# Mitochondrial Dysfunction: A Pharmacological Approach to Cardiovascular Diseases and advances in therapy

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## ABSTRACT

Mitochondrial dysfunction is increasingly recognized as a key factor in the development and progression of cardiovascular diseases (CVDs), including heart failure, ischemic heart disease, hypertension, and cardiomyopathy. Dysregulated mitochondrial function leads to impaired adenosine triphosphate (ATP) production and the activation of apoptotic and necrotic pathways, collectively contributing to the progression of cardiovascular diseases (CVDs). This understanding has propelled the development of Mitochondria-targeting Pharmacological therapies as a promising new frontier. This review summarizes the multifaceted roles of Mitochondria and details how their dysfunction contributes to disease progression. Then explore current Pharmacological strategies, highlighting advancements in targeted drug delivery systems, such as mitochondria-specific lipophilic cations and nanocarriers, designed to precisely deliver therapeutic agents to the organelle.

## 1. INTRODUCTION

Cardiovascular diseases (CVDs) continue to be the top cause of illness and death globally, creating a substantial health and economic challenge [1]. Although there have been considerable improvements in diagnostic and treatment methods in recent decades, the prevalence and effects of CVDs are still increasing, highlighting the urgent need for new understanding of their underlying biology and the creation of more effective treatments. While conventional risk factors like high blood pressure, abnormal cholesterol levels, diabetes, obesity, and smoking are well-recognized contributors to the development and progression of CVDs, recent research has emphasized mitochondrial dysfunction as a key unifying mechanism behind a variety of cardiovascular disorders [2].This encompasses chronic conditions such as heart failure (both reduced ejection fraction, HFrEF, and preserved ejection fraction, HFpEF), acute instances like myocardial ischemia-reperfusion injury (IRI), as well as common issues like atherosclerosis, hypertension, and diabetic cardiomyopathy [3]. The heart is an organ that constantly contracts and has a very high metabolic rate along with significant energy requirements [4]. Cardiomyocytes, the heart's specialized muscle cells, are rich in mitochondria, which make up about 30-35% of their total cell volume. This high mitochondrial density underscores their critical function in producing most of the cell's ATP through the efficient process of oxidative phosphorylation (OXPHOS) [5]. In addition to energy production, mitochondria are complex and dynamic organelles that play key roles in various essential cellular functions [6]. These include maintaining calcium balance within cells, managing the production and detoxification of

reactive oxygen species (ROS), regulating programmed cell death (apoptosis) and necrosis, influencing important signaling pathways related to cell survival, growth, and differentiation, and assisting in the metabolism of lipids and amino acids.

When the diverse functions of mitochondria are impaired, it sets off a sequence of harmful reactions within heart muscle cells, resulting in energy deficits, increased oxidative stress, inflammation, and eventually, cell injury and death. These consequences play a key role in the onset, development, and worsening of various cardiovascular diseases [3]. Thus, grasping the complex processes through which mitochondrial dysfunction leads to cardiovascular disease (CVD) is essential for pinpointing new treatment targets and creating innovative solutions. The aim of the study find the specific molecular mechanisms involved in mitochondrial dysfunction related to CVD, investigate new biomarkers for diagnosis and discuss both current and advanced pharmacological treatments, showcase recent breakthroughs in cell therapy, gene therapy, and nanomedicine at restoring mitochondrial function and enhancing cardiovascular health. The goal is to offer a comprehensive overview of the current insights and future paths in this critical and rapidly changing field.

## 1. METHODS:

### 1.1. Literature collection

**Search 1:** Markers:

To obtain an overview of which blood-derived markers have been used to detect mitochondrial dysfunction, we first performed a database search in PubMed with the following keywords: “mitochondrial dysfunction” AND (blood or plasma or serum) NOT review. Filters were active for

human studies and English language. This search was last performed on January 1st, 2021.

**Search 2:** Primary mitochondrial diseases A list of primary mitochondrial diseases with pathological changes in known OXPHOS genes, was obtained from Taylor et al., Zhu et al and Fernandez-Vizarra et al. (Taylor and Turnbull, 2005; Zhu et al., 2009; Fernandez-Vizarra and Zeviani, 2020) We additionally used the search term “mitochondrial disorder” and “mitochondrial disease” to find articles that contained possible primary MD patients.

**“Search 1” and “search 2”** were combined to find studies that investigated the potential markers of mitochondrial dysfunction in blood cells or blood of patients with confirmed primary MD. We excluded studies that used cellular hybrids i.e. patients mitochondrial DNA injected into immortalized cell lines as it is debatable if mitochondrial function of transformed cells reflects the mitochondrial function of innate host cells. Filters were active for human studies and English language. This search was last performed on January 1st, 2021. References of the retrieved articles were checked for additional relevant articles.

## 1. MECHANISM PRINCIPAL OF MITOCHONDRIALDYSFUNCTION IN CARDIOVASCULAR DISEASES

Mitochondrial dysfunction in cardiovascular disease is not a simple, standalone issue but a complicated and interrelated set of problems that collectively disrupt cellular energy levels, undermine cellular integrity, and lead to ongoing heart damage [6]. These underlying mechanisms often form a self-reinforcing cycle that worsens the condition [3]. Chronically elevated cardiac filling pressure is a critical cause of heart failure development, as mechanical stress overload disrupts intra- and intercellular homeostasis, with mitochondrial dysfunction playing an important role [145, 146]. The investigations are reported use the mice and rats with vasoconstriction models proved that HF is associated with reduced fatty acid oxidation and increased glycolysis, as well as impaired mitochondrial respiration [148]. Mitochondrial dysfunction in failing hearts has been linked to mechanical stress-induced structural abnormalities and deficiencies in several enzymes, including acyl-coenzyme A (CoA), a key regulator of fatty acid metabolism, which is notably reduced in both mice and humans [149]. Likewise, impaired catabolism of branched-chain amino acids (BCAAs) has also been shown to contribute to heart failure [60]. In both human heart failure (HF) and transverse aortic

constriction (TAC)-induced HF in mice, key enzymes involved in branched-chain amino acid (BCAA) catabolism—such as BCAT2, BCKD subunits, and PP2Cm—are downregulated, leading to impaired BCAA metabolism [60]. The accumulation of branched-chain alpha-keto acids (BCKAs), intermediates of BCAA catabolism, directly inhibits mitochondrial complex I–mediated respiration and increases superoxide production, whereas pharmacological reduction of BCKAs helps preserve cardiac function [60].

In addition, mitochondrial dysfunction in HF induced by mechanical stress is also related to the nervous system. Monoamine oxidase (MAO)-B, a mitochondrial flavoenzyme that regulates neurotransmission through oxidative deamination, promotes dopamine catabolism and lipid peroxide production in the hearts of TAC mice [154]. Activation of MAO enhances mtROS formation and reduces mitochondrial membrane potential, suggesting a novel pathogenesis of HF under mechanical stress [154]. Metabolic abnormalities caused by pressure overload impair mitochondrial respiration and induce oxidative stress, with mechanosensitive receptor–related pathways playing a key role in this process. Importantly, enhancing metabolism and mitochondrial function supports the heart's resistance to mechanical stress–induced pathologies, such as cardiac hypertrophy [155]. Enhancing mitochondrial function improves metabolite utilization by cardiomyocytes, highlighting therapeutic opportunities in heart failure rooted in both mechanical and metabolic dysfunctions. In healthy cardiomyocytes, fatty acid oxidation (FAO) is the primary energy source, supplying approximately 70% of ATP through the TCA cycle and electron transport chain (ETC), while glucose oxidation plays a secondary role [49]. This metabolic preference aligns with the heart’s high energy demands and dense mitochondrial content [50]. Heart failure is marked by impaired cardiac contractility and relaxation, leading to diminished cardiac output and systemic perfusion. A central feature of heart failure is mitochondrial dysfunction, which contributes to energy depletion, oxidative stress, and cardiomyocyte apoptosis [47]. These deficits are further exacerbated by reduced mitochondrial biogenesis and the downregulation of fatty acid oxidation [41]. Human studies have consistently shown lower ATP levels in failing hearts compared to non-failing controls [43]. Impaired oxidative phosphorylation and ATP production are central to mitochondrial dysfunction, where the efficiency and capacity of the electron transport chain (ETC) and ATP synthase activity are compromised.

## 3. BIOMARKERS FOR DIAGNOSIS OF MITOCHONDRIAL DYSFUNCTION IN CARDIOVASCULAR DISEASES.

## 4. CELL, GENE AND NANO MEDICINE BASED THERAPIES IN CVD.

**Stem cell therapy**: Cell therapy techniques utilize the regenerative, immune-modulating, and paracrine properties of different cell types to counteract mitochondrial dysfunction and enhance cardiac performance. A key emerging mechanism behind the efficacy of certain cell therapies is the direct transfer of healthy mitochondria. Particularly mesenchymal stem cells (MSCs), have shown promise in cardiac repair. They can differentiate into cardiomyocytes and endothelial cells, promoting tissue regeneration and angiogenesis. However, challenges such as low engraftment rates and potential tumorigenicity remain [Sarathkumar et al., 2021]. Cardiac Progenitor Cells (CPCs) are resident cells in the heart capable of differentiating into various cardiac cell types. Therapies involving CPCs aim to enhance myocardial repair and function post-injury.

**Gene-Based Therapies in Cardiovascular Disease**: Gene therapy holds significant promise for directly addressing genetic defects or modifying the expression of genes crucial to mitochondrial function, consequently improving mitochondrial health in cardiomyocytes. CRISPR/Cas9 and base- editing technologies are being explored to correct genetic mutations underlying CVDs. For instance, Verve Therapeutics is developing a base-editing therapy targeting the PCSK9 gene to reduce LDL cholesterol levels permanently. Early trials have shown promising results with significant LDL-C reduction.

**Nanomedicine in Cardiovascular Disease**: Nanotechnology presents groundbreaking prospects for accurately targeted drug delivery, addressing the drawbacks of traditional systemic administration while ensuring elevated, localized concentrations of therapeutic agents at sites of mitochondrial dysfunction in cardiomyocytes. The benefits of

nanomedicine in this context are considerable: improved drug availability at the cellular and mitochondrial levels, decreased systemic toxicity and off-target effects, enhanced drug stability, and the capacity to deliver complex therapeutics (like peptides, biologics, and nucleic acids) across biological barriers that traditional drugs struggle to penetrate. This targeted approach can address the limitations of systemic administration and ensure higher therapeutic concentrations at critical sites of mitochondrial dysfunction.

**Nanoparticle-Based Drug Delivery**: Nanoparticles can encapsulate drugs and target them to specific sites, reducing systemic side effects. For example, liposomes loaded with VEGF have been shown to improve heart function and vascular density when administered after myocardial infarction.

**Nanozymes**: Engineered nanoparticles with enzyme-like activities, known as nanozymes, can mimic natural enzymes to scavenge reactive oxygen species (ROS) and reduce oxidative stress in cardiac tissues. Mito-Fenozymes, which target mitochondria, have demonstrated improved cardiac function in ischemic models.

**Nanotheranostics**: Nanotheranostics combines therapeutic and diagnostic capabilities into a single nanoparticle. These platforms allow for targeted therapy and real-time monitoring of treatment efficacy in cardiovascular diseases. Advancements in multimodal imaging techniques, such as PET and MRI, have enhanced the precision of nanotheranostic applications.

## 3. DISCUSSION

The advancing and sophisticated understanding of mitochondrial dysfunction as a key factor in the development and progression of cardiovascular diseases indicates a significant paradigm shift in cardiovascular research and treatment. For many years, treatment strategies for cardiovascular diseases (CVD) primarily focused on managing traditional risk factors (like using statins for dyslipidemia or ACE inhibitors for hypertension) and alleviating symptoms (such as using beta-blockers for heart rate control or diuretics for fluid overload). While these strategies have proven effective, they often neglect the underlying cellular energetic and quality control failures that contribute to much of the myocardial damage. Thus, improving mitochondrial health offers a more fundamental, disease-modifying, and potentially curative strategy.

The variety of therapeutic methods discussed—ranging from advanced pharmacological agents to innovative cell and gene therapies, as well as upcoming nanomedicine platforms—highlights the complex nature of targeting mitochondrial biology. Each method presents unique advantages and challenges. Small molecule drugs are beneficial due to their oral bioavailability and ease of use, yet they often face issues with specificity, off-target effects, and efficient mitochondrial delivery. Cell therapies, including direct delivery of healthy mitochondria or mesenchymal stem cells (MSCs), provide direct functional support but encounter challenges such as delivery methods, scalability, immunogenicity (in the case of allogeneic sources), and ensuring the long-term viability of the transplanted material. Gene therapy shows great potential for long-term correction of genetic issues or sustained modulation of important mitochondrial pathways, but it is hampered by the complexities of efficient, safe delivery to cardiac tissues, with concerns about off-target gene modifications and safety, particularly when addressing the unique mitochondrial genome. Nanomedicine enables unprecedented precision in drug delivery, enhancing mitochondrial bioavailability and minimizing systemic toxicity; however, it necessitates thorough evaluation of biocompatibility, biodegradability, and long-term safety. Converting these promising preclinical outcomes into broad clinical practice poses significant challenges. A key factor is the inherent complexity and variability of mitochondrial dysfunction itself.

Specific mitochondrial defects differ across various types of CVD (for example, ischemia-reperfusion injury compared to chronic heart failure) and among individual patients within the same disease category, due to genetic traits, comorbidities, and lifestyle influences. This highlights the need to move towards personalized medicine.
Future studies should concentrate on the following areas:

Precision Medicine and Patient Stratification: It is essential to develop advanced diagnostic tools and reliable, non-invasive biomarkers (as outlined in Section 3) to accurately identify patients with specific mitochondrial defects or dysfunction patterns. This will allow for the customization of mitochondrial- targeted therapies based on individual patient characteristics, maximizing treatment effectiveness and minimizing the risk of ineffective therapies. Genetic profiling and advanced metabolic phenotyping will be vital for this personalized strategy. Combination Therapies: Due to the complex interrelated nature of various mitochondrial pathways, relying on a single therapeutic agent that addresses only one aspect of mitochondrial dysfunction may not lead to full recovery. Future approaches will likely incorporate combination therapies that simultaneously target multiple complementary aspects of mitochondrial health, such as pairing an antioxidant with a biogenesis enhancer or an mPTP inhibitor with a mitophagy activator. This synergistic strategy could achieve better and more lasting results. Refinement of Delivery Systems: Ongoing innovation is crucial in creating more efficient, specific, and safer delivery systems for mitochondrial therapies. This includes enhancing the design of nanocarriers, creating highly cardiotropic and mitochondriotropic viral vectors, and discovering new methods for targeted cell-free mitochondrial delivery that can overcome anatomical obstacles and ensure effective intracellular entry. Robust Clinical Trial Design and Biomarker Validation: The successful implementation of these therapies depends on meticulously designed and conducted clinical trials. These trials should evaluate both the efficacy and safety of new mitochondrial-targeted treatments while also validating reliable, non- invasive biomarkers that can effectively monitor mitochondrial function in vivo, predict treatment responses, and track long-term results. Elucidating Inter-Organelle Crosstalk: Mitochondrial dysfunction often does not occur in isolation; it can trigger broader cellular reactions and interacts extensively with other organelles (like the endoplasmic reticulum, peroxisomes, and lysosomes) and intracellular signaling pathways. A more comprehensive understanding of this complex inter-organelle communication and its impact on cellular health and disease progression is crucial for developing integrated therapeutic strategies that consider the entire cellular environment. Repurposing Existing Drugs: The unanticipated cardiovascular benefits of medications such as SGLT2 inhibitors, which were initially developed for diabetes, and their emerging positive impacts on mitochondrial function and cardiac metabolism, present a promising research opportunity. Continued investigation into existing drugs for new mitochondrially

driven mechanisms could expedite the discovery of new therapeutic uses.

## 3. CONCLUSION

Mitochondrial dysfunction has clearly established itself as a key pathogenic factor in a wide variety of cardiovascular diseases. The complex mechanisms involved—from reduced ATP production and excessive ROS generation to disrupted mitochondrial dynamics and mtDNA damage—collectively lead to cardiomyocyte injury, energy deficits, and ultimately, declines in myocardial function. Acknowledging this fundamental role marks the beginning of a new era in cardiovascular therapy development and earlier diagnosis of the diseases. The review directly addressing cellular energy imbalances and quality control issues, mitochondrial-targeted therapies offer a transformative shift, moving beyond merely alleviating symptoms to fundamentally altering disease progression. The continuous collaborative efforts to understand and therapeutically manage mitochondrial health are critical to unlocking new possibilities in cardiovascular treatment. The future of cardiovascular medicine will likely adopt a multifaceted approach that combines innovative diagnostic biomarkers with precisely targeted mitochondrial interventions, potentially in combination, to restore cellular energy balance and address the challenges posed by cardiovascular diseases.

**Declaration of Competing Interest**:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**REFERENCE:**


1. Xi Li, Wei Ou, Maodi Xie, Jing Yang, Qian Li, Tao Li. Nanomedicine-Based Therapeutics for Myocardial 12: 20. Aug 8, 2023. Special Issue: Transformative Medical Materials https://doi.org/10.1002/adhm.202300161.

2. Elangovan Sarathkumar, Marina Victor, Jaivardhan A. Menon, Kunnumpurathu Jibin, Suresh Padmini [b] and Ramapurath S. Jayasree Nanotechnology in cardiac stem cell therapy: cell modulation, imaging and gene delivery. DOI: 10.1039/D1RA06404E (Review Article) *RSC Adv.*, 2021, **11**, 34572-34588.

3. Virna Margarita Martín Giménez, Diego E. Kassuha, and Walter Manucha. Nanomedicine applied to cardiovascular diseases: latest developments. Ther Adv Cardiovasc Dis 2017, Vol. 11(4) 133 –142 https://doi.org/10.1177/1753944717692293 https://doi.org/10.1177/1753944717692293 DOI: 10.1177/1753944717692293.

4. Aseem Setia, Abhishesh Kumar Mehata, Vishnu Priya, Datta Maroti Pawde, Dharmendra Jain Sanjeev
5. Kumar Mahto, Madaswamy S. Muthu**.** Current Advances in Nanotheranostics for Molecular Imaging and Therapy of Cardiovascular Disorders. *Molecular Pharmaceutics*. Vol 20/Issue 10.

6. C. Wu, Z. Zhang, W. Zhang, X. Liu, Mitochondrial dysfunction and mitochondrial therapies in heart failure, Pharm. Res 175 (2022) 106038.

7. D.F. Dai, E.J. Hsieh, Y. Liu, T. Chen, R.P. Beyer, M.T. Chin, M.J. MacCoss, P. S. Rabinovitch, Mitochondrial proteome remodelling in pressure overloadinduced heart failure: the role of mitochondrial oxidative stress, Cardiovasc Res. 93 (2012) 79–88.

8. J. Mojumder, J.S. Choy, S. Leng, L. Zhong, G.S. Kassab, L.C. Lee, Mechanical stimuli for left ventricular growth during pressure overload, Exp. Mech. 61 (2021) 131–146.

9. T. Doenst, T.D. Nguyen, E.D. Abel, Cardiac metabolism in heart failure: implications beyond ATP production, Circ. Res 113 (2013) 709–724.

10. J.R. Goldenberg, A.N. Carley, R. Ji, X. Zhang, M. Fasano, P.C. Schulze, E. D. Lewandowski, Preservation of Acyl Coenzyme A attenuates pathological and metabolic cardiac remodeling through selective lipid trafficking, Circulation 139 (2019) 2765–2777.

11. H. Sun, K.C. Olson, C. Gao, D.A. Prosdocimo, M. Zhou, Z. Wang, D. Jeyaraj, J.Y. Youn, S. Ren, Y. Liu, C.D. Rau, S. Shah, O. Ilkayeva, W.J. Gui, N.S. William, R.M. Wynn, C.B. Newgard, H. Cai, X. Xiao,
12. D.T. Chuang, P.C. Schulze, C. Lynch, M.K. Jain, Y. Wang, Catabolic defect of branched-chain amino acids promotes heart failure, Circulation 133 (2016) 2038–2049.

13. N. Kaludercic, A. Carpi, T. Nagayama, V. Sivakumaran, G. Zhu, E.W. Lai, D. Bedja, A. De Mario, K. Chen, K.L. Gabrielson, M.L. Lindsey, K. Pacak, E. Takimoto, J.C. Shih, D.A. Kass, F. Di Lisa, N. Paolocci,

Monoamine oxidase B prompts mitochondrial and cardiac dysfunction in pressure overloaded hearts, Antioxid. Redox Signal 20 (2014) 267–280.

14. I. Shimizu, T. Minamino, Physiological and pathological cardiac hypertrophy, J. Mol. Cell Cardiol. 97 (2016) 245–262.

15. Youle, R. J. Mitochondria—Striking a balance between host and endosymbiont. Science 365, eaaw9855 (2019).

16. Virbasius, J. V. & Scarpulla, R. C. Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. Proc. Natl Acad. Sci. 91, 1309–1313 (1994).

17. McCully, J. D. et al. Injection of isolated mitochondria during early reperfusion for cardioprotection. Am. J. Physiol.-heart C. 296, H94–H105 (2009).

18. Phinney, D. G. et al. Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. Nat. Commun. 6, 8472 (2015).

19. Hayakawa, K. et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535, 551–555 (2016).