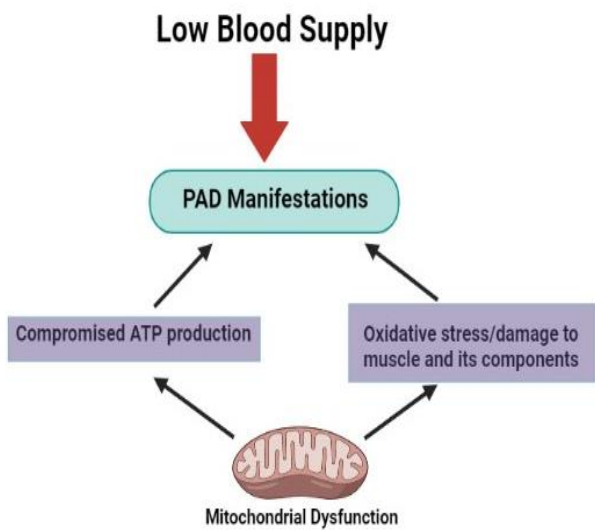


Figure 3: Suggested pathophysiological mechanism for peripheral arterial disease (PAD)

Pyruvate dehydrogenase (PDH) can oxidize pyruvate in healthy people with appropriate muscle blood flow, which then involves it in the TCA cycle (as acetyl-CoA). A terminal electron acceptor for the ETC (electron transport chain) is provided by sufficient cellular O₂, which enables e⁻ transfer and the formation of the electrochemical potential required for oxidative phosphorylation (ATP production). Moreover, electron transport to complex IV (IV) of the ETC inhibits electron (e⁻) stagnation in the chain, avoiding the generation of superoxide (O₂⁻). Around 2/3rds of the Creatine (Cr) pool is kept as Phosphocreatine (PCr), when the Creatine Phosphokinase (CPK) reaction is still in a basal state of flux.

In contrast, hypoxia and associated changes in muscle bioenergetics occur in individuals with PAD due to decreased muscle blood flow. In particular, pyruvate cannot undergo oxidation within the mitochondrion in hypoxic tissue and is instead transformed into lactate by lactate dehydrogenase in the cell cytoplasm. Similar to this, decreased availability of oxygen in the mitochondria inhibits electron transfer and respiration, causing electron buildup in the ETC, which may result in O₂⁻ generation at complexes I and III and subsequently oxidative stress. It's important to note that decreased availability of oxygen and resulting impairment in oxidative phosphorylation will cause a decrease in ATP levels and a concurrent increase in ADP levels in the muscle of patients with PAD. As a result of this modification in the cellular ATP to ADP ratio, PCr will be broken down by the CPK reaction to buffer cellular ATP. The claudication (localized muscular cramping and discomfort) that persons with PAD feel may be brought on by this trait. When the rate of turnover of ATP increases, such as during muscle contraction brought on by physical activity or exercise, it is particularly visible in the muscles of patients with PAD²¹.

MITOCHONDRIOPATHY OF HEART FAILURE

Heart failure (HF) is a syndrome brought on by the heart pump's inability to supply the body with the energy it needs²². The myocardium requires a steady supply of cellular energy in the form of ATP to do work. One of the body's greatest ATP consumers, the heart consumes more ATP each day than it weighs. The mitochondrion generates over 95% of the body's ATP, largely by oxidative phosphorylation and to a lesser extent, glucose and amino acid oxidation^{23,24}. As a result, mitochondria are essential for proper cardiac function in terms of bioenergetics²⁵. In order to maintain energetic homeostasis in the cell, optimal cellular bioenergetics depends on the following factors:

- (1) sufficient oxygen and substrates delivery to the mitochondria;
- (2) the mitochondria's oxidative ability;
- (3) sufficient amounts of high-energy phosphate levels and PCr/ATP ratio;
- (4) efficient energy transfer from mitochondria to energy utilization sites;
- (5) sufficient local regulation of ATP/ADP ratios close to ATPases; and
- (6) effective feedback signaling from energy utilization sites.

Cardiovascular disorders such as dilated and hypertrophic cardiomyopathies of diverse origins, cardiac conduction problems, and ischemic heart diseases have all been linked to anomalies at these distinct stages of the cardiac energy pathways. A newly suggested underlying mechanism to explain myocardial dysfunction in HCM is compromised energetics²⁶.

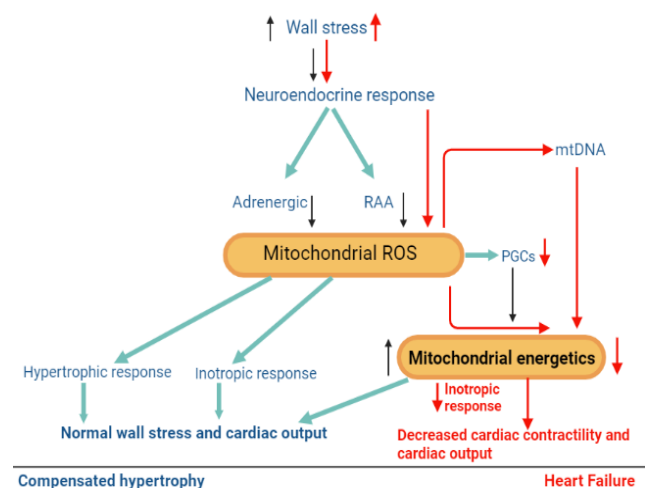


Figure 4: Molecular mechanism responsible for cardiac hypertrophy and failure

Because the ATP produced by mitochondria is necessary for both diastolic and systolic heart activities, the mitochondrial bioenergetic decrease may be a contributor to HF development. The normal myocardium can alternate between using fatty acids and glucose as

fuel (metabolic flexibility). In a healthy heart, up to 90% of the ATP is generated by the breakdown of fatty acids²⁷. The majority of experimental²⁸⁻³⁰ and clinical³¹⁻³³ research discover that metabolic rigidity, as indicated by a reduction in fatty acid oxidation, coexists with pathological cardiac hypertrophy and heart failure. A major decline in fatty acid oxidation is linked to overt cardiac failure³⁴. Significantly more ATP per molecule is produced by palmitate than glucose in terms of ATP synthesis. Consequently, a large increase in glucose oxidation must coincide with a relatively slight drop in fatty acid oxidation to maintain a steady ATP concentration. According to the majority of research^{29,35}, an increase in glucose oxidation does not make up for the decline in FA oxidation. The widespread assumption is that the failing heart is an energy-compromised organ and that there is no real metabolic transition characterized by a reduction in fat oxidation and a proportional increase in glucose oxidation³⁶.

THERAPY OF BIOENERGETICS IN CARDIOVASCULAR DISEASE

1. Citicoline may have neuro regenerative effects in the subacute and chronic stages of stroke by promoting neurogenesis, synaptogenesis, and angiogenesis^{37,38}, as well as through modifying neurotransmitter metabolism³⁹ and brain bioenergetics⁴⁰. By controlling brain cell differentiation, citicoline may speed up the recovery process following a stroke. Neurotransmitters regulate post-stroke healing. Citicoline affects the release of DA (Dopamine) and encourages alterations in brain DA receptors⁴¹. Aging is linked to a decline in the number of DA and Ach (Acetylcholine) receptors, and ischemic stroke primarily affects the elderly³⁹. Moreover, citicoline may improve frontal lobe bioenergetics, hence enhancing attention, memory, and information-processing functions. The majority of clinical investigations have shown that both short-term and long-term treatment with citicoline is safe, effective, and improves functional results⁴².
2. To treat mitochondrial malfunction, relatively recently developed medicines and probes have been specifically aimed at the mitochondria¹. The lipophilic TPP (Triphenyl phosphonium) is covalently bonded to the antioxidant MitoQ, which builds up 1,000-fold in mitochondria and reduces oxidative damage⁴³. MitoQ has been found helpful in mouse models of atherosclerosis, cardiac hypertrophy⁴⁴, and ischaemic-reperfusion injury⁴⁵. However, too much MitoQ can potentially interfere with mitochondrial activity⁴⁶. This series has produced a range of Mito compounds, including the probes MitoB⁴⁷, MitoSOX⁴⁸, and MitoPerox⁴⁹.
3. Another potential target is AMPK (AMP-activated protein kinase), which is thought to be the cell's primary regulator of bioenergetic capacity. AMPK has been linked to both favorable alterations in numerous illness models, including cardiovascular disorders, and lifetime extension^{50,51,52}.
4. Understanding the precise molecular and biochemical defect may enable the effective use of metabolic intermediates (such as succinate), coenzymes, and vitamins acting as electron donors and transporters (such as vitamin K, thiamine, ascorbate, and riboflavin) to at least partially bypass the defect in OXPHOS (Oxidative Phosphorylation) and increase ATP production in the treatment of mitochondrial based cardiac disorders⁵³. Idebenone, a synthetic derivative of coenzyme Q10, has recently been shown to be beneficial in restoring cardiac function in patients with severe respiratory complex activity deficiencies¹⁹ and cardiomyopathy associated with Friedreich ataxia⁵⁵.
5. Targeted medicines that boost glucose consumption and pyruvate oxidation energy at the expense of fatty acid oxidation can be used to address deficiencies in CPT-II, carnitine acylcarnitine translocase, or MTP (Mitochondrial Trifunctional Protein) that frequently result in an increased incidence of cardiac conduction abnormalities or arrhythmias⁸. Inhibiting CPT-I activity with perhexiline and amiodarone therapy can also successfully reverse long-chain fatty acid buildup and associated effects^{56,57}. CF (Cardiac Failure) patients are making progress in their treatment with carvedilol, an adrenoreceptor blocker that can significantly increase cardiac energy efficiency by switching the oxidative substrates for myocardial synthesis from fatty acids to glucose⁵⁸.
6. Dual-specificity tyrosine-regulated kinase 1B (DYRK1B) expression is elevated in hypertrophic mouse hearts and failing human myocardium. Although DYRK1B deficiency reduces transverse aortic constriction-induced hypertrophic cardiomyopathy and heart failure, DYRK1B overexpression causes cardiac dysfunction and impairs mitochondrial bioenergetics. By directly binding to STAT3 (Signal Transducer and Activators of Transcription 3), DYRK1B promotes its phosphorylation, nuclear accumulation, and eventual downregulation of PGC-1 α (Peroxisome proliferator-activated receptor gamma coactivator-1 α), which in turn causes cardiac dysfunction. A DYRK1B deficit can improve mitochondrial bioenergetics and restore heart function. New treatment strategies for treating ventricular hypertrophy and heart failure may include the pharmacological suppression of DYRK1B or STAT3⁵⁹.
7. The production of more reactive oxygen species (ROS) from the mitochondria and disturbed membrane potential are thought to be the early symptoms of mitochondrial malfunction⁶⁰. TGF- β 1 (Transforming Growth Factor- β 1) decreases the potential of the mitochondrial membrane and boosts the production of ROS (Reactive Oxygen Species) in PAEC (Pulmonary Arterial Endothelial Cells). Significant increases in baseline mitochondrial respiration and decreases in both the maximal and spare respiratory capacities show that TGF- β 1 also has an impact on mitochondrial bioenergetics⁶¹.
8. As the principal controller of energy metabolism, PGC-1 α , restoring PGC-1 α transcriptional activity has the



potential to enhance the cardiac energetic state and provide a novel strategy for the treatment of heart failure⁶². Targeting PGC-1 α , which is upstream of all regulation of energy metabolism, is a novel strategy that enables a harmonic enhancement of energy metabolism^{63,64}. By raising mi-CK expression, normalizing PGC-1 α concentration in the failing heart may enhance substrate consumption, oxidative capability, antioxidant defenses, and maybe mitochondrial dynamic and energy transmission⁶².

CONCLUSION

Cardiovascular illnesses include dilated and hypertrophic cardiomyopathy, cardiac conduction abnormalities and sudden death, ischemic and alcoholic cardiomyopathy, and myocarditis have all been linked to problems in mitochondrial structure and function. Many pieces of data suggest that mitochondrial dysfunction plays a significant part in the pathophysiology of various cardiovascular diseases. Extraordinary efforts have been made over several years to create drugs that directly target mitochondria for the management of heart disease. Many methods to treat mitochondrial dysfunction include the drugs that target the mitochondria, which can be used to lower free radical levels and examine respiratory chain activity; genome editing and manipulating technologies like TALENS and zinc finger nucleases; cell therapy; exercise and last but not least, new research areas include technologies that focus on the recycling of mitochondrial components and that preserve the viability of the proteasome.

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