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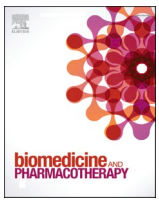

Review

Mechanical stress induced mitochondrial dysfunction in cardiovascular diseases: Novel mechanisms and therapeutic targets

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide. Others and our studies have shown that mechanical stresses (forces) including shear stress and cyclic stretch, occur in various pathological conditions, play significant roles in the development and progression of CVDs. Mitochondria regulate the physiological processes of cardiac and vascular cells mainly through adenosine triphosphate (ATP) production, calcium flux and redox control while promote cell death through electron transport complex (ETC) related cellular stress response. Mounting evidence reveal that mechanical stress-induced mitochondrial dysfunction plays a vital role in the pathogenesis of many CVDs including heart failure and atherosclerosis. This review summarized mitochondrial functions in cardiovascular system under physiological mechanical stress and mitochondrial dysfunction under pathological mechanical stress in CVDs (graphical abstract). The study of mitochondrial dysfunction under mechanical stress can further our understanding of the underlying mechanisms, identify potential therapeutic targets, and aid the development of novel treatments of CVDs.

1. Introduction

Mitochondria (mitochondrion) is an organelle found in most eukaryotic cell with a double membrane structure that use aerobic respiration to generate adenosine triphosphate (ATP), it is the source of chemical energy throughout the cell [1]. Mitochondria is delicate and multifunctional, with outer membrane like cell membrane and pleated inner membrane called cristae that provide large enough membrane areas for enzymes to adhere [2]. Benefiting from its rich proteome, mitochondria are widely involved in cellular functions and biological processes [3]. In addition to energy conversion, mitochondrial fatty acid synthesis [4], uptake, storage and release of calcium ions [5–8] and cellular proliferation regulation [9], mitochondria are also involved in signaling through apoptosis-programmed cell death [10], calcium signaling [11], regulation of cellular metabolism [12], steroid synthesis [6], hormonal signaling [13] and immune signaling [14]. Besides, mitochondrial proton and electron leak have significant impacts on mitochondrial coupling efficiency and production of reactive oxygen species (ROS) [15–17]. Uncoupling proteins (UCPs) and uncoupled mitochondrial respiration have been found to involve in modulating ROS production and metabolism [16,18–20]. Furthermore, thermogenesis was promoted by inducing mitochondrial proton leak in brown adipose tissue (BAT) mitochondria to adapt the cold environment which promote therapeutic strategies for treating metabolic diseases [21–23]. The main functions of mitochondria were summarized in Fig. 1.

In cardiovascular system, mitochondria are the main source of ATP due to oxidative phosphorylation, while by-products of the respiratory chain maintain redox balance [24–26]. Mitochondrial quality control, including antioxidant defense, protein quality control, mitochondrial DNA repair, mitochondrial dynamics, mitophagy and mitochondrial biogenesis, plays an important role in whole cardiovascular homeostasis [27,28]. However, mitochondrial dysfunction is often accompanied by metabolic disorders, excessive oxidative stress and ion overload, and is involved in the occurrence and development of various CVDs [17, 29–32].

Others and we have shown that mechanical stress is closely associated with cardiovascular homeostasis and dysfunction [33–49]. The deformation caused by cardiac contraction and relaxation as well as hemodynamic generated by blood flow continuously stimulate cells and regulate the downstream mechanical signals [47,50,51]. Physiological

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mechanical stress is necessary for cardiovascular development and homeostasis, whereas abnormal mechanical stresses including high cyclic stretch and disturb flow are pathogenic [36,44,45,52–57]. Many studies have revealed the connection between mechanical stress and mitochondria in the cardiovascular system, indicating that mitochondria, as mechanosensitive organelles, participate in cardiovascular pathophysiological processes [26,57–62]. Here, we discuss the mechanism of mitochondria in cardiovascular physiology and signal pathways during mitochondrial dysfunctions induced by different mechanical stress in CVDs to find the potential therapeutics by targeting mitochondria dysfunctions.

2. Mitochondrial functions in cardiovascular system

2.1. ATP supply and metabolic flexibility

It is well known that mitochondria produce ATP through oxidative phosphorylation, in which metabolic intermediates such as glucose, lipids, amino acids, and nucleotides enter the tricarboxylic acid cycle (TCA) and are eventually oxidized [3]. Proton circuits generated by the electron transport complex (ETC) play a central role in mitochondrial physiological function [63]. Wu et al. revealed the structure of respiratory chain complexes in mammalian [64], the L-shaped complex I forms oligomerization with complexes III and IV through NDUFA11, NDUFB4, NDUFB8, NDUFB9 and other subunits, forming a super complex that adheres to the mitochondrial inner membrane [64]. These structures provide the physical basis for the transfer of protons from the mitochondrial matrix into the inner membrane space, thereby forming an electrochemical gradient and enabling complex V to synthesize ATP [64]. Specifically, NADH and succinate donate electrons for complex I and II respectively, and then quinone carries the electrons from complex I and II to complex III_2 [65]. Cytochrome c (cyt c) carries electrons from complex III_2 to complex IV, where its electron promotes the reduction of oxygen [65]. Finally, complex V (also an ATP synthase) uses the resulting electrochemical gradient to phosphorylate ADP to ATP [65]. Generally, oxidative phosphorylation is the main source of ATP required to meet the needs of cellular activities, while glycolysis-derived ATP accounts for only a small part [66].

Metabolic flexibility was found in cardiovascular cells. Seahorse, a cell energy metabolism analyzer, is a familiar instrument to measure mitochondrial bioenergetics [67]. Oxygen-consuming reagents are added to cells to detect oxygen consumption rate (OCR), which indicates some parameters of respiration such as basal respiration, ATP production, maximal respiration and spare respiratory capacity [61,68–70]. Acidizing reagents are used to detect extracellular acidification rate (ECAR), which reflects mitochondrial abilities related to glycolysis [68,

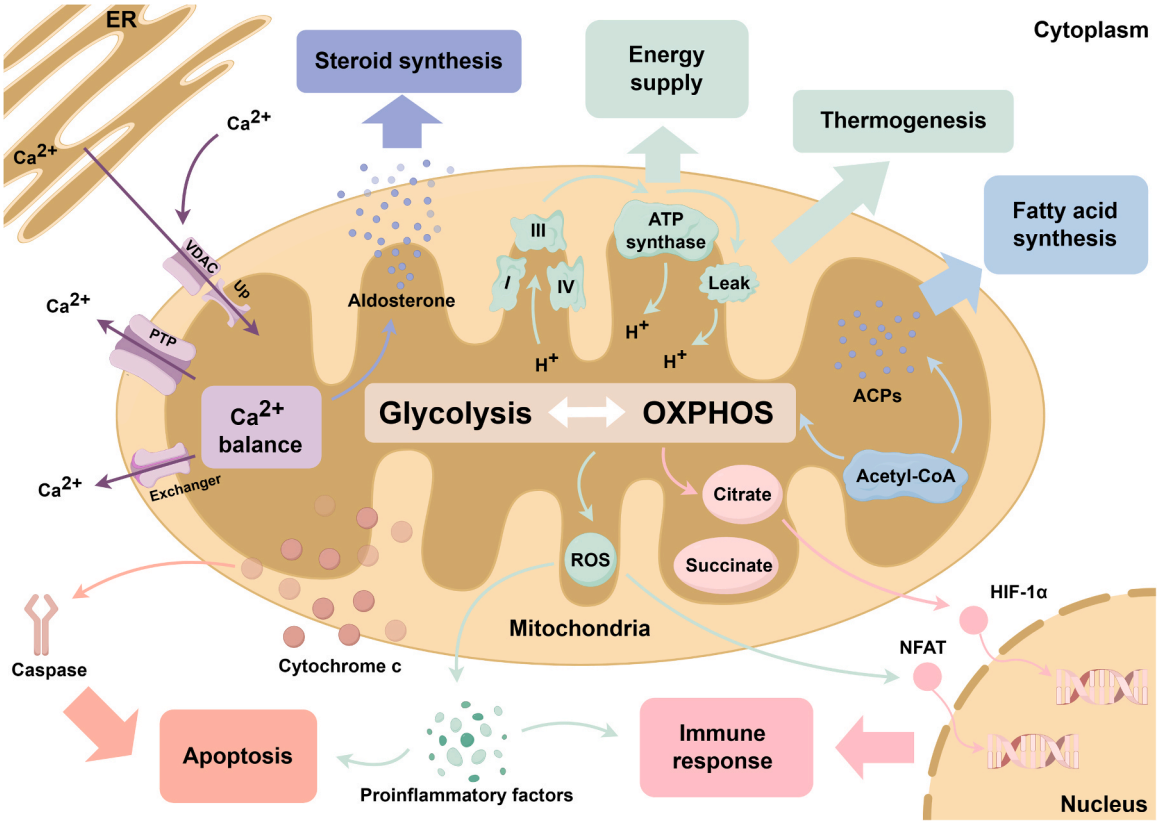

Fig. 1. Mitochondrial functions in energy supply, thermogenesis, fatty acid and steroid synthesis, calcium balance, ROS production, immune response and apoptosis. Mitochondria transform their metabolic patterns between oxidative phosphorylation (OXPHOS) and glycolysis to meet the needs of cellular activities. Electrons released from oxidizable substrates transfer in the respiration chain and form electrochemical gradient, which pumps protons from mitochondrial matrix into intermembrane space through mitochondrial complex I, III and IV, creating a protonmotive force (Δp). One way that relieves Δp is relied on ATP synthase to produce ATP, a direct source for energy supply. Another way termed proton leak contributes to thermogenesis instead of ATP production. During the process of respiration, thimbleful electrons react with oxygen molecular to produce ROS, which is associated to Δp. Acetyl-coenzyme (CoA) is vital to respiration as well as involving in acyl carrier proteins (ACPs)-related mitochondrial fatty acid synthesis. Mitochondria enable endoplasmic reticulum (ER) and cytoplasm calcium influx attribute to voltage-dependent anion channel (VDAC) and uniporter (Up) while calcium in mitochondrial matrix outflows through permeability transition pore (PTP) and ions exchanger. Mtiochondrial calcium elevation promotes aldosterone synthesis. Mitochondria suffer stress signals will release cytochrome c, which actives caspase-related pathways, eventually induces apoptosis. Stimulated mitochondria produce exceed ROS, increase inflammatory factors, then involve in immune response and apoptosis. Some immune cells have broken tricarboxylic acid cycle that induces intermediates such as citrate and succinate accumulation in mitochondrial matrix. These intermediates serve as signaling molecules to regulate immune response.

69,71]. Fetal cardiomyocytes have a high proliferative capacity and rely on glycolysis as an energy source [24]. As cardiomyocytes mature, they switch glycolysis to oxidative phosphorylation with cell cycle arrest, providing sufficient energy for cardiac contraction and maintaining long-term homeostasis [24]. However, heart failure is accompanied by poor metabolic flexibility with reduced ATP production through glycolysis [72]. The metabolic flexibility is also critical in angiogenesis as endothelial tip and non-tip cells have different metabolic pattern [68, 69]. The mitochondrial respiration of tip cells is more vigorous than non-tip cells, while glycolysis is necessary for tip cell differentiation [68, 69]. Furthermore, both types of cells can adapt their metabolic pathways to produce ATP if the primary metabolic pathway is inhibited [68, 69]. Neonatal mouse lung endothelial cells (ECs) can enhance fatty acid metabolism through Cpt1/l-carnitine to protect themself from hyperoxia and inhibit apoptosis [70]. During skin injury repair, the macrophages promptly transfer from an early-stage pro-angiogenic phenotype to a late-stage pro-resolving phenotype regulated by mitochondrial metabolism [73].

Therefore, cardiovascular cells adjust their metabolic patterns according to physiological needs. It seems that glycolysis pattern favors cellular "changes", as proliferation and differentiation rely on amounts of gene expression that are accompanied by changes of quantity, morphology, or function. Relatively, energy-consuming cellular activities such as contraction are inseparable from oxidative phosphorylation. Although numerous metabolites and signaling pathways have been elucidated in different metabolic modes, the mechanisms of metabolic flexibility are poorly understood and and require further exploration.

2.2. ETC effects beyond respiration

In addition to ATP production, mitochondrial ETC is associated with a variety of other processes, including cytochrome c release, lipid peroxidation, and glutathione (GSH) loss, which are generally regarded as parts of cellular stress [74–77].

Under physiological conditions, cyt c forms ETC in the inner member of mitochondria, carrying electrons to promotes ATP synthesis [65]. However, during cellular stress, cyt c is released from mitochondria into cytoplasm, activating the caspase family and playing a crucial role in apoptosis [74]. Initiation of cyt c release relies on Bcl-2 protein-induced permeabilization of the outer members of the mitochondria, thereby forming a pore through which cyt c passes [78,79]. The released cyt c activates caspase-3 and promotes apoptosis, which is an important cause of cardiomyocyte loss during cardiomyopathy and ultimately leads to heart failure [80]. In ischemia/reperfusion (IR) models, complex I deficiency is accompanied by cyt c release and reduced respiration due to limited electrons transport, revealing mechanisms of cardiac injury associated with ETC [81,82]. Hexokinase II (HKII) binding to mitochondria [83] and deletion of subunit1 in calpain1/2 [84] reduced cyt c release in IR hearts. Cyt c induced apoptosis was also detected in vascular cells such as EC and VSMC [85,86]. Besides, the activity of complex III regulates Bak-induced cyt c release, which is involved in microvascular EC permeability [87].

Recently, ETC has received attention as a modulator of lipid peroxidation and GSH level that are responsible for ferroptosis (iron-dependent cell death) [76,88]. In isolated heart mitochondria, complex I rather than complex III produced ROS promoted mitochondrial lipid peroxidation, which was reflected through lipid peroxy radicals [76]. Both inhibition of complex I and complex III aggravated RSL3 (ferroptosis inducer) induced cardiomyocytes ferroptosis [77]. Meanwhile, GSH synthesis can protect cells from oxidative stress induced cell death such as ferroptosis [89]. Although mitochondria cannot produce GSH, they transport GSH into matrix by dicarboxylate carrier (DIC) and oxoglutarate carrier (OGC), which contain 10–15% of total cellular GSH [77]. Inhibition of DIC and OGC increased mitochondrial ROS, membrane depolarization, and GSH depletion and aggravated ferroptosis [77]. Besides, the accumulation of ferroptotic PEox species in mitochondria during cardiac IR proved that mitochondria involved in ferroptosis-related cardiac dysfunction [77].

Hence, electron transport through ETC is critical during respiration. Of note, electron carrier cyt c is released from ETC into cytoplasm, with excess ROS production, enhances apoptosis and ferroptosis during cellular stress. In addition to lipid peroxidation, other harmful reactions such as thiol oxidation [75] and complex I sulfonation [90] also involve in mitochondrial dysfunction and CVDs. Indeed, molecular mechanisms underlying ETC-related stress response in the context of CVDs are still unclear, especially in large blood vessels.

2.3. Calcium homeostasis with protective effect

Mitochondria have a highly permeable outer mitochondrial membrane (OMM) and a more selectively permeable inner mitochondrial membrane (IMM), which act as ion barriers to regulate ion balance between the cytosol and mitochondrial matrix [91]. Voltage-dependent anion channels in the OMM and mitochondrial calcium uniporters (MCUs) located in the IMM facilitate Ca^{2+} influx when cytoplasmic Ca^{2+} concentration increases due to endoplasmic reticulum (ER) calcium pool release or extracellular uptake [92,93]. On the contrary, the mitochondrial permeability transition pore (PTP) and mitochondrial Na^{+}/Ca^{2+} (NCLX), H^{+}/Ca^{2+} (mHCX) exchangers are responsible for Ca^{2+} efflux, which maintains intracellular Ca^{2+} homeostasis along with influx mechanism [91,93,94].

Healthy heart requires physiological mitochondrial matrix Ca^{2+}, which is neither too high nor too low [95]. The influx and efflux of Ca^{2+} protect cardiomyocytes from pathological changes [96,97]. Cardiomyocytes resist the damage of chronic β-adrenergic receptor (β-AR) activation through calmodulin kinase II δB (CaMKIIδB), which transfers to nucleus and phosphorylates cAMP-response element binding protein (CREB), thereby increasing MCU transcription level [96]. MCU expression is increased by the β-AR/CaMKIIδB/CREB pathway to maintain cardiac cytoplasmic Ca^{2+} and energy metabolism, while MCU knockout mice display more cell death and severe cardiac hypertrophy [96]. In addition, the overexpression of mitofusin-2 can alleviate Ca^{2+} overload caused by abnormal ER-mitochondria contact and inhibit CaMKIIδ-RIP3/MLKL pathway, thereby effectively rescuing cardiomyocyte necroptosis and cardiac dysfunction [97].

Similarly, endothelial histidine triad nucleotide-binding 2 (HINT2) prevents mitochondrial matrix Ca^{2+} overload through directly binding MCU, which attenuates cardiac microvascular IR injury [98]. In large vessels, calcium homeostasis is critical for maintaining vascular smooth muscle cells (VSMCs) contractile phenotype, whereas calcium and phosphate overload contribute to an osteoblast phenotype and ultimately vascular calcification [99,100]. Dynamin-related protein 1 (DRP1), a protein needed for mitochondrial fission, play an important role in calcification [101]. The suppression of senescence related protein p53 in VSMCs restores the expression of DRP1 and promotes mitochondrial fission, protecting against inorganic phosphate (a mixture of NaH_2PO_4 and Na_2HPO_4) induced calcification [101]. Intriguingly, β-glycerophosphate (β-GP) induced VSMC calcification leads to increased DRP1 expression and exceeded mitochondrial fission, which can be rescued by melatonin and irisin through the activation of AMP-activated protein kinase (AMPK) [102,103]. Besides, abnormal enzymes related to energy metabolism such as pyruvate dehydrogenase kinase 4 (PDK4) and carnitine O-octanoyltransferase (CROT) are targets that impair mitochondrial functions and induce vascular calcification [104,105].

In short, mitochondria and their Ca^{2+} channels act as buffers to maintain cytoplasmic Ca^{2+} balance. According to the function of Ca^{2+} transport, MCU is regulated by other proteins and participates in complex Ca^{2+}-related signaling pathways, which significantly affects cardiovascular homeostasis. Besides, modulation of ER-mitochondrial Ca^{2+} transfer may be a potential treatment for CVD s [106,107].

2.4. Dual characters of ROS production

ROS are formed when an oxygen molecular (O_2) receives one electron, the ROS include superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-) and some nitrogen oxides [108–110]. In the cardiovascular system, accumulating evidence indicates that the major enzymatic sources of ROS are NADPH oxidase (NOX), uncoupled endothelial nitric oxide synthase (eNOS), mitochondria and xanthine oxidase (XO)1 [109–116].

Usually mitochondria with regular shape, retaining membranes and being neatly distributed means normal and functional whereas damaged mitochondria lose membrane integrity, exhibit fission, and vacuoles [117,118]. In normal mitochondria, more than 98% of the electrons are used to produce ATP through the respiratory chain, while only 1–2% of the electrons are involved in the production of ROS [119]. MitoSOX is a common indicator of superoxide targets to mitochondria in living cells, which is oxidized and fluoresce red or green [71,98,120–122]. Physiological concentration of mitochondrial ROS (mtROS) broadly regulate differentiation, apoptosis, pH balance, metabolic process, and immunity [108], while excess ROS induced oxidative stress is related to numerous CVDs [123–125]. Physiologically stable mtROS is not only a guarantee to fulfill the cardiovascular function but also a vital therapeutic target [126]. Excess mtROS is a key cause of heart injury during IR-induced myocardial infarction (MI) [123]. Overexpression of Ndufs1, a mitochondrial complex I protein, in cardiomyocytes promotes the maintenance of physiological mtROS and reduces apoptosis by maintaining normal mitochondrial morphology [120]. Physiological mtROS in macrophages induces endocytosis and contributes to post-MI cardiac repair, whereas Ndufs4 KO mice produce more ROS and have higher mortality [127]. Song et al. found that miR-210 targets GPD2, a ROS-producing mitochondrial dehydrogenase, thereby controlling mtROS in cardiomyocytes to improve cardiac function [71]. Another point is related to mitochondrial dynamics, as asiatic acid can restore cardiomyocyte mitochondrial fission and polarization, thereby reducing mtROS production and inhibiting apoptosis through p38/MAPK and JNK/MAPK pathways [117]. Clear the damaged mitochondria by blocking the lysosomal cation channel MCOLN1/TRPML1 prevents detrimental ROS accumulation, thereby inhibiting IR injury [128]. In addition, maintaining intravascular physiological mtROS has a significant protective effect on vascular lesions. Lipid metabolism and mitochondrial homeostasis-related protein FBXW7 restores endothelial mitochondrial respiration and reduces mtROS levels through the NAD^+/Sirt3 axis under hyperglycemia, promotes DNA damage repair and resists oxidative stress damage in diabetic retina [129]. Metformin inhibits methylglyoxal induced endothelial mtROS production and endothelial apoptosis through the ROS-mediated PI3K/Akt and Nrf2/HO-1 pathways [118]. Some antioxidants also have therapeutic potential via scavenging ROS. In vitro, astaxanthin regulates the activity of ROS-related enzymes, reduces the activity of NOX and XO, and simultaneously increases the activity of superoxide dismutase, thereby protecting VSMC from angiotensin II-induced oxidative stress damage [130]. This may partially explain why astaxanthin reduces ROS levels in the media, lowers blood pressure and attenuates aortic wall fibrosis in spontaneously hypertensive rats [130]. Besides, mitochondria-targeted antioxidant MitoQ resolves mtROS overproduction and alleviates PM2.5-induced aortic fibrosis via PINK1/Parkin-mediated mitophagy [121]. The antioxidative effect of MitoQ also benefit EC integrity in acute lung injury [131].

In summary, the physiological production of mtROS relies on well-off mitochondrial respiration, dynamics, and timely clearance of damaged mitochondria. Blocking any of these processes may produce excess mtROS and cause pathogenic oxidative stress. Multiple ROS-mitigating targets/reagents, such as mitochondrial complexes, dehydrogenases, mitochondrial dynamics-related pathways, and antioxidants, have shown beneficial effects on CVD-related animal models, suggesting that ROS may be the key to unraveling the entangled mechanisms of CVDs.

3. Mitochondrial responses to mechanical stress in cardiovascular cells

Mechanical stress represents various of mechanical forces that regulate cellular pathways and tissue functions, including stress (a force normalized by an oriented wall surface area) [132], stretch, pressure, compression and stiffness [44,47,133]. In cardiovascular system, cells in heart tissue and blood vessel walls (cardiovascular cells) are exposed to mechanical environment due to the contraction and relaxation of the heart. The mechanical forces are mainly in three directions: shear stress, hydrostatic pressure and cyclic stretch [47,133]. Shear stress is accompanied by blood flow, hydrostatic pressure is generated by the gravity of the blood, while cyclic stretch is caused by the rhythmically distending and relaxing of the heart [132,134]. Flow shear stresses are divided into different patterns: normal shear stress (laminar shear stress, LSS), low shear stress (low LSS) and oscillatory shear stress (OSS) [44]. The main mechanical stresses in cardiovascular system are shown in Fig. 2. In cardiovascular cells, numerous studies have shown that physiological mechanical stress, mainly shear stress and cyclic stretch, maintain mitochondrial homeostasis while pathological mechanical stress disturbs mitochondrial quality control, impairs ATP production in ETC, and leads to abnormal Ca^{2+} transit as well as ROS accumulation that triggers oxidative stress [58,135].

In vitro, 10% cyclic uniaxial stretch increased mitochondrial mass and ATP production in cardiomyocyte without ROS overproduction nor Ca^{2+} overload [136], and a shear stress of 15 dynes/cm^2 favors endothelial mitochondrial ATP production through decreasing plasma member cholesterol [137], indicating physiological mechanical stress is necessary to maintain mitochondrial energy supply. Besides, mechanical stress modulation of mitochondrial function relies on the adaptation of mitochondrial morphology and structure. Contracture (induced by Na^+-for-Li^+ substitution perfusion buffer with caffeine), rest (high-K^+ version of Krebs-Henseleit solution induced cardioplegia) and stretch (induced by intraventricular balloon inflation during rest) of rabbit heart revealed that stretch induced more elongated mitochondrial shape compared to rest [138]. Mitochondria are parallel to microtubules,

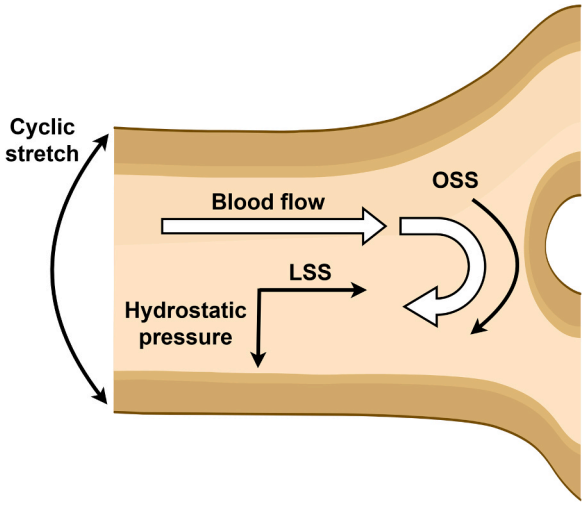

Fig. 2. Schematic diagram of mechanical stress in cardiovascular system. Unobstructed and direct parts with direct and regulated blood flow produce laminar shear stress (LSS) while vascular branches and cardiac valves with disturbed blood flow produce oscillatory shear stress (OSS). The gravity of the blood generates hydrostatic pressure that is perpendicular to the blood vessel wall and heart. The deformation caused by cardiac contraction and relaxation as well as hemodynamic generated by blood flow continuously produce circumferential cyclic stretch in heart and vessels. Hollow arrows represent the directions of blood flow and solid arrows represent the directions of mechanical stress.

showing "long-winded" and "tortuous" structures, and are connected by ultrastructural tethers and membranous bridges to form an integrated mitochondrial network [138]. The mitochondrial network is thought to enhance mitochondrial communication, transmit electrons more rapidly and enable a cell-wide mechanical signal conduction [138]. Physiological (25%) variability maintained mitochondrial network structure with maximized ATP and minimized mtROS production compared to static (0%), abnormally small (6%) or pathologically high (50%) stretch [122]. Similarly, physiological mitochondria is observed in descending thoracic aorta where generates unidirectional flow, but not in bifurcation site with disturbed flow [139].

Mitochondrial responses to extracellular mechanical stress depend, at least in part, on mechanosensitive ion channels. Piezo1 is associated with shear stress mechanotransduction and Ca^{2+} influx into cells [140]. Laminar shear stress (LSS) activates the ERK5/Klf2 axis in ECs at least partially through a Piezol1-related pathway and may be accomplished by mitophagy [141]. Therefore, Piezo1 may be an important receptor related to mitochondrial mechanical response, regulating the anti-inflammatory factor Klf2 and arterial lesion formation. Besides, Piezo1 channel activation induces ATP production via promoting mitochondrial respiration and glycolysis in vascular ECs, indicating a novel role of Piezo1 channel in endothelial ATP production [62]. Lu et al. found that the activation of another mechanosensitive Ca^{2+} channel TRPV4 leads to intracellular Ca^{2+} increase and PKC-dependent eNOS phosphorylation with impaired mitochondrial respiration and excessive ROS, this revealed a novel mechanism of mechanical ventilation (cyclic stretch dominant) induced pulmonary capillary damage in acute respiratory distress syndrome patients [142]. In addition, Nicolás-Ávila et al. elucidated an unusual mechanism by which cardiomyocytes adapt to intense mechanical stress in a way called “cardiac exophers” [38]. Cardiomyocyte eject damaged mitochondria by releasing “cardiac exophers”, which is similar to C. elegans under neurotoxic stress [143]. These cardiac exophers are degraded in cardiac macrophages, ultimately inhibiting the activation of inflammasomes, and preventing apoptosis [38].

Overall, cardiovascular cells expose to mechanical microenvironment persistently, with specific structures and mechanisms to adapt mechanical stress, and mitochondria play a vital role in this adaptation. Notably, whether mitochondria can directly sense mechanical stimulation and the molecular mechanism in this process remain to be further elucidated.

4. Mechanical stress induced mitochondrial dysfunction in CVDs

4.1. Pressure overload induced heart failure

Heart failure (HF) is a chronic and progressive disease characterized by multifaceted cardiac dysfunction such as impaired cardiac systole and/or diastole, reduced ejection fraction, ventricular remodeling, and systemic congestion [144]. Chronically elevated cardiac filling pressure is a critical cause of HF development, as mechanical stress overload disrupts intra- and intercellular homeostasis, in which mitochondrial dysfunction plays an important role [145,146]. Of note, mechanical forces during pressure overload involve both effects of myocardial stretch and stress [147], inducing mechanical stress overload collectively.

Mechanical stress overload induces abnormal mitochondrial metabolism in HF. Studies in 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 dysfunctions are attributed to mechanical stress-induced mitochondrial microstructural abnormalities and deficiencies of multiple enzymes, such as acyl-coenzyme A (CoA), a regulator of fatty acid metabolism, which is reduced in failing hearts in mice and humans [149]. In mice, overexpression of acyl-CoA synthetase 1 (ACSL1) prevents obstruction of long-chain fatty acid oxidation and increases mitochondrial energy potential (PCr:ATP), thereby reducing cardiac hypertrophy and improving cardiac function [149]. Mechanical unloading with left ventricular assist device rescues acyl-CoA expression in HF patients, similar to ACSL1 overexpression in mice [149]. Similar catabolic defects in branched-chain amino acids (BCAA) also promote HF [60]. Both human HF and transverse aortic constriction (TAC)-induced HF in mice express downregulation of key branched-chain amino acid (BCAA) catabolic enzymes, including BCAT2, BCKD subunits, and PP2Cm, resulting in defects in BCAA catabolism [60]. Accumulation of the BCAA catabolic mediator branched-chain alpha-keto acid (BCKA) directly inhibits mitochondrial complex I-mediated respiration and exacerbates superoxide production, while pharmacological reduction of BCKA preserves cardiac function [60]. Impaired mitochondrial respiration induces excessive mtROS production as mentioned above, leading to cardiac damage. Nicotinamide riboside protects against stress load induced cardiac dysfunction by attenuating mtROS production and NLRP3 inflammasome activation via the NAD+/Sirtuin3/MnSOD axis [150]. Mechanosensitive proteins are also involved in the transduction of pathological mechanical stress to mitochondria in HF. Piezo1 expression is increased in human failing hearts, with 38.2% of cardiomyocytes and 42.1% of ECs expressing Piezo1 [151]. After myocardial infarction, abnormal mechanical stress activates Piezo1 and induces intracellular Ca^{2+} overload, further activating calmodulin kinase II (CaMKII), leading to Ca^{2+} leakage and arrhythmias [151]. Consistently, activation of CaMKII in mitochondria (mtCaMKII) leads to mitochondrial permeability transition pore opening and increases mitochondrial Ca^{2+} uniporter currents, thereby triggering myocardial death [152]. Increased mtCaMKII activity accompanied by impaired cytoplasmic Ca^{2+} homeostasis and abnormal mitochondrial metabolism are important causes of dilated cardiomyopathy [153]. Therefore, overloading mechanical stress-induced hyperactivation of Piezo1 is the initiation of mitochondrial signaling during HF. Recently, Peng et al. found that Yes-associated protein 1 (Yap1), a well-known mechanosensitive transcriptional cofactor involved in the Hippo pathway, impairs mitochondrial biogenesis due to mechanical stress overload and then induces cardiomyocyte hypertrophy [61]. Activation of Yap1 bound to the TEAD1 motif (TEAD1-Yap1) inhibits the expression of Drp1 and Mitofusin1 (Mfn1), leading to more filamentous and branched abnormal mitochondrial morphology and reduced respiration [61]. 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] The molecular mechanisms of mitochondrial dysfunction in pressure overload induced HF was shown in the left panel of Fig. 3.

Metabolic abnormality caused by pressure overload impair mitochondrial respiration and induce oxidative stress, in which mechanosensitive receptor related pathways play an important role in this process. Importantly, promoting metabolism and enhancing mitochondrial function helps the heart resist mechanical stress-related pathologies such as cardiac hypertrophy [155]. Improving mitochondrial function favors metabolite utilization by cardiomyocytes, revealing therapeutic perspectives in heart failure derived from mechanics and metabolism.

4.2. Atherogenhic shear stress induced endothelial dysfunction

Monolayer vascular ECs are in direct contact with blood flow and constantly sense mechanical stimuli [44]. ECs serve as an important barrier to inhibit excessive infiltration of leukocytes, and their damage is usually the beginning of atherosclerosis [156]. Atherosclerotic plaques tend to localize to arterial curvatures and branches with oscillatory

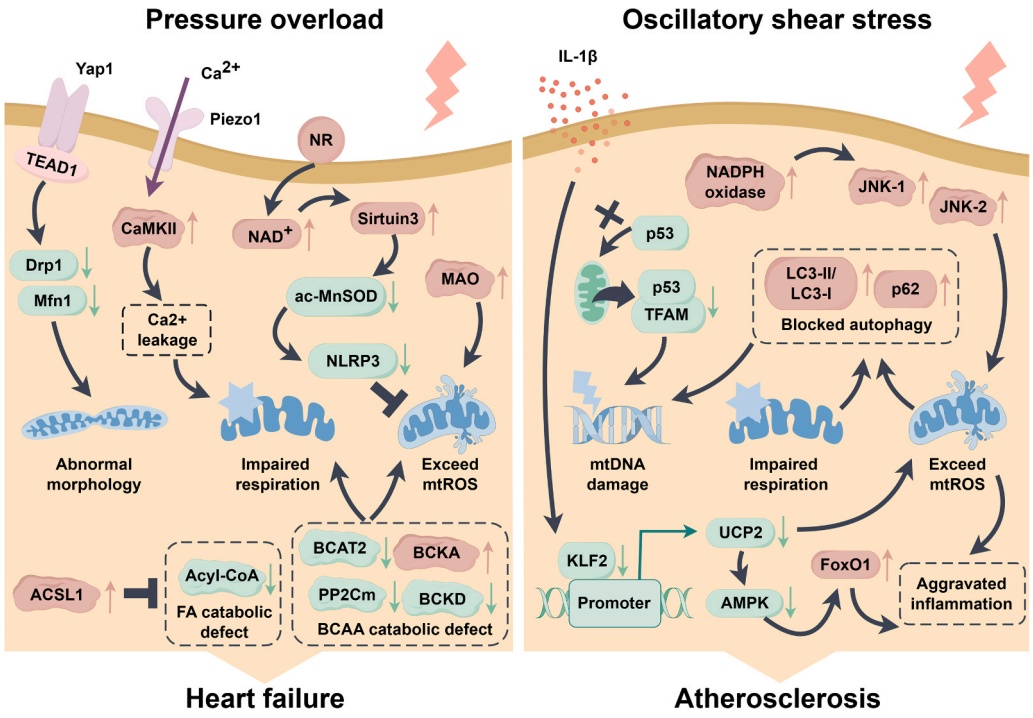

Fig. 3. Molecular mechanisms of mitochondrial dysfunction in pressure overload induced heart failure (HF) and oscillatory shear stress induced atherosclerosis. In HF, cardiomyocyte response to mechanic signals through mechanosensitive receptors such as Piezo1 and Yap1. Pressure overload induces exceed extracellular calcium flows into cytoplasm through Piezo1 that breaks calcium balance between cytoplasm and mitochondria matrix. Calcium activates CaMKII further leads to calcium leakage, which results in abnormal mitochondrial metabolism and associates to arrhythmias as well as dilated cardiomyopathy. Pressure overload activated Yap1 binds to TEAD1 motif that downregulates Drp1 and Mfn1 expression, inducing abnormal mitochondrial morphology and impaired respiration. Decrease of metabolic enzymes induced fatty acid (FA) and BCAA catabolic defects is found in failing heart while overexpression of ACSL1 in mice rescues mitochondrial energy potential. In failure heart of TAC mice, nicotinamide riboside (NR) restores NAD+ content, activates Sirtuin3 and reduces acetylation of MnSOD (ac-MnSOD), then inhibits NLRP3 and alleviates mtROS production, which recovers heart functions. In atherosclerosis, OSS activates NADPH oxidase and JNK to enhance mtROS production, blocking autophagy and results in mtDNA damage. Meanwhile, OSS fails the translocation of p53 into mitochondria where p53 binds to TFAM, intensifying the risk of mtDNA damage. OSS and proinflammatory stimuli such as IL-1β decrease KLF2 expression, down-regulating UCP2 in mitochondria transcriptionally. Reductive UCP2 not only enhances mtROS production, but also inactivates AMPK and activates orkhead box protein O1 (FoxO1), both aggravates inflammatory response. Red thin arrow indicates increase or activation while green thin arrow indicates decrease or inactivation.

shear stress (OSS) compared with straight portions of arteries with LSS, suggesting that shear stress is critical for endothelial homeostasis [156].

LSS is known to benefit endothelial barrier function and homeostasis, in which mitochondria play an important role in this process [157]. It is required for mitochondrial dynamics, biogenesis, respiration and antioxidant function, maintains endothelial Ca^{2+} homeostasis and promotes an anti-inflammatory effect [137,141,158,159]. On the contrary, disturbed flow or OSS is always harmful. In vitro studies of bovine aortic ECs demonstrate that OSS enhances mtROS production through NADPH oxidase and c-Jun NH2-terminal kinase (JNK) activation [160]. OSS impairs mitochondrial respiration and induces oxidative stress, thereby blocking autophagic flux with a concomitant increase in LC3-II/LC3-I ratio and p62 levels and causing mitochondrial DNA (mtDNA) damage [161]. Under disturbed flow, mtDNA is more vulnerable as p53 fails to translocate into the mitochondrial matrix where it binds to mitochondrial transcription factor A (TFAM) to maintain mtDNA integrity [162]. Recently, Luo et al. elucidated that OSS and proinflammatory stimuli inhibit UCP2, a key mitochondrial antioxidant protein, through altered KLF2 expression [57]. Elevating UCP2 level may have therapeutic potential against atherosclerosis [57] The molecular mechanisms of mitochondrial dysfunction in atherosclerosis induced by OSS were shown in the right panel of Fig. 3.

Therefore, mitochondria in ECs have different responses and signal transduction under different shear stress. Elucidating the molecular mechanisms of mitochondria in ECs under different shear stress will help to find suitable potential therapeutic targets. Furthermore, understanding the changes in mitochondrial function in other cell types such as VSMCs, macrophages, and foam cells during shear stress-induced atherosclerosis is indeed important. It will provide valuable insights into the underlying mechanisms driving disease progression and may provide potential therapeutic targets for alleviating atherosclerosis-related complications.

4.3. Mechanical perspective of mitochondria-related VSMC phenotype transformation

The plasticity of VSMC phenotype has been extensively explored [163]. Contractile VSMCs convert to a synthetic macrophage-like phenotype when stimulated by pathological factors that contribute to a variety of vascular diseases [164–166]. Importantly, mitochondria regulate VSMC phenotypes through metabolism reprogramming and Ca^{2+} homeostasis [167–169]. Mitochondrial network interacts with the cytoskeleton in response to stiffness and hemodynamics, suggesting that the role of mitochondria in VSCM phenotypic transitions is modulated by mechanical stress [169]. However, the specific mechanisms of how mechanical stress regulates VSMC phenotypes through mitochondrial in different vascular diseases need to be further explored.

5. Conclusion

Mitochondria produce ATP depending on electron transport in ETC. Inhibited ETC triggers severe stress responses such as cyt c release, GSH loss and lipid peroxidation, thereby accelerating cell death. Cardiovascular cells adjust their metabolic patterns to adapt variable

microenvironment, which is accompanied by changes in cell phenotype. Normal respiration produces very little physiological ROS, which maintains redox balance. Voltage-dependent anion channels and MCU enable Ca^{2+} influx into mitochondria while PTP and ion exchangers regulate Ca^{2+} efflux, contributing to intracellular Ca^{2+} homeostasis. However, abnormal mechanical stress such as pressure overload, OSS and excessive stretch directly or indirectly induce mitochondrial dysfunction. The malformation of mitochondrial structure, the inhibition of mitochondrial biogenesis and dynamic, as well as the accumulation of damaged mitochondria lead to metabolic disorder, excessive oxidative stress and Ca^{2+} overload, which at least partly explain the pathogenesis of multiple CVDs. The implantation of a left ventricular assist device in patients with HF is associated with a restoration of acyl-CoA, which serves as clinical evidence for the mitochondrial protection of heart function. The proactive intervention of mitochondrial quality control and mitochondrial reactive oxygen species (mtROS) production also contribute to a stable cardiovascular microenvironment. As mitochondria are not only simple power house but also a center of cellular signal transduction. Therefore, targeting mitochondria as a therapeutic approach for CVDs may be of great interest.

Numerous current studies use mitochondrial dysfunction as an indicator of cardiovascular dysfunction, but how mitochondria induce pathological processes of cardiovascular cells, such as abnormal cellular morphology, cell death or others need further study. Besides, more evidence is required to prove if mitochondria can directly perceive mechanical stimuli. In addition to HF and atherosclerosis, more research is needed to explore the role and mechanisms of mechanical stress induced mitochondrial functional changes in other cardiovascular diseases such as arrhythmia, aneurysms, hypertension, and endothelial injury. Furthermore, the interactions of different stress in the cardiovascular system and their molecular mechanisms need to be clarified. Therefore, the incomplete understanding of the mechanotransduction-induced mitochondrial-related signaling pathways impedes the search for new targets for the treatment of CVDs.

In summary, mitochondrial dysfunction caused by mechanical stress is an important and undeniable factor in explaining the mechanisms of CVDs. and can be used as an important potential target for the treatment of CVDs. It could be used as a significant potential target for CVD treatment.

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CRediT authorship contribution statement

Weiyi Hu: Writing – review & editing, Writing – original draft. **KAI HUANG:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **He Ren:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Tao Jiang:** Writing – review & editing. **Qingping Yao:** Writing – review & editing, Funding acquisition. **Yingxin Qi:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

I declare that this manuscript has no conflict to disclose. All the figures were created by Figdraw (http://www.figdraw.com).

Data Availability

No data was used for the research described in the article.

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