Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 August; 6 (1): 716-722

Mitochondrial Dysfunction in Cardiovascular Diseases Pathways and Therapeutic Avenues

1 Dr. Anup S. Hendre, 2 Dr. Sudarshan N. Shelke, 3 Dr. Sagita R. Patil, 4 Dr. Mandakini S. Kshirsagar, 5 Dr. Ganesh H. Ghanwat

1 Assistant Professor Department of Biochemistry , Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth Deemed To Be University, Karad Email ID-anupviews@gmail.com
2 Associate Professor Department of Biochemistry , Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth Deemed To Be University, Karad
3 Associate Professor Department of Biochemistry , Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth Deemed To Be University, Karad
4 Assistant Professor Department of Biochemistry , Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth Deemed To Be University, Karad
5 Tutor Department of Biochemistry , Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth Deemed To Be University, Karad

Received: 24- June -2023
Revised: 27- July -2023
Accepted: 21- August -2023

Abstract

Mitochondrial dysfunction has emerged as a pivotal factor in the pathogenesis and progression of cardiovascular diseases (CVDs), influencing diverse cellular pathways and contributing significantly to disease pathophysiology. This review synthesizes current knowledge regarding the impact of mitochondrial dysfunction on CVDs, exploring the intricate relationships between dysfunctional mitochondria and various cardiovascular conditions such as heart failure, atherosclerosis, and ischemia-reperfusion injury. The interplay between mitochondrial alterations, including oxidative stress, impaired energy production, disrupted calcium handling, and mitochondrial DNA mutations, and their implications in the context of cardiovascular health is comprehensively analyzed. Moreover, the review delves into potential therapeutic strategies targeting mitochondrial pathways, encompassing mitochondrial antioxidants, modulators of mitochondrial dynamics, agents stimulating mitochondrial biogenesis, and emerging mitophagy inducers. The challenges, future directions, and translational implications of understanding mitochondrial dysfunction in cardiovascular diseases are also discussed, highlighting the need for personalized therapeutic approaches and innovative interventions.

Keywords: Mitochondrial dysfunction, Cardiovascular diseases, Oxidative stress, Mitochondrial pathways, Therapeutic strategies

Introduction

The essential cellular organelles known as mitochondria are involved in calcium homeostasis, apoptotic signaling, and the synthesis of cellular energy. Numerous cardiovascular diseases' (CVDs) etiology and progression have been linked in large part to their malfunction. The complex relationship that exists between cardiovascular health and mitochondrial function emphasizes how important it is to fully comprehend the consequences of mitochondrial malfunction in these illnesses [1-5].

There are several facets to the association between mitochondrial dysfunction and CVDs. Oxidative stress, reduced energy production, changed calcium handling, and dysregulated apoptosis are all associated with dysfunctional mitochondria and can have a negative effect on heart health and blood vessel function. Furthermore, evidence points to the pathophysiology of CVD being influenced by mutations in mitochondrial DNA, abnormalities in mitochondrial dynamics, and disruptions in mitophagy pathways. Determining the pathophysiology of CVDs requires an understanding of the pathways impacted by mitochondrial dysfunction. Critical pathways such as oxidative phosphorylation, the production of reactive oxygen species (ROS), the opening of the mitochondrial permeability transition pore (mPTP), and mitochondrial-nuclear signaling are all impacted by mitochondrial dysfunction and have important consequences for cardiovascular health [3-6].

Investigating therapeutic approaches that target mitochondrial pathways is a promising route, given the central role that mitochondrial dysfunction plays in CVDs. It may be possible to improve mitochondrial dysfunction and

slow the development of CVDs by utilizing tactics such mitochondrial antioxidants, dynamics regulators, and medicines that target mitochondrial biogenesis [7-10].

Comprehending the intricate relationship between mitochondrial malfunction and cardiovascular well-being is essential for creating tailored treatment approaches. The objective of this review is to examine and summarize the state of the art on mitochondrial dysfunction in CVDs, emphasizing prospective treatment approaches and underlying mechanisms.

1. Dysfunctional Mitochondria in Cardiovascular Conditions

One important component in the etiology and development of many cardiovascular diseases (CVDs) is mitochondrial dysfunction [1]. A wide range of illnesses, such as heart failure, atherosclerosis, ischemia-reperfusion damage, and cardiomyopathies, are characterized by this dysfunction [2]. There is a complex relationship between cardiovascular health and mitochondrial health, and disease pathogenesis is greatly influenced by dysfunctional mitochondria [3].

Research has clarified how defective mitochondria cause oxidative stress, which is a defining characteristic of CVDs [4]. Reactive oxygen species (ROS) are produced in excess when the electron transport chain in defective mitochondria is compromised, which damages cells and encourages the development of atherosclerotic plaque [5]. Moreover, aberrant fusion and fission processes that result from compromised mitochondrial dynamics disturb cellular homeostasis, which affects cardiac and vascular function [6].

Moreover, cardiac myocytes' ability to handle calcium is hampered by mitochondrial dysfunction, which impairs excitation-contraction coupling and promotes arrhythmogenesis [7]. Moreover, abnormal opening of the mitochondrial permeability transition pore (mPTP), which is frequently linked to malfunctioning mitochondria, initiates pathways leading to cell death, aggravating tissue damage during myocardial infarction [8].

Moreover, abnormalities in mitochondrial-nuclear signaling pathways, impaired mitophagy, and mutations in mitochondrial DNA (mtDNA) are linked to the pathophysiology of CVDs [9]. These molecular abnormalities exacerbate oxidative stress and cellular dysfunction by facilitating the build-up of damaged mitochondria, which in turn affects cardiovascular health [10].

Comprehending the many mechanisms that underlie CVDs requires an understanding of the multidimensional impact of mitochondrial dysfunction on several pathways [11]. Determining these molecular subtleties through research provides promising paths for the development of tailored medicines intended to reduce mitochondrial dysfunction and slow the course of cardiovascular illnesses [12].

2. The Pathways That Mitochondrial Dysfunction Affects

Heart disease (CVD) pathophysiology is greatly impacted by the complex effects of mitochondrial dysfunction on several cellular pathways [1]. Oxidative phosphorylation (OXPHOS), the basic mechanism controlling ATP synthesis in mitochondria, is one of the main routes impacted [2]. Reduced energy generation from impaired OXPHOS resulting from mitochondrial dysfunction compromises the high energy requirements of cardiac muscle and vascular tissues, which accelerates the development of CVDs [3].

One such important mechanism linked to the pathophysiology of CVD is the production of excessive reactive oxygen species (ROS) as a result of malfunctioning mitochondria [4]. Byproducts of electron leakage from the electron transport chain, ROS exacerbate cellular damage and encourage atherosclerosis in addition to contributing to oxidative stress [5]. Additionally, ROS behave as signaling molecules, influencing a number of physiological pathways, such as endothelial dysfunction and inflammation, which exacerbates the pathogenesis of CVD [6].

Additionally, calcium homeostasis in cardiomyocytes is disturbed by mitochondrial dysfunction, which affects excitation-contraction coupling and contractile performance [7]. Heart failure and other cardiac disorders are attributed to the pathophysiology of dysregulated calcium handling caused by defective mitochondria, which results in arrhythmias and decreased cardiac contractility [8].

Moreover, one important mechanism impacted by mitochondrial malfunction is the opening of the mitochondrial permeability transition pore (mPTP) [9]. Apoptotic pathways are triggered by excessive mPTP opening, which is

frequently linked to defective mitochondria. This leads to cardiomyocyte mortality and exacerbates myocardial damage following ischemia events [10].

The control of cellular reactions to stress and energy demands is likewise greatly influenced by mitochondrial-nuclear signaling pathways [11]. The pathophysiology of CVDs is aided by the disruption of these signaling pathways by dysfunctional mitochondria, which affects gene expression, cellular metabolism, and stress responses [12].

Furthermore, aberrant fusion and fission processes associated with poor mitochondrial dynamics upset cellular homeostasis, which affects cardiac and vascular function [13]. The buildup of damaged mitochondria and the acceleration of the progression of CVD are caused by altered mitochondrial dynamics, which also have an impact on mitochondrial quality control systems and energy production [14].

The intricate relationship between mitochondrial health and cardiovascular function is highlighted by the cumulative effects of mitochondrial malfunction on these several pathways. Comprehending these complex interplays is crucial in developing focused therapy approaches intended to address mitochondrial dysfunction and slow down the advancement of cardiovascular disorders.

3. Medication Strategies for Mitochondrial Dysfunction

Mitochondrial Antioxidants: Targeting the excessive production of reactive oxygen species (ROS) linked to mitochondrial dysfunction in cardiovascular disorders is the goal of strategies employing mitochondrial antioxidants [1]. In preclinical and clinical investigations, compounds such as coenzyme Q10 (CoQ10), MitoQ, and antioxidants targeting mitochondrial enzymes, like superoxide dismutase mimetics, show promise in lowering oxidative stress and improving mitochondrial dysfunction [2].

Mitochondrial Dynamics Modulators: Using modulators of fusion and fission processes to regulate mitochondrial dynamics offers an additional therapeutic approach [3]. In cardiovascular diseases, compounds that promote fission (P110) and regulate mitochondrial fusion (Mdivi-1) may be able to restore mitochondrial homeostasis and function [4].

Agents that Aim to Stimulate Mitochondrial Biogenesis: In cardiovascular disorders, stimulating mitochondrial biogenesis offers a promising strategy to improve mitochondrial function [5]. Exercise mimetics and pharmaceutical treatments like bezafibrate are examples of activators of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) that show promise in increasing mitochondrial biogenesis, improving energy production, and improving cardiac and vascular function [6].

Inducers of Mitophagy:

Encouraging mitophagy, or the deliberate elimination of damaged mitochondria, appears to be a promising treatment approach [7]. In the context of cardiovascular disorders, substances such as urolithin A, rapamycin, and small compounds that target mitophagy pathways show promise in eliminating defective mitochondria, hence reducing oxidative stress and enhancing cellular function [8].

Metabolic Modulators: One novel strategy to lessen mitochondrial dysfunction is to target cellular metabolism [9]. By increasing energy generation and lowering oxidative stress, metabolic modulators—like metformin or ketogenic diets—aim to regulate cellular metabolism, enhance mitochondrial function, and slow the advancement of cardiovascular illnesses [10].

Gene Therapy and Novel Techniques:

Novel therapeutic approaches, such as CRISPR-Cas9 gene editing technologies, have the potential to target mitochondrial DNA abnormalities linked to cardiovascular disorders [11]. Furthermore, novel approaches that employ peptides or nanoparticles targeted at mitochondria appear promising for selectively delivering therapeutic drugs to malfunctioning mitochondria, providing a highly tailored therapeutic approach [12].

The range of therapeutic approaches aimed at addressing mitochondrial dysfunction highlights the possibility of creative approaches in the treatment of cardiovascular disorders. These strategies present encouraging possibilities

for reducing the negative effects of mitochondrial dysfunction on cardiovascular health, even if more investigation and clinical testing are required to confirm their safety and efficacy.

4. Experimental Models and Technologies

Animal Models: Studies of mitochondrial dysfunction in cardiovascular disorders continue to rely heavily on animal models, including bigger mammals such as pigs and dogs as well as rodents like mice and rats [1]. These models facilitate the simulating of illness circumstances, evaluation of mitochondrial function, and in vivo investigation of the effectiveness of therapeutic therapies. Transgenic mice with specific mutations in their mitochondrial genes are one type of genetically engineered model that offers important insights into the precise effects of mitochondrial changes on heart and vascular physiology [2].

Cell Culture Systems: These systems are useful for researching mitochondrial dysfunction at the cellular level. Of particular interest are cardiac myocytes and endothelial cells obtained from either animal or human sources [3]. These technologies make it possible to modify mitochondrial activity, evaluate how cells react to stress on the mitochondria, and find possible medicinal drugs that target the mitochondria [4].

High-Resolution Imaging Techniques: The structure, behavior, and function of mitochondria within cells and tissues can be seen thanks to advanced imaging methods such as electron microscopy, confocal microscopy, and super-resolution microscopy [5]. These high-resolution imaging methods clarify changes linked to cardiovascular disorders by offering comprehensive insights into the structure, organization, and interactions of the mitochondria with other cellular constituents [6].

Omics Approaches: Omics technologies provide a thorough understanding of the molecular changes linked to mitochondrial dysfunction in cardiovascular disorders. These technologies include proteomics, metabolomics, transcriptomics, and genomics [7]. By using these methods, scientists can examine worldwide variations in metabolite concentrations, protein profiles, and gene expression, which helps them decipher complex signaling cascades and find possible biomarkers linked to mitochondrial malfunction [8].

Bioenergetics Analysis: Real-time evaluation of mitochondrial function and cellular metabolism is made easier by bioenergetics analysis tools, such as high-resolution respirometry and Seahorse extracellular flux analysis [9]. These techniques make it possible to determine the rates at which ATP is produced, oxygen consumption, and mitochondrial respiratory chain activities. This information is crucial for understanding the role of mitochondrial bioenergetics in cardiovascular diseases [10].

CRISPR-Cas9 Gene Editing: With the development of CRISPR-Cas9 technology, scientists can now precisely edit the genome to change nuclear genes linked to mitochondrial function or mitochondrial DNA (mtDNA) [11]. With the aid of this ground-breaking instrument, it will be possible to address genetic abnormalities associated with mitochondrial malfunction and create fresh experimental models to investigate the role of mitochondria in cardiovascular disorders [12].

Investigating mitochondrial dysfunction in cardiovascular disorders can be done comprehensively thanks to the combination of these experimental models with state-of-the-art technologies. With the aid of these instruments, scientists can decipher the subtleties of mitochondrial biology, pinpoint potential treatment targets, and open the door for novel approaches to the management of CVDs.

5. New Developments in Cardiovascular Disease Mitochondrial Targeting Therapies

Peptides and Nanoparticles Targeted at Mitochondria

Advances in nanomedicine have opened the door to novel approaches that target defective mitochondria in cardiovascular disorders. Therapeutic medicines can be delivered to mitochondria directly with the use of peptides and nanoparticles that are specifically targeted towards mitochondria [1]. Thanks to their specific targeting ligand design, these nanostructures are able to deliver therapeutic chemicals such as bioenergetic modulators or antioxidants locally within mitochondria, all while piercing biological barriers [2]. With its ability to maximize therapeutic efficacy and minimize off-target effects, tailored delivery systems have great potential in the treatment of cardiovascular diseases linked to mitochondrial dysfunction [3].

Technologies for Editing Mitochondrial Genes

The precise alteration of mitochondrial DNA (mtDNA) made possible by the advent of mitochondrial gene editing technologies, most notably CRISPR-Cas9, has transformed the field [4]. Corrective actions to restore mitochondrial function and stop the progression of the disease are made possible by targeted changes of mtDNA mutations linked to cardiovascular disorders [5]. Notwithstanding obstacles like transport into mitochondria and possible side effects, these gene editing instruments offer a novel strategy for tackling the underlying causes of mitochondrial malfunction in cardiovascular diseases [6].

Metabolism of Mitochondria and Exercise Models

An exciting treatment option for mitochondrial dysfunction in cardiovascular diseases is to stimulate mitochondrial biogenesis with pharmaceuticals called exercise mimetics [7]. By activating the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a master regulator of mitochondrial biogenesis, compounds such as resveratrol and bezafibrate imitate the effects of exercise [8]. With their potential to increase mitochondrial density, enhance respiratory function, and improve cardiac and vascular health, these medicines provide an alternate approach to treating CVDs [9].

Redox modulators and antioxidants Targeted at the Mitochondrion

The goal of ongoing research is to create new antioxidants and redox modulators that target the mitochondria in order to counteract oxidative stress, which is a defining feature of mitochondrial dysfunction in CVDs [10]. MitoQ, SkQ1, and SS-31 are examples of compounds that preferentially concentrate inside mitochondria, scavenging reactive oxygen species and maintaining mitochondrial function [11]. These specific antioxidants show promise in improving cardiovascular diseases linked to mitochondrial dysfunction, reducing oxidative damage, and reestablishing redox equilibrium [12].

Modulators of Mitochondrial Selective Ion Channels

Maintaining cellular homeostasis and mitochondrial function depend heavily on ion channels found in the mitochondrial membrane. New research investigates the therapeutic potential of specific modulators that target mitochondrial ion channels in order to attenuate the course of CVD and restore ionic equilibrium [13]. One possible method for controlling mitochondrial function and reducing cardiac ischemia-reperfusion injury or heart failure is to modulate channels like the mitochondrial calcium uniporter or ATP-sensitive potassium channels [14].

The therapy landscape for cardiovascular disorders linked to mitochondrial dysfunction could be completely changed by further investigation and improvement of these new developments in mitochondrial targeted medicines. Introducing these cutting-edge tactics into clinical practice could open the door to more individualized and successful CVD management techniques.

6. Challenges and Future Directions

Complex Interactions and Multifactorial Nature: Because cardiovascular illnesses and mitochondrial dysfunction are multifactorial problems, comprehending the complex interactions between these conditions remains a substantial difficulty [1]. Deciphering the intricate relationships among mitochondrial modifications, cellular processes, and the advancement of disease necessitates an all-encompassing strategy that incorporates multidisciplinary cooperation and cutting-edge research techniques [2].

Absence of Targeted medicines: Although a number of treatment strategies aimed at addressing mitochondrial dysfunction exhibit potential, it is still difficult to produce efficient targeted medicines for cardiovascular illnesses [3]. A major obstacle is identifying particular molecular targets within mitochondrial pathways and turning these findings into therapeutically feasible therapies [4]. To confirm the effectiveness, safety, and specificity of targeted medicines in clinical settings, more investigation is required.

Mitochondrial Dysfunction Biomarkers: Finding and validating trustworthy biomarkers to measure mitochondrial dysfunction in cardiovascular disorders is a continuous task [5]. For clinical diagnosis and monitoring, biomarkers with the ability to identify early mitochondrial changes, forecast disease development, and assess therapy

responses are essential [6]. One of the top priorities for expanding mitochondrial research in cardiovascular medicine is the development of sensitive and targeted biomarkers.

Translational Research and Clinical Applications: In the realm of mitochondrial dysfunction and cardiovascular disorders, there is a significant problem in translating fundamental research discoveries into clinical applications [7]. Strict preclinical research, strong clinical trials, and regulatory approval procedures are needed to close the gap between benchside discoveries and bedside uses [8]. It is essential to develop strategies that make it easier for potential therapeutic approaches to go from preclinical models to human trials.

Methods in Precision Medicine:

Future directions in the treatment of cardiovascular disorders include the application of precision medicine techniques adapted to individual differences in mitochondrial function and genetic predispositions [9].

Optimizing treatment efficacy and outcomes may be possible through personalized therapy techniques that take into account the unique mitochondrial profiles, genetic variants, and disease symptoms of each patient [10].

Technological Developments and Therapeutic Targets: New technologies, including gene editing methods, sophisticated imaging modalities, and high-throughput screening platforms, present opportunities for finding new therapeutic targets and improving those that already exist [11]. Prospective avenues for future study in alleviating mitochondrial dysfunction in CVDs include discovering novel therapeutic candidates, improving drug delivery systems, and focusing on certain mitochondrial pathways [12-15].

It will take interdisciplinary cooperation, creative methodology, and a dedicated focus on translational applications to address these issues and pursue new avenues in mitochondrial research in the field of cardiovascular disorders. Redefining the management and treatment of cardiovascular disorders linked to mitochondrial dysfunction could be possible if these obstacles are overcome and progress made in these directions.

References

1. Zaragoza, C., Gomez-Guerrero, C., Martin-Ventura, J. L., Blanco-Colio, L., Lavin, B., Mallavia, B., Tarin, C., Mas, S., Ortiz, A., & Egido, J. (2011). Animal models of cardiovascular diseases. *Journal of biomedicine & biotechnology*, *2011*, 497841. https://doi.org/10.1155/2011/497841
2. Ong, S. B., Hall, A. R., & Hausenloy, D. J. (2013). Mitochondrial dynamics in cardiovascular health and disease. *Antioxidants & redox signaling*, *19*(4), 400–414. https://doi.org/10.1089/ars.2012.4777
3. Yang, J., Guo, Q., Feng, X., Liu, Y., & Zhou, Y. (2022). Mitochondrial Dysfunction in Cardiovascular Diseases: Potential Targets for Treatment. *Frontiers in cell and developmental biology*, *10*, 841523. https://doi.org/10.3389/fcell.2022.841523
4. Giedt, R. J., et al. (2016). Computational imaging reveals mitochondrial morphology as a biomarker of cancer phenotype and drug response. *Scientific Reports*, 6, 32985.
5. Poznyak, A. V., Ivanova, E. A., Sobenin, I. A., Yet, S. F., & Orekhov, A. N. (2020). The Role of Mitochondria in Cardiovascular Diseases. *Biology*, *9*(6), 137. https://doi.org/10.3390/biology9060137
6. Hill, B. G., et al. (2012). Integration of cellular bioenergetics with mitochondrial quality control and autophagy. *Biological Chemistry*, 393(12), 1485-1512.
7. Nicholls, D. G., Darley-Usmar, V. M., Wu, M., Jensen, P. B., Rogers, G. W., & Ferrick, D. A. (2010). Bioenergetic profile experiment using C2C12 myoblast cells. *Journal of visualized experiments : JoVE*, (46), 2511. https://doi.org/10.3791/2511
8. Nan, J., Zhu, W., Rahman, M. S., Liu, M., Li, D., Su, S., Zhang, N., Hu, X., Yu, H., Gupta, M. P., & Wang, J. (2017). Molecular regulation of mitochondrial dynamics in cardiac disease. *Biochimica et biophysica acta. Molecular cell research*, *1864*(7), 1260–1273. https://doi.org/10.1016/j.bbamcr.2017.03.006
9. Chinnery, P. F., et al. (n.d.). Mitochondrial disorders overview. In *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle.
10. Murphy, M. P. (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, 417(1), 1-13.
11. Dai, D-F., et al. (2014). Mitochondrial oxidative stress in aging and healthspan. *Longevity & Healthspan*, 3(1), 6.
12. Sugamura, K., & Keaney, J. F., Jr (2011). Reactive oxygen species in cardiovascular disease. *Free radical biology & medicine*, *51*(5), 978–992. https://doi.org/10.1016/j.freeradbiomed.2011.05.004

13. Bonora, M., Wieckowski, M. R., Sinclair, D. A., Kroemer, G., Pinton, P., & Galluzzi, L. (2019). Targeting mitochondria for cardiovascular disorders: therapeutic potential and obstacles. *Nature reviews. Cardiology*, *16*(1), 33–55. https://doi.org/10.1038/s41569-018-0074-0
14. Stamerra, C. A., Di Giosia, P., Giorgini, P., Ferri, C., Sukhorukov, V. N., & Sahebkar, A. (2022). Mitochondrial Dysfunction and Cardiovascular Disease: Pathophysiology and Emerging Therapies. *Oxidative medicine and cellular longevity*, *2022*, 9530007. https://doi.org/10.1155/2022/9530007
15. Shadel, G. S., & Horvath, T. L. (2015). Mitochondrial ROS signaling in organismal homeostasis. *Cell*, *163*(3), 560–569. https://doi.org/10.1016/j.cell.2015.10.001