

Mitochondrial Dysfunction in Cardiovascular Diseases: Mechanistic Insights and Therapeutic Perspectives – A Narrative Review

S.Priyanka¹, M.Rasika¹, M.Sujan Sharma^{2*}

Swamy Vivekanandha College of Pharmacy

Department Of Pharmacy Practice

The Tamilnadu Dr.M.G.R Medical University

¹*Student, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal, Tamilnadu, INDIA*

²*Assistant professor, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal, Tamilnadu, INDIA*

**Corresponding Author: Author: DR .M .Sujan Sharma*

Affiliation: Assistant Professor, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal, Tamilnadu, INDIA

Date of Submission: 08-03-2026

Date of Acceptance: 22-03-2026

Abstract:

Growing evidence suggests that mitochondrial malfunction plays a crucial role in the pathophysiology of cardiovascular illnesses (CVDs), such as myocardial infarction, ischemia-reperfusion injury, heart failure, atherosclerosis, and cardiac hypertrophy. Disruption of mitochondrial homeostasis has a significant impact on cardiac function because the myocardium depends heavily on mitochondrial ATP generation. The mechanistic role of mitochondrial dysfunction in cardiovascular disease was assessed by a narrative review of the available experimental and clinical literature. Changes in oxidative phosphorylation (OXPHOS), reactive oxygen species (ROS) production, mitochondrial biogenesis, mitophagy, metabolic remodeling, and ferroptosis were the subject of the studies that were reviewed. Cardiomyocyte damage and vascular dysfunction are caused by impaired mitochondrial ATP synthesis, overproduction of ROS, mitochondrial DNA damage, and faulty mitophagy. Myocardial damage is worsened in ischemia-reperfusion injury by calcium overload and the opening of the mitochondrial permeability transition pore (MPTP). Decreased complex I activity and inhibition of the PGC-1 α regulatory axis restrict mitochondrial biogenesis and metabolic flexibility in heart failure. Mitochondrial oxidative stress contributes to endothelial dysfunction, macrophage metabolic reprogramming, and ferroptosis-mediated plaque growth in atherosclerosis. Pathologic cardiac hypertrophy is also driven by persistent mitochondrial

abnormalities. Bioenergetic failure; oxidative stress, metabolic inflexibility, and programmed cell death are all brought together under a single paradigm of cardiovascular pathology by mitochondrial dysfunction. A promising therapeutic approach for enhancing cardiovascular outcomes involves targeting mitochondrial pathways via the modulation of ferroptosis, restoration of redox balance, and improvement of mitochondrial biogenesis.

Key words: Mitochondrial dysfunction, Cardiovascular diseases, ATP production, Reactive oxygen species, Mitochondrial biogenesis, Metabolic remodeling

I. Introduction:

To sustain continuous contractile activity, the myocardium uses around 6–30 kg of adenosine triphosphate (ATP) every day. This ATP's more than 95% generation inside mitochondria highlights their important part in cardiac physiology. Increasing research on mitochondria shows how absolutely vital their integrity is for maintaining cardiovascular health ⁽¹⁾. Since mitochondrial dysfunction has become a major source of the beginning and progression of cardiovascular disorders (CVDs), scientists are increasingly interested in mitochondria-focused treatments ⁽²⁾. This malfunction is defined by disturbed mitochondrial dynamics, decreased ATP production, and high buildup of reactive oxygen species (ROS). These developments upset intracellular equilibrium, lead to cardiomyocyte death, injure endothelial

cells, and induce vascular remodeling ⁽⁵⁾. Mitochondrial activity is controlled by coordinated interactions between nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Oxidative stress may increase either from mutations in the genome or from deregulations that reduce OXPHOS efficiency. Since mitochondria provide the energy needed for myocardial contraction and relaxation, the buildup of malfunctioning mitochondria is very important in the development of CVD ⁽³⁾. Developing targeted therapeutic strategies relies on knowledge of these mechanisms ⁽⁴⁾. Cardiac energy metabolism is defined by amino acids, lactate, ketone bodies, glucose, and fatty acids among other substrates. Together, glycolysis, the tricarboxylic acid (TCA) cycle, and electron transport chain (ETC) reactions produce ATP ⁽⁶⁾. Glucose breakdown. Mitochondrial malfunction increases ROS generation and promotes oxidative stress since they control oxygen use and cellular respiration ⁽⁷⁾.

Cardiovascular Disorders and Mitochondrial Dysfunction:

Mitochondrial abnormalities are deeply involved in the multifunctional pathogenesis of cardiovascular disorders. Approximately one – third of cardiovascular volume consists of mitochondria, reflecting the heart’s substantial oxidative demands ⁽⁸⁾. Mitochondrial dysfunction is highly associated with disorders like atherosclerosis, hypertension, cardiomyopathy and ischemic heart disease ⁽⁹⁾. Reduced ATP production, aberrant intracellular signaling, elevated ROS levels, and deregulated cellular pathways are all a result of impaired mitochondrial function. These disruptions result in maladaptive cell growth, programmed cell death and inflammatory reactions ⁽¹⁰⁻¹³⁾. Mitochondrial biogenesis is tightly regulated by transcriptional networks. Peroxisome proliferator – activator receptor gamma co – activator – 1 alpha (PGC - 1 α) functions as a master regulator by stimulating nuclear respiratory factors (NRF-1 and NRF-2) and mitochondrial transcription factor A (TFAM), thereby enhancing mitochondrial gene transcription and preserving energy equilibrium ⁽¹⁴⁾.

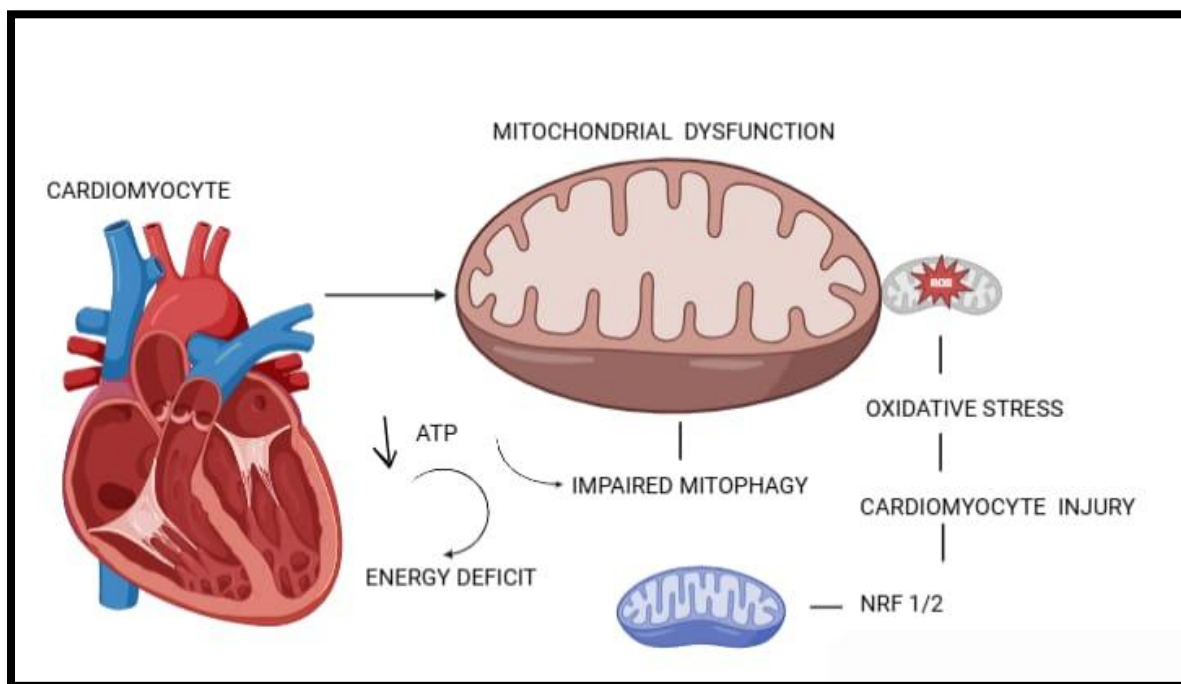


FIGURE 1: Mitochondrial dysfunction – Mediated Cardiomyocyte injury.

Reduced ATP output and the ensuing energy shortage stem from malfunctioning cardiomyocyte mitochondria. Insufficient mitophagy encourages the accumulation of

dysfunctional mitochondria, which worsens bioenergetic capability. Higher mitochondrial reactive oxygen species (ROS) production causes oxidative stress, which harms cardiomyocytes.

Emphasizing their possible protective function in keeping the integrity of cardiac cells, the nuclear respiratory factors (NRF1/2) are shown to be crucial controllers of redox homeostasis and mitochondrial biogenesis.

Ischemia – Reperfusion and Reoxygenation Injury:

A main cause of both myocardial infarction (MI) and ischemia – reperfusion injury (IRI) is mitochondrial dysfunction. The effectiveness of heart protective actions might vary depending on age, gender, statin use and comorbidities including diabetes and metabolic syndrome. ATP depletion during ischemia stimulate mitochondrial potassium channels sensitive to ATP, which leads to a brief release of ROS and a potassium influx. The body

starts defensive cascades that stop the mitochondrial permeability transition pore (MPTP) from opening during reperfusion by controlling the generation of reactive oxygen species (ROS), therefore reducing tissue damage⁽¹⁵⁾. Even with developments in therapy, acute myocardial infarction (AMI) remains a leading cause of death worldwide, particularly among older males. Dyslipidemia, diabetes mellitus, hypertension, on-alcoholic steatohepatitis (NASH), and other disorders are often connected^(16, 17). Metabolic remodeling following AMI has revealed encouraging molecular targets. Metformin demonstrates cardioprotective properties by modulating mitochondrial complex – I activity and MPTP opening⁽¹⁸⁾. Higher doses have been shown to stabilize mitochondrial structure, improve calcium regulation and enhance post – ischemic myocardial contractility⁽¹⁹⁾.

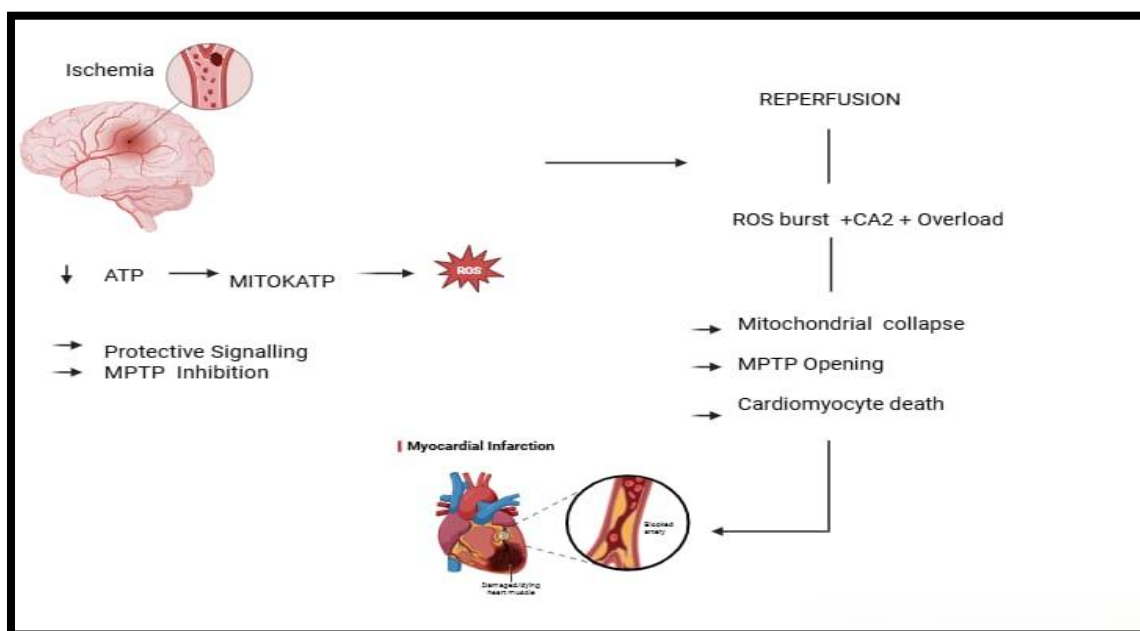


Figure 2: Mitochondrial mechanisms in ischemia – reperfusion injury.

During ischemia, ATP depletion triggers moderate reactive oxygen species (ROS) signaling and activates mitochondrial ATP – sensitive potassium (mitoKATP) channels, which may block the opening of the mitochondrial ATP - sensitive potassium (mitoKATP) channels, which may block the opening of the mitochondrial permeability transition pore (MPTP) and promote protective pathways. Excessive ROS formation and calcium (ca²⁺) overload during reperfusion cause mitochondrial dysfunction, MPTP opening and

cardiomyocyte death, which eventually result in myocardial infarction.

Myocardial Injury and Heart Failure:

A major component in the onset of heart failure (HF) resulting from MI, IRI, cardiomyopathy and arrhythmias is mitochondrial malfunction. HF is marked by low myocardial performance and poor cardiac output. Defective mitochondrial bioenergetics is a distinguishing characteristics of HF that causes oxidative stress, energy loss and cardiomyocyte loss^(20,21). Incomplete mitochondrial

complex I activity has been linked to the progression of HF and is also seen in some neurodegenerative disorders and diabetic cardiomyopathy^(22,23). Among HF patients, clinical data⁽²⁴⁻⁴³⁾ show major changes in mitochondrial energy metabolism. Taking 200 mg of coenzyme Q10 daily may help people with heart failure (HF) or coronary artery disease (CAD) have better

cardiovascular outcomes⁽⁴⁴⁾. Under normal physiological circumstances, oxidation of fatty acids provides 60-90% of cardiac ATP. Pathological remodeling, however, changes substrate preference towards glucose utilization, therefore boosting glycolytic activity and inhibiting fatty acid oxidation to eventually lower metabolic efficiency⁽⁴⁵⁾.

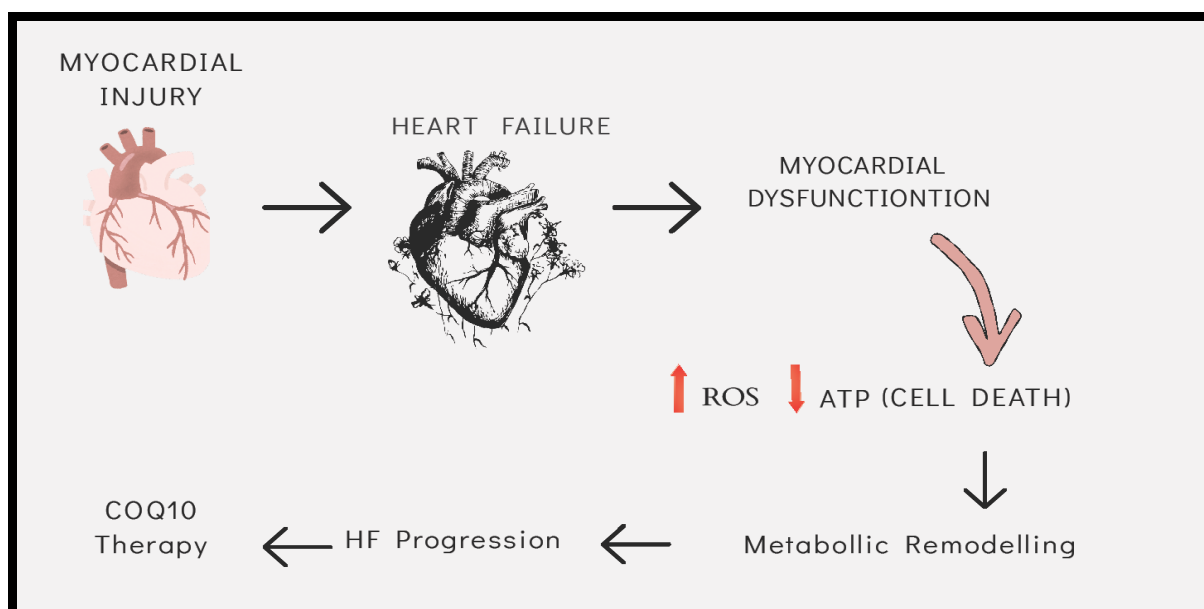


FIGURE 3: Mitochondrial dysfunction–driven progression from myocardial injury to heart failure.

Myocardial damage causes structural degeneration those results in heart failure. Persistent myocardial dysfunction is characterized by increased reactive oxygen species (ROS) generation and reduced ATP synthesis, which lead to cardiomyocyte death and impaired heart function. Metabolic changes brought on by these mitochondrial flaws speed up the course of cardiac failure. The coenzyme Q10 (CoQ10) treatment’s mitochondrial – targeted approach is believed to help to restore redox balance and bioenergetic capacity, therefore slowing down the course of the disease.

Atherosclerosis:

Changes in mtDNA and poor mitophagy lower OXPHOS efficiency and raise ROS production⁽⁴⁶⁻⁵²⁾. These disorders help endothelial malfunction, therefore beginning atherosclerotic plaque development. Atherosclerosis development depends much on macrophage metabolic

reprogramming⁽⁵³⁾. Increased mitochondrial fatty acid oxidation in endothelial cells subjected to oxidative stress reduces nitric oxide (NO) synthesis, therefore aggravating vascular dysfunction⁽⁵⁴⁾. Oxidative stress caused by mitochondria helps plaque progress, inflammation and foam cell formation as well as foam cell development⁽⁵⁵⁾. Statins and vitamin E among other antioxidant treatments have shown promise in lowering oxidative damage and increasing plaque stability^(56,57). New research underlines how ferroptosis and iron – driven oxidative damage contribute to atherosclerosis⁽⁵⁸⁾. In macrophages, iron buildup boosts inflammatory signaling⁽⁵⁹⁾, but ferroptosis inhibition lowers lipid peroxidation and enhances endothelial integrity⁽⁶⁰⁾. Other regulatory chemicals including PDSS2⁽⁶¹⁾, HMOX1⁽⁶²⁾, microRNA-132⁽⁶³⁾ and NRF2⁽⁶⁴⁾ strengthen the case for ferroptosis as a therapeutic target.

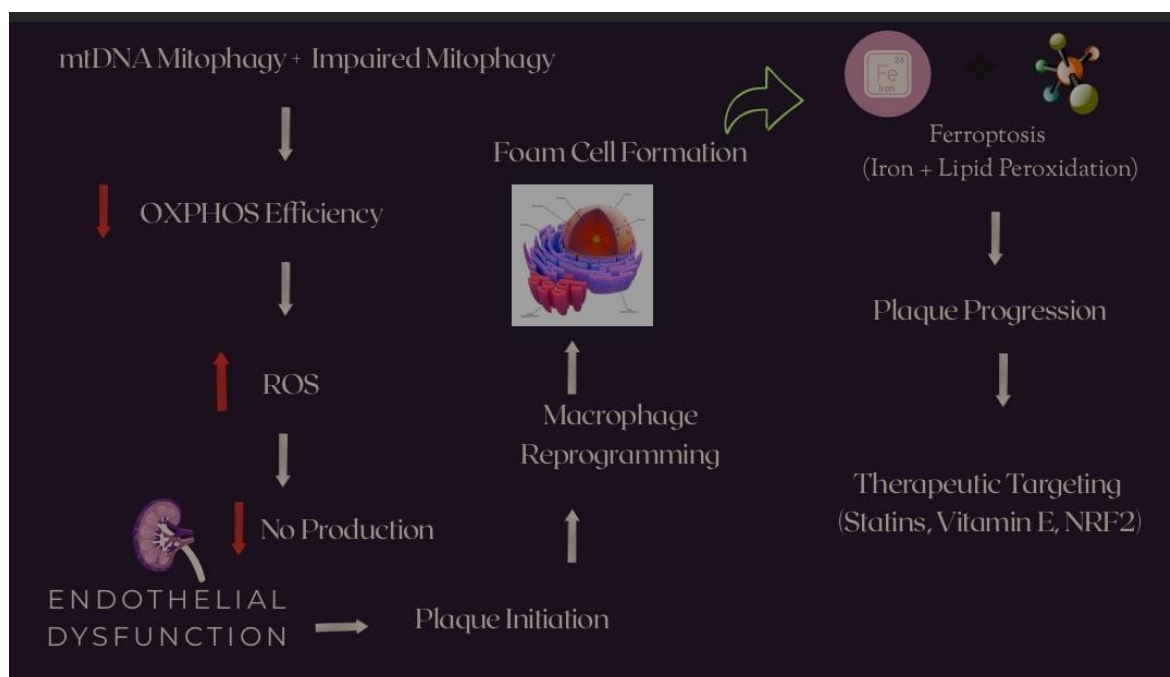


FIGURE 4: Mitochondrial dysfunction-mediated mechanisms in atherosclerosis progression.

Insufficient OXPHOS caused by mutations in mtDNA and defective mitophagy promotes greater ROS generation and lower nitric oxide (NO) bioavailability, therefore promoting endothelial dysfunction and plaque formation. Macrophages modify their mitochondrial metabolism, which helps to foster the generation of foam cells and supports plaque formation. Ferroptosis is induced by iron buildup and lipid peroxidation, therefore accelerating plaque formation. Macrophages modify their mitochondrial metabolism, which helps to foster the generation of foam cells and supports plaque formation. One possible treatment strategy is to concentrate on redox signaling pathways and mitochondrial oxidative stress (Eg: statins, vitamin E and NRF2 activation).

Cardiac Hypertrophy:

Cardiac hypertrophy and associated problems⁽⁶⁵⁻⁶⁹⁾ are caused by mitochondrial genomic changes, faulty mitophagy, poor OXPHOS activity and too much ROS production. Aortic aneurysm and dissection both have elevated oxidative stress associated with them⁽⁷⁰⁾. Cardiovascular disease is accelerated by compromised cellular homeostasis brought on by mitochondrial malfunction in cardiomyocytes, vascular smooth muscle cells and endothelial cells. By down regulating OXPHOS – related genes, decreased PGC - 1 α expression helps the development from pressure – overload hypertrophy to heart failure⁽⁷¹⁾. In those with diabetes, these mitochondrial changes have a major influence on morbidity and mortality⁽⁷²⁾.

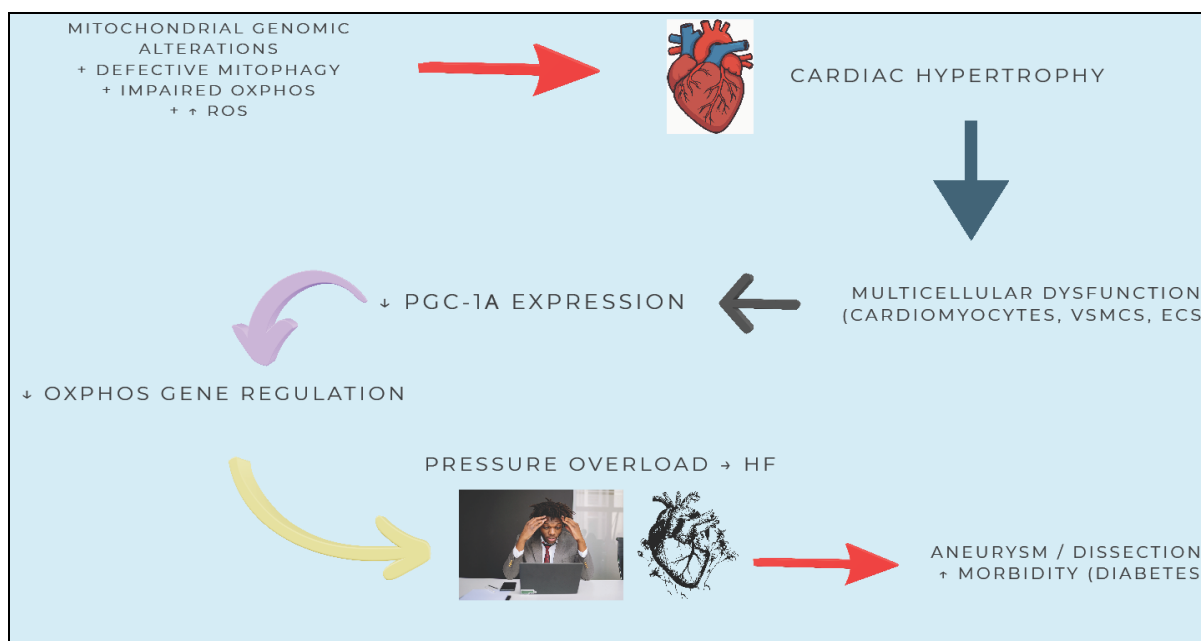


FIGURE 5: Mitochondrial dysfunction drives cardiac hypertrophy and cardiovascular remodeling.

Elevated ROS synthesis from mitochondrial genomic flaws, compromised mitophagy, and hampered OXPHOS starts cardiac hypertrophy. Reduced PGC-1 α expression affects the regulation of mitochondrial genes, which leads to multicellular malfunction in endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Particularly during times of metabolic stress, continual pressure overload speeds the onset of heart failure by increasing the possibility of vascular problems including aneurysms and dissections.

II. Discussion:

By combining aberrant oxidative phosphorylation, decreased ATP synthesis, increased reactive oxygen species production, deficient mitophagy, and changes in mitochondrial biogenesis into a shared framework of cellular damage and maladaptive remodeling, mitochondrial dysfunction serves as a vital and unifying mechanism in the etiology of cardiovascular diseases. In ischemia-reperfusion injury, the permeability transition pore opens and cardiomyocytes die as a result of mitochondrial ATP loss and calcium overload; meanwhile, continuous oxidative stress worsens tissue damage beyond the initial ischemic damage. Sustained bioenergetic shortage, lower complex I activity, and downregulation of transcriptional networks mediated by PGC-1 α all of which contribute to contractile dysfunction in chronic heart failure.

Although initially compensating, a pathological shift from fatty acid oxidation to glycolysis ultimately lowers metabolic efficiency and supports disease progression. Similarly, oxidative stress originating in mitochondria decreases the accessibility of nitric oxide in atherosclerosis, promotes endothelial dysfunction, and triggers inflammatory activity; metabolic reprogramming of macrophages and lipid peroxidation driven by ferroptosis result in plaque formation and instability. These convergence mechanisms indicate that mitochondria play a major role in regulating cell destiny definition, inflammation, and redox signaling—they have a far larger range of activities beyond simple energy generation. Clinical translation of mitochondrial-targeted treatments in experimental models remains difficult because of the diversity of diseases and the variance in metabolic profiles among patients.

III. Conclusion:

Currently considered a major contributor in the pathophysiology of cardiovascular disease, mitochondrial dysfunction unifies bioenergetic breakdown, redox imbalance, mitophagy disruption, mitochondrial DNA stability, metabolic inflexibility, and ferroptotic cell death into one paradigm of cardiac injury. Disturbing mitochondrial equilibrium during pressure-overload-induced hypertrophy, atherosclerosis, heart failure, ischemia-reperfusion damage, and myocardial infarction causes lower ATP production, greater

oxidative stress, and activation of inflammatory and apoptotic signaling pathways, all of which worsen the maladaptive remodeling and progression of the disease. By inhibiting the PGC-1 α control axis, metabolic diseases including diabetes worsen clinical results by reducing mitochondrial biogenesis and so limiting adaptive ability in response to pathophysiological stress. Notwithstanding the promise shown by redox-directed approaches and mitochondrial-targeted treatments including bioenergetic modulators, the diversity of the condition and the absence of a thorough mechanical solution continue to hamper translational success. Full mitochondrial biology's potential in therapy calls for integration with precision cardiology, biomarker-guided intervention, and systems-level profiling. By highlighting mitochondria in cardiac medicine, we might finally cause a major change in our views on prevention, risk assessment, and disease management.

References:

- [1]. Bisaccia G, Ricci F, Gallina S, Ghinassi B. Mitochondrial dysfunction and heart disease: critical appraisal of an overlooked association. *J Clin Med*. 2021; 10(14):3185.
- [2]. Lim AY, Chen YC, Hsu CC, Fu TC, Wang JS. The effects of exercise training on mitochondrial function in cardiovascular diseases: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022; 19(3):1231.
- [3]. Liu Y, Huang Y, Xu C, An P, Luo Y, Li Y. Mitochondrial dysfunction and therapeutic perspectives in cardiovascular diseases. *Front Cardiovasc Med*. 2022; 9:823913.
- [4]. Ciccarelli G, Conte S, Cimmino G, Giordano A. Mitochondrial dysfunction: the hidden player in the pathogenesis of atherosclerosis? *Antioxidants (Basel)*. 2022; 11(5):901.
- [5]. Yang HM. Mitochondrial dysfunction in cardiovascular diseases. *J Korean Circ Soc*. 2020; 50(10):861-874.
- [6]. Pietrangelo D, Lopa C, Litterio M, Lombardi A. Metabolic disturbances involved in cardiovascular diseases: the role of mitochondrial dysfunction, altered bioenergetics and oxidative stress. *Int J Mol Sci*. 2022; 23(11):6111.
- [7]. Yan F, Li K, Zhang H. Role of iron-related oxidative stress and mitochondrial dysfunction in cardiovascular diseases. *Oxid Med Cell Longev*. 2022; 2022:1–15.
- [8]. Jennings RB, Ganote CE. Mitochondrial structure and function in acute myocardial ischemic injury. *Circ Res*. 1976; 38:180–191.
- [9]. Forte M, Schirone L, Ameri P, Basso C, Catalucci D, Modica J, et al. The role of mitochondrial dynamics in cardiovascular diseases. *Br J Pharmacol*. 2021; 178:2060–2076.
- [10]. Zhou, B.; Tian, R. Mitochondrial dysfunction in pathophysiology of heart failure. *J. Clin. Investig.* 2018, 128, 3716–3726.
- [11]. Iglewski M, Hill JA, Lavandero S, Rothermel BA. Mitochondrial fission and autophagy in the normal and diseased heart. *Curr Hypertens Rep*. 2010; 12:418–425.
- [12]. Lee CF, Chavez JD, Garcia-Menendez L, Choi Y, Roe ND, Chiao YA, et al. Normalization of NAD⁺ redox balance as a therapy for heart failure. *Circulation*. 2016; 134:883–894.
- [13]. Luongo TS, Lambert JP, Gross P, Nwokedi M, Lombardi AA, Shanmughapriya S, et al. The mitochondrial Na⁺/Ca²⁺ exchanger is essential for Ca²⁺ homeostasis and viability. *Nature*. 2017; 545:93–97.
- [14]. Fernandez-Marcos, P.J.; Auwerx, J. Regulation of PGC-1 α , a mitochondrial function modulator. *Nat. Rev. Mol. Cell Biol*. 2016, 17, 197–205. 15. Suliman, H.B.; Piantadosi, C.A. Mitochondrial biogenesis: Regulation by endogenous gases during inflammation and injury. *Antioxidants* 2020, 9, 312.)
- [15]. Suliman HB, Piantadosi CA. Mitochondrial biogenesis: Regulation by endogenous gases during inflammation and injury. *Antioxidants*. 2020; 9:312.
- [16]. Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al. 2025 heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2025; 151:e41–e660.
- [17]. Andreadou I, Daiber A, Baxter GF, Brizzi MF, Di Lisa F, Kaludercic N, et al. Influence of cardiometabolic comorbidities on myocardial function, infarction, and cardioprotection: role of cardiac redox signaling. *Free Radic Biol Med*. 2021; 166:33–52.
- [18]. Mohsin AA, Chen Q, Quan N, Rousselle T, Maceyka MW, Samidurai A, et al. Mitochondrial complex I inhibition by

- metformin limits reperfusion injury. *J Pharmacol Exp Ther.* 2019; 369:282–290.
- [19]. Li Z, Wang H, Zougrana LI, James A, Slotabec L, Didik S, et al. Administration of metformin rescues age-related vulnerability to ischemic insults through mitochondrial energy metabolism. *Biochem Biophys Res Commun.* 2023; 659:46–53.
- [20]. Ventura-Clapier R, Garnier A, Veksler V, Joubert F. Bioenergetics of the failing heart. *Biochim Biophys Acta Mol Cell Res.* 2011; 1813:1360–1372.
- [21]. Neubauer S. The failing heart—an engine out of fuel. *N Engl J Med.* 2007; 356:1140–1151.
- [22]. Wirth C, Brandt U, Hunte C, Zickermann V. Structure and function of mitochondrial complex I. *Biochim Biophys Acta Bioenerg.* 2016; 1857:902–914.
- [23]. Forte M, Palmerio S, Bianchi F, Volpe M, Rubattu S. Mitochondrial complex I deficiency and cardiovascular diseases: current evidence and future directions. *J Mol Med.* 2019; 97:579–591.
- [24]. Chou CH, Fu TC, Tsai HH, Hsu CC, Wang CH, Wang JS. High-intensity interval training enhances mitochondrial bioenergetics of platelets in patients with heart failure. *Int J Cardiol.* 2019; 274:214–220.
- [25]. Adamopoulos S, Coats AJ, Brunotte F, Arnolda L, Meyer T, Thompson CH, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol.* 1993; 21:1101–1106.
- [26]. Esposito F, Mathieu-Costello O, Wagner PD, Richardson RS. Acute and chronic exercise in patients with heart failure with reduced ejection fraction: evidence of structural and functional plasticity and intact angiogenic signalling in skeletal muscle. *J Physiol.* 2018; 596:5149–5161.
- [27]. Esposito F, Reese V, Shabetai R, Wagner PD, Richardson RS. Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. *J Am Coll Cardiol.* 2011; 58:1353–1362.
- [28]. Groennebaek T, Sieljacks P, Nielsen R, Pryds K, Jespersen NR, Wang J, et al. Effect of blood flow restricted resistance exercise and remote ischemic conditioning on functional capacity and myocellular adaptations in patients with heart failure. *Circ Heart Fail.* 2019; 12:e006427.
- [29]. Hambrecht R, Niebauer J, Fiehn E, Kälberer B, Offner B, Hauer K, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol.* 1995; 25:1239–1249.
- [30]. Santoro C, Cosmas A, Forman D, Morghan A, Bairos L, Levesque S, et al. Exercise training alters skeletal muscle mitochondrial morphometry in heart failure patients. *J Cardiovasc Risk.* 2002; 9:377–381.
- [31]. Southern WM, Ryan TE, Kepple K, Murrow JR, Nilsson KR, McCully KK. Reduced skeletal muscle oxidative capacity and impaired training adaptations in heart failure. *Physiol Rep.* 2015; 3:e12353.
- [32]. Stratton JR, Dunn JF, Adamopoulos S, Kemp GJ, Coats AJ, Rajagopalan B. Training partially reverses skeletal muscle metabolic abnormalities during exercise in heart failure. *J Appl Physiol.* 1994; 76:1575–1582.
- [33]. Toth MJ, Miller MS, Ward KA, Ades PA. Skeletal muscle mitochondrial density, gene expression, and enzyme activities in human heart failure: minimal effects of the disease and resistance training. *J Appl Physiol.* 2012; 112:1864–1874.
- [34]. Williams AD, Carey MF, Selig S, Hayes A, Krum H, Patterson J, et al. Circuit resistance training in chronic heart failure improves skeletal muscle mitochondrial ATP production rate: a randomized controlled trial. *J Card Fail.* 2007; 13:79–85.
- [35]. Lin ML, Fu TC, Hsu CC, Huang SC, Lin YT, Wang JS. Cycling exercise training enhances platelet mitochondrial bioenergetics in patients with peripheral arterial disease: a randomized controlled trial. *Thromb Haemost.* 2021; 121:900–912.
- [36]. Hiatt WR, Regensteiner JG, Wolfel EE, Carry MR, Brass EP. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. *J Appl Physiol.* 1996; 81:780–788.
- [37]. Murrow JR, Brizendine JT, Djire B, Young HJ, Rathbun S, Nilsson KR Jr, et al. Near infrared spectroscopy-guided exercise training for claudication in peripheral arterial disease. *Eur J Prev Cardiol.* 2019; 26:471–480.
- [38]. VanSchaardenburgh M, Wohlwend M, Rognum Ø, Mattsson E. Calf raise exercise

- increases walking performance in patients with intermittent claudication. *J Vasc Surg.* 2017; 65:1473–1482.
- [39]. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognum Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation.* 2007; 115:3086–3094.
- [40]. Hsu CC, Tsai HH, Fu TC, Wang JS. Exercise training enhances platelet mitochondrial bioenergetics in stroke patients: a randomized controlled trial. *J Clin Med.* 2019; 8:2186.
- [41]. Zoll J, Steiner R, Meyer K, Vogt M, Hoppeler H, Flück M. Gene expression in skeletal muscle of coronary artery disease patients after concentric and eccentric endurance training. *Eur J Appl Physiol.* 2006; 96:413–422.
- [42]. Fiorenza M, Gunnarsson TP, Ehlers TS, Bangsbo J. High-intensity exercise training ameliorates aberrant expression of markers of mitochondrial turnover but not oxidative damage in skeletal muscle of men with essential hypertension. *Acta Physiol.* 2019; 225:e13208.
- [43]. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 1997; 29:1067–1073.
- [44]. Martelli A, Testai L, Colletti A, Cicero AFG. Coenzyme Q10: clinical applications in cardiovascular diseases. *Antioxidants.* 2020; 9:341.
- [45]. Pascual F, Coleman RA. Fuel availability and fate in cardiac metabolism: a tale of two substrates. *Biochim Biophys Acta.* 2016; 1861:1425–1433.
- [46]. Nakajima T, Yokota T, Shingu Y, Yamada A, Iba Y, Ujihira K, et al. Impaired mitochondrial oxidative phosphorylation capacity in epicardial adipose tissue is associated with decreased concentration of adiponectin and severity of coronary atherosclerosis. *Sci Rep.* 2019; 9:3535.
- [47]. Vilne B, Skogsberg J, Foroughi Asl H, Talukdar HA, Kessler T, Björkegren JLM, Schunkert H. Network analysis reveals a causal role of mitochondrial gene activity in atherosclerotic lesion formation. *Arteriosclerosis.* 2017; 267:39–48.
- [48]. Jacinto TA, Meireles GS, Dias AT, Aires R, Porto ML, Gava AL, et al. Increased ROS production and DNA damage in monocytes are biomarkers of aging and atherosclerosis. *Biol Res.* 2018; 51:1–13.
- [49]. Sergin I, Evans TD, Zhang X, Bhattacharya S, Stokes CJ, Song E, et al. Exploiting macrophage autophagy-lysosomal biogenesis as a therapy for atherosclerosis. *Nat Commun.* 2017; 8:15750.
- [50]. Nahapetyan H, Moulis M, Grousset E, Faccini J, Grazide MH, Mucher E, et al. Altered mitochondrial quality control in Atg7-deficient VSMCs promotes enhanced apoptosis and is linked to unstable atherosclerotic plaque phenotype. *Cell Death Dis.* 2019; 10:1–15.
- [51]. Qiu J, Fu Y, Chen Z, Zhang L, Li L, Liang D, et al. BTK promotes atherosclerosis by regulating oxidative stress, mitochondrial injury, and ER stress of macrophages. *Oxid Med Cell Longev.* 2021; 2021:1–15.
- [52]. Wang Y, Wang GZ, Rabinovitch PS, Tabas I. Macrophage mitochondrial oxidative stress promotes atherosclerosis and nuclear factor- κ B-mediated inflammation in macrophages. *Circ Res.* 2014; 114:421–433.
- [53]. O'Neill LAJ, Kishton RJ, Rathmell J. Metabolic reprogramming in macrophage activation. *Nat Rev Immunol.* 2021; 21:684–696.
- [54]. Li Y, Zhang H, Wang Q, Li X, Huang Y, Yan B, et al. Increased mitochondrial fatty acid oxidation in endothelial cells impairs nitric oxide production in hypertension. *Hypertension.* 2022; 79:1456–1467.
- [55]. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. *Nat Rev Immunol.* 2013; 13:709–721.
- [56]. Antoniades C, Bakogiannis C, Leeson P, Guzik TJ, Zhang MH, Tousoulis D, et al. Rapid effects of rosuvastatin on arterial stiffness and endothelial function in healthy humans: evidence for mitochondrial protection. *Circulation.* 2016; 134:136–147.
- [57]. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet.* 1996; 347:781–786.

- [58]. Gimbrone MA Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res*. 2016; 118:620–636.
- [59]. Hu X, Cai X, Ma R, Fu W, Zhang C, Du X. Iron load exacerbates the severity of atherosclerosis by inducing inflammation and enhancing glycolysis in macrophages. *J Cell Physiol*. 2019; 234(10):18792–18800.
- [60]. Bai T, Li M, Liu Y, Qiao Z, Wang Z. Inhibition of ferroptosis alleviates atherosclerosis through attenuating lipid peroxidation and endothelial dysfunction in mouse aortic endothelial cells. *Free Radic Biol Med*. 2020; 160:92–102.
- [61]. Yang K, Song H, Yin D. PDSS2 inhibits ferroptosis of vascular endothelial cells in atherosclerosis by activating Nrf2. *J Cardiovasc Pharmacol*. 2021; 77(6):767–776.
- [62]. Meng Z, Liang H, Zhao J, et al. HMOX1 upregulation promotes ferroptosis in diabetic atherosclerosis. *Life Sci*. 2021; 284:119935.
- [63]. Liu Z, Cao S, Chen Q, Fu F, Cheng M, Huang X. MicroRNA-132 promotes atherosclerosis by inducing mitochondrial oxidative stress-mediated ferroptosis. *Nan Fang Yi Ke Da Xue Xue Bao*. 2022; 42(1):143–149.
- [64]. Yu W, Liu W, Xie WQ, et al. High level of uric acid promotes atherosclerosis by targeting NRF2-mediated autophagy dysfunction and ferroptosis. *Oxid Med Cell Longev*. 2022; 2022:9304383.
- [65]. Yan M, Li Y, Luo Q, Zeng W, Shao X, Li L, et al. Mitochondrial damage and activation of the cytosolic DNA sensor cGAS–STING pathway lead to cardiac pyroptosis and hypertrophy in diabetic cardiomyopathy mice. *Cell Death Discov*. 2022; 8:1–12.
- [66]. Kumar V, Sanawar R, Jaleel A, Kumar TRS, Kartha CC. Chronic pressure overload results in deficiency of mitochondrial membrane transporter ABCB7, contributing to iron overload, mitochondrial dysfunction, metabolic shift, and worsened cardiac function. *Sci Rep*. 2019; 9:1–16.
- [67]. Zou R, Tao J, Qiu J, Shi W, Zou M, Chen W, et al. Ndufs1 deficiency aggravates mitochondrial membrane potential dysfunction in pressure overload-induced myocardial hypertrophy. *Oxid Med Cell Longev*. 2021; 2021:1–21.
- [68]. Fu YL, Tao L, Peng FH, Zheng NZ, Lin Q, Cai SY, Wang Q. GJA1-20k attenuates angiotensin II-induced pathological cardiac hypertrophy by regulating gap junction formation and mitochondrial function. *Acta Pharmacol Sin*. 2021; 42:536–549.
- [69]. Matsuda S, Umemoto S, Yoshimura K, Itoh S, Murata T, Fukai T, Matsuzaki M. Angiotensin II activates MCP-1 and induces cardiac hypertrophy and dysfunction via Toll-like receptor 4. *J Atheroscler Thromb*. 2015; 22:833–844.
- [70]. Ranjbarvaziri S, Kooiker KB, Ellenberger M, Fajardo G, Zhao M, Roest ASV, et al. Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation*. 2021; 144:1714–1731.
- [71]. Riehle C, Wende AR, Zaha VG, Pires KM, Wayment B, Olsen C, et al. PGC-1 deficiency accelerates the transition to heart failure in pressure overload hypertrophy. *Circ Res*. 2011; 109:783–793.
- [72]. Li K, Zhai M, Jiang L, et al. Tetrahydrocurcumin ameliorates diabetic cardiomyopathy by attenuating high glucose-induced oxidative stress and fibrosis via activation of the SIRT1 pathway. *Oxid Med Cell Longev*. 2019; 2019:6746907.