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Nitric oxide and mitochondrial function in cardiovascular diseases

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ABSTRACT

Nitric oxide (NO) has been highlighted as an important factor in cardiovascular system. As a signaling molecule in the cardiovascular system, NO can relax blood vessels, lower blood pressure, and prevent platelet aggregation. Mitochondria serve as a central hub for cellular metabolism and intracellular signaling, and their dysfunction can lead to a variety of diseases. Accumulating evidence suggests that NO can act as a regulator of mitochondria, affecting mitochondrial function and cellular activity, which in turn mediates the onset and progression of disease. However, there is a lack of comprehensive understanding of how NO regulates mitochondrial function in the cardiovascular system. This review aims to summarize the regulation of mitochondrial function by nitric oxide in cardiovascular related diseases, as well as the multifaceted and complex roles of NO in the cardiovascular system. Understanding the mechanism of NO mediated mitochondrial function can provide new insights for the prevention and treatment of cardiovascular diseases.

1. Introduction

Cardiovascular diseases are the main cause of death worldwide, and the economic burden it brings to people and society is increasing, making it a major public health issue. Therefore, great efforts have been made to understand the risk factors and underlying mechanisms of cardiovascular disease development and progression. The heart consumes a large amount of ATP every day to maintain basic energy metabolism and pumping function, with the majority of ATP generated through mitochondrial oxidative phosphorylation [1]. Myocardial injury may cause disruption of mitochondrial function and structure in myocardial cells, leading to changes in the demand and efficiency of energy substrate metabolism [2].

Mitochondria are organelles involved in the regulation of a variety of important cellular processes. In addition to serving as the cell's energy factories to produce large amounts of ATP, they also play an important role in cell signaling, cell differentiation, apoptosis, and other processes [3–5]. As essential regulators of cellular function, mitochondria not only influence metabolism but also contribute to the onset and progression of various diseases through mechanisms such as modulating cellular signaling and epigenetic modifications.

Enhancing and stabilizing mitochondrial metabolic function is therefore of significant clinical importance in the treatment of cardiovascular diseases. Evidence is rapidly accumulating that nitric oxide can regulate mitochondrial function and affect disease progression [6,7].

Nitric oxide (NO), as a biologically active signaling molecule in living organisms, plays a critical role in biological systems. Extensive research has revealed that NO, as a molecule that can transmit signals between cells, is ubiquitously present in a variety of cells, tissues and organs. It is involved in cardiovascular homeostasis [8], immune response [9], neuro transmission [10] and multiple physiological pathways related to apoptosis and proliferation [11] (Fig. 1). By targeting cardiovascular cells through specific metabolic pathways, nitric oxide can influence myocardial energy metabolism and modulate the progression of certain pathological processes [12,13]. Therefore, in this review, we will present the metabolic changes of NO in various cardiovascular diseases. And we will focus on the recent progress of NO signaling in regulation of mitochondrial function, especially cell metabolism.

2. Nitric oxide

2.1. Physical properties

NO was long regarded as a pollutant or an electrochemical byproduct until its role as a biologically active molecule was established in 1987

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Abbreviations :

Acetyl-CoA	Acetyl-coenzyme A
ACO2	mitochondrial aconitase
α-KG	alpha-ketoglutarate
ATP	Adenosine 5′-triphosphate
ETC	electron transport chain
FADH2	flavin adenine dinucleotide;
GLUT	glucose transporter
GSNO	S-nitrosoglutathione
NADH	nicotinamide adenine dinucleotide;
NO	nitric oxide;
NOS	nitric oxide synthase
eNOS	endothelial NOS
iNOS	inducible NOS
mtNOS	mitochondrial NOS
nNOS	neuronal NOS
O2	superoxide;
ONOO−	peroxynitrite;
RNS	reactive NO species
ROS	reactive oxygen species
PDH	pyruvate dehydrogenase
TCA	tricarboxylic acid

[14], a discovery that led to the awarding of the Nobel Prize in Physiology or Medicine in 1998 due to its importance in physiological regulation. As a new type of gas signal molecule, NO is physically inactive and belongs to a free radical [15]. It possesses an unpaired electron on the nitrogen atom, making it highly reactive with superoxide radicals, oxygen, and transition metal ions [16].

Given nitric oxide's significance in both physiological and pathological processes, its precise, quantitative, and dynamic detection is essential. However, due to its instability, high lipophilicity, and reactive nature, NO is challenging to measure accurately. Over recent years, several techniques have been developed for the qualitative and quantitative analysis of NO and its derivatives. For instance, various detection methods including colorimetry, chemiluminescence, fluorescent probe, electrochemical sensing, electron spin resonance (ESR) spectroscopy and magnetic resonance imaging (MRI) [17–21]. The detection of external NO often adopts the method of indirect detection of nitrite and nitrate ions, such as Griess assay, HPLC. Although these techniques offer high sensitivity, accuracy, ease of use, and cost-effectiveness, they often fail to accurately reflect in vivo NO concentrations due to interference from other biological substances. With the rapid development of analytical chemistry, molecular biology and materials science, some new NO detection methods in vivo have emerged as the times require [22]. Nanomaterial-based electrochemical biosensors have gained attention for their ability to provide highly sensitive detection of specific targets [23]. Additionally, genetically encoded NO probes have become an indispensable tool in modern cell research, enabling real-time monitoring of NO and its metabolites in single live-cell assays [24–26].

2.2. Generation

The sources of NO in organisms include both endogenous supply and exogenous production (Fig. 2). Exogenous NO mainly comes from food supplementation, exercise production, and other external factors. Endogenous NO production is largely mediated by nitric oxide synthase (NOS), an enzyme that utilizes L-arginine and molecular oxygen as substrates, with cofactors such as tetrahydrobiopterin (BH4), reduced nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), and flavin mononucleotide(FMN) [27].

NOS mainly includes three isoforms: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [28]. All of them have regulatory functions in the cardiovascular system. eNOS is mainly expressed in endothelial cells, vascular smooth muscle cells, cardiomyocytes, certain neurons of the brain and other tissues, which is the most important for the maintenance of cardiovascular system homeostasis among three isoforms [29]. eNOS-derived NO mediates endothelium-dependent vasodilation, required for normal vascular homeostasis, and inhibits important events promoting atherosclerosis, such as platelet aggregation, smooth muscle cell proliferation and migration, leukocyte adhesion and oxidative stress [30]. nNOS is constitutively expressed in specific neurons of the brain [31]. The

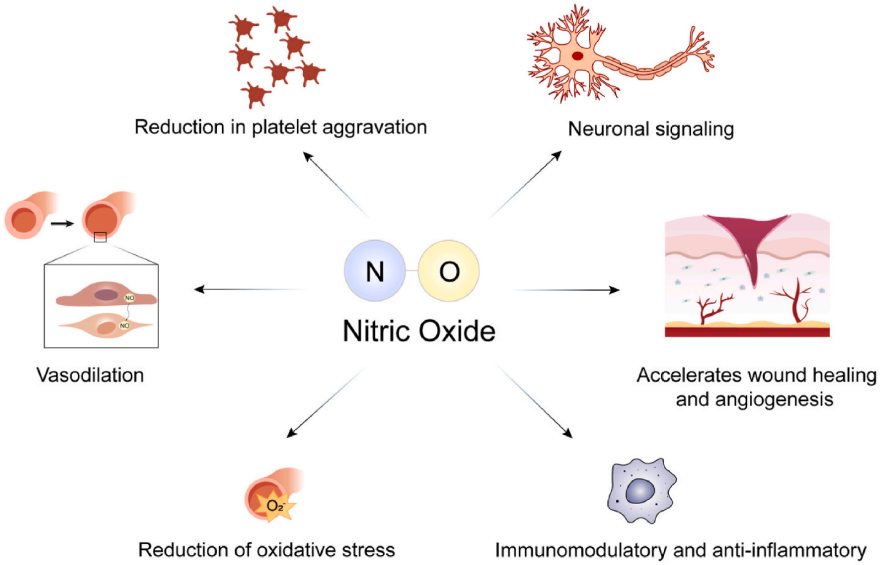

Fig. 1. Role of Nitric Oxide (NO) in Various Physiological Systems. NO is produced endogenously by cells and released from them, participating in various physiological and pathological processes.

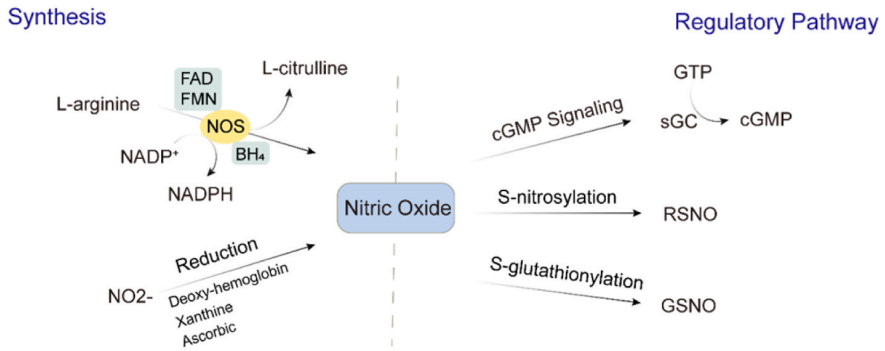

Fig. 2. The generation and singling patway of NO. NOS catalyzes the formation of NO from L-arginine and O_2. Another pathway for NO source is through the reduction of nitrite (NO^{2-}). NO signaling can increase the production of cyclic guanosine monophosphate (cGMP) and control cellular function by activating its receptor soluble guanosine cyclase (sGC). By adding nitroso ions (NO^-) to metals to form nitroso compounds (RNO), or adding S-nitroso (SNO) compounds to thiols, gene expression and protein function regulation can be altered through S-nitrosylation.

activity of both is regulated by Ca^{2+} and calmodulin (CaM) as well as by post-translational modifications of itself [32,33]. An important mediator associated with immune activation and inflammation is iNOS. When induced in macrophages, iNOS produces large amounts of NO to target tumors and bacteria. Unlike eNOS and nNOS, the calcium-independent nature of iNOS makes it have high catalytic activity. Increased intracellular Ca^{2+} levels can promote the production of NO from eNOS and nNOS. In addition, mitochondrial nitric oxide synthase (mtNOS) has been reported to be present in the mitochondrial matrix and inner membrane to regulate mitochondrial oxygen consumption and biogenesis [34]. mtNOS has been suggested to be the α-subtype of nNOS, but the nature of the enzyme has not yet been conclusively determined.

Electron transport through the FMN and FAD domains is enhanced when the calcium signaling protein calmodulin (CaM) is bound. Then in the presence of heme and BH4, the homodimer formed by the NOS monomer is able to utilize the donated NADPH electrons to catalyze L-arginine. L-arginine is hydroxylated, and then the hydroxylated intermediate is oxidized, resulting in NO and L-citrulline [35].

In addition to the NOS-catalyzed pathway, NO can also be generated via the reduction of its oxidative metabolite, nitrite. Nitrite can be converted to NO through reactions with protons or via enzymatic pathways [36]. Several metal-containing proteins are capable of catalyzing the reduction of nitrite to NO. These proteins typically contain heme or molybdenum cofactors, such as deoxyhemoglobin (deoxyHb), neuroglobin (Ngb), and xanthine oxidase, among others.

2.3. Singling pathway

The biological effects of NO are exerted through the activation of guanylate cyclase or post-translational modification of S-nitrosylation (Fig. 2). NO activates guanylate cyclase (GC), which converts guanosine triphosphate (GTP) into the secondary messenger cGMP [37]. cGMP subsequently activates cGMP-dependent protein kinases (PKG/PKA), regulates phosphodiesterases (PDE), and modulates cyclic nucleotide-gated (CNG) ion channels [38].

NO can also affect protein function by attaching to cysteine residues. This process, S-nitrosylation, is related to the physiological and pathological aspects of NO activity. S-nitrosylation of cysteine residues regulates proteins and enzymes, including NF-κB, AP-1, and CREB. Various signaling cascades, including G proteins, the Ras pathway, the mitogen-activated protein kinase (MAPK) signaling pathway, and the phosphatidylinositol-3 kinase (PI3K) pathway are also regulated by S-nitrosylation of their components [39]. S-nitrosylation also regulates many NO-dependent signaling pathways, including induction of Ca^{2+}-dependent potassium channels in vascular smooth muscle and inhibition of granulosa cytochrome oxidase [40]. S-nitrosoglutathione (GSNO) is an endogenous S-nitrosothiol (SNO), the major biologically active form of NO in the body, which can be irreversibly catabolized by S-nitrosoglutathione reductase (GSNOR) [41]. Therefore, GSNOR can act as a major regulator in the NO signaling pathway to modulate the response.

3. NO and mitochondrial metabolism

NO directly or indirectly mediates mitochondrial metabolic reprogramming by regulating enzyme activities or signaling intermediates in metabolic pathways (Fig. 3).

3.1. Mitochondrial respiratory chain

The mitochondrial respiratory chain is located on the inner membrane of mitochondria and comprises five complexes. Complex I (NADH ubiquinone oxidoreductase) transfers electrons from NADH to ubiquinone, complex II (succeed ubiquinone oxidoreductase) transfers electrons from succinic acid to ubiquinone, and complex III (ubiquinone cytochrome *c* oxidoreductase) transfers electrons carried by ubiquinone to cytochrome *c* and then to complex IV (cytochrome *c* oxidation), where oxygen obtains electrons and is reduced to water on complex IV (ATP synthesis). The electron transfer process is coupled with proton pumping from the mitochondrial matrix into the inter membrane space, and the subsequent proton electrochemical gradient is used to generate ATP through ATP synthase [42].

Mitochondrial complex I mainly receive NO inhibition through S-nitrosylation or tyrosine nitration [43–45]. As the concentration of reduced glutathione (GSH) in cells decreases, the inhibition of NO on complex I also increases [46]. The inhibition of NO in complex II is attributed to the damage of the iron sulfur center and the release of iron from the center [12]. Complex III activity can be reversibly inhibited by high levels of NO in submitochondrial particles [47]. NO reacts with superoxide anion produced by mitochondrial OXPHOS to generate peroxynitrite, which destroys key mitochondrial components in the matrix, inner and outer membranes, and intermembrane space [48].

Cytochrome C oxidase is located in the inner membrane of the granulosa and contains several metal cofactors and 13 subunits responsible for transferring electrons from cytochrome C to molecular oxygen [49]. The complex also includes two heme pigments (cytochrome *a* and cytochrome *a*3) and two copper centers (CuA and CuB). Cytochrome *a*3 and CuB form a binuclear center that serves as a reduction site for oxygen. Some commonalities in the chemistry of NO and O_2 allow NO to compete with O_2 for binding to cytochrome C oxidase, thereby inhibiting electron transfer [50,51]. This inhibition is reversible and dose-dependent. Cytochrome *c* oxidase is particularly sensitive to NO inhibition compared to other mitochondrial complexes, with evidence showing that mitochondrial respiration mediated by

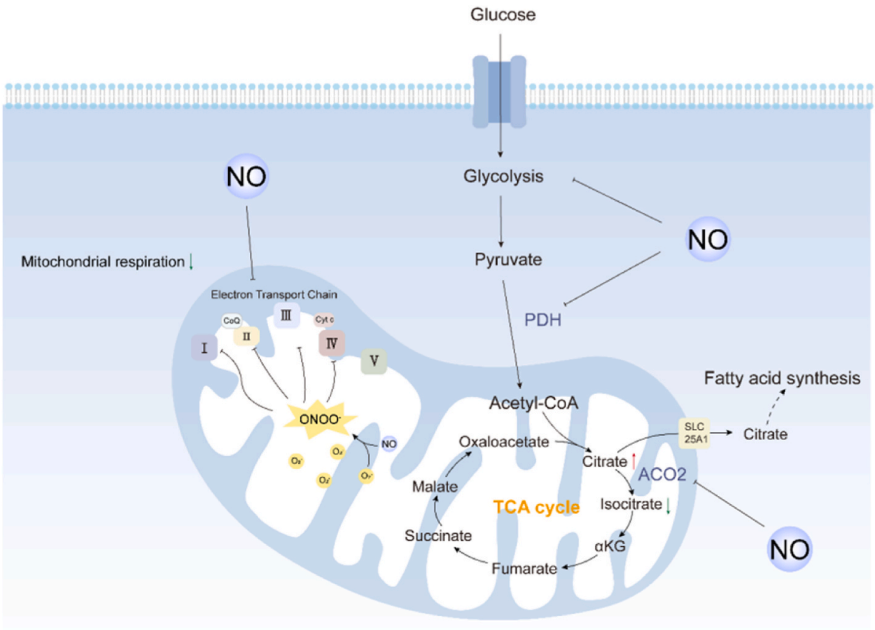

Fig. 3. NO and mitochondrial metabolism. NO inhibits or promotes the process of glycolysis according to different concentrations. NO inhibits complexes in the electron transfer chain through nitrite or direct competition with cytochrome *c* oxidase. NO production inhibits PDH, reduces glucose derived carbon entry into TCA, and enhances fatty acid metabolism. Within mitochondria, NO can inhibit aconitase, thereby enhancing the accumulation of citrate and playing an important role in lipid synthesis under hypoxic conditions.

cytochrome *c* oxidase can be inhibited by nanomolar concentrations of NO under physiological conditions [52,53]. Low concentrations of NO specifically and reversibly inhibit cytochrome *c* oxidase from competing with oxygen, whereas higher concentrations of NO and its derivatives lead to irreversible inhibition of the respiratory chain, uncoupling, and cell death [54–56]. The binding of NO to the heme/copper center of cytochrome *c* oxidase is considered a significant mechanism through which NO can alter cellular metabolism and regulate various cellular processes [52].

3.2. Metabolic alterations in the glycolysis and TCA cycle

Studies have shown that nitric oxide exerts a dual role in regulating glycolysis, with physiological nitric oxide promoting glycolysis and excessive nitric oxide inhibiting glycolysis [57]. NO stimulates glycolysis in astrocytes via mitochondrial inhibition, leading to AMPK activation, elevated levels of F-2,6-BP (a potent PFK-1 activator), and glucose uptake [58,59]. Pyruvate kinase (PK) is a rate-limiting enzyme in the last step of glycolysis pathway which catalyzes the pyruvate production from phosphoenolpyruvate. The mechanism of iNOS-produced nitric oxide promoting glycolysis was further revealed to be through EGFR/ERK2 induced PKM2 nuclear translocation [60].

Mitochondrial aconitase (Aco2), an iron-sulfur cluster-containing protein in which the metal center is involved in the catalysis of non-redox reactions, catalyzes the conversion of citrulline to isocitrulline in the TCA cycle, generating NADH and FADH2, which drive ATP synthesis via OXPHOS [61]. NO binds to the iron center and reversibly inhibits aconitase [62]. Inhibition of aconitase by NO leads to citrate accumulation, and excess citrate inhibits key glycolytic enzymes as well as pyruvate dehydrogenase (PDH) and succinate dehydrogenase (SDH), which affects the ATP production pathway. Citrate also stimulates fatty acid synthesis by activating the gluconeogenic enzymes fructose 1, 6-bisphosphatase (FBPase1) and ACC [63,64].

PDH converts pyruvate oxidatively decarboxylated to acetyl CoA into the TCA cycle [65]. In mitochondrial metabolism, PDH acts as a "gatekeeper" in pyruvate metabolism, controlling the final step in the tricarboxylic acid cycle where pyruvate is converted to acetyl CoA and maintaining glucose homeostasis [66]. It has been shown that NO targets the PDH complex by generating nitro (HNO) using lipoic acid salts that interact with thiols to form irreversible modifications [67]. Down-regulation of PDH results in the conversion of glucose into fatty acids as a source of energy production. When NO levels are elevated, PDH inhibition limits further utilization of glucose carbon, leading to increased compensatory glutamine influx and increased production of intermediate metabolites such as citrate and clathrate for energy production and lipid synthesis [68].

In mitochondrial metabolic pathways, NO regulates metabolism by targeting metal centers, such as heme-iron or iron-sulfur centers, to produce nitrosylated metal species or cysteine thiols to produce S-nitrosothiols [69,70]. It has been shown that S-nitrosylation inhibits physiologically relevant metabolic enzymes and that this NO-related post-translational modification may play an important role in the regulation of cellular metabolic processes and mitochondrial function [71].

4. NO and cardiovascular diseases

NO plays an important role in the development and prevention of cardiovascular diseases. The cardioprotective effects of NO include regulating blood pressure and vascular tension, inhibiting platelet aggregation and leukocyte adhesion, and preventing smooth muscle cell proliferation [72,73]. NO participates in the regulation of myocardial contractility and contributes to myocardial protection during ischemic preconditioning and postconditioning [74]. Disruptions in NO bioavailability can lead to a loss of cardiac protective functions and, in some cases, accelerate the progression of cardiovascular diseases.

4.1. Atherosclerosis

Atherosclerosis(AS) is a chronic progressive disease characterized by lipid peroxidation, endothelial cell dysfunction, macrophage activation and release of inflammatory factors, and migration and proliferation of

vascular smooth muscle cells in the arterial intima [75]. The above key molecular events of atherosclerosis are promoted by vascular oxidative stress and inhibited by endothelial NO.

Relevant research results show that the effects of NO in atherosclerosis (AS) are dependent on its source. NO derived from eNOS and nNOS has an anti-AS effect, while NO from iNOS can promote the occurrence of AS [76].In atherosclerosis, ECs exhibit significant eNOS decoupling, resulting in elevated ROS levels and reduced NO-mediated vasodilation [77,78]. The basis of eNOS uncoupling is the decreased levels of essential cofactors (NADPH, CoQ10, BH4) resulting from deregulation of metabolic pathways or enzymatic activities, and the methylation of the eNOS substrate arginine (ADMA). Impaired NO generation disturbs vasodilation needed for vessel homeostasis and promotes atherosclerosis by supporting oxidative stress, platelet aggregation, leukocyte adhesion, and smooth muscle cell migration and proliferation [79].

The upregulation of glycolysis and changes in TCA cycle intermediates are key determinants of macrophage inflammatory phenotype [68]. Oxidative stress and mitochondrial dysfunction participate in inflammatory reaction, thus promoting atherosclerosis [80]. The iNOS induced by mild inflammatory stimulation increases glycolysis and cell proliferation by producing low dose of nitric oxide, while the iNOS induced by excessive inflammation inhibits glycolysis and cell proliferation by producing excessive nitric oxide. Experimental studies have shown that there is complementary synergistic regulation between NO and itaconate to coordinate the response to injury and infection. NO regulates the levels of citrate and succinate, the metabolites essential for the TCA cycle, as well as the inflammatory mediator itaconate [81]. Furthermore, NO regulates macrophage respiratory function by altering the abundance of key N module subunits in complex I (Fig. 4). High level of NO concentrations exacerbate advanced atherosclerotic lesions by altering low-density lipoprotein (LDL) oxidation in fatty acid metabolism [82]. Oxidized LDL is a major factor modulating the eNOS/iNOS mechanism, promoting endothelial dysfunction and vascular inflammation [83].

Some amino acids (AAs) exert their atherogenic and anti-atherogenic effects by regulating macrophage activity and foam cell formation [84]. L-arginine can act as a preventive agent to inhibit miR-221 expression and increase eNOS expression in atherosclerotic rat aortic endothelial cells, and can exert some anti-atherogenic effects by reducing monocyte adhesion to the endothelium and reducing foam cell formation [85]. Studies have shown that oxLDL triggers the transfer of arginase 2 from mitochondria to cytoplasm in aortic endothelial cells, and with the increase of arginase activity, eNOS uncouples [86].

Based on the protective effect of nitric oxide and its importance in vascular homeostasis, a variety of direct or indirect NO donors have emerged for the treatment of atherosclerosis. For example, organic nitrates, nicorandil, Molsidomine have played an antiatherosclerotic role in clinic [87]. In addition, the use of mitochondrial targeted drugs to treat atherosclerosis and related diseases is currently in the preclinical research stage or clinical trial stage [88,89]. Recent clinical trials have also shown that mitochondrial targeted antioxidants (MitoQ) can cause changes in the circulatory environment, including a decrease in oxidized low-density lipoprotein, thereby enhancing the production of nitric oxide and reducing mitochondrial oxidative stress in endothelial cells [90]. However, the potential of drug research strategies related to the regulation of mitochondria by nitric oxide is still relatively limited and requires further translational experimental research.

4.2. *Hypertension*

Hypertension primarily results from increased systemic arterial pressure and is a major risk factor for cardiovascular diseases [91]. NO plays a crucial role in regulating vascular diastolic function. Endothelial injury, caused by various physical or chemical factors in vivo and in vitro, can lead to increased endothelin production and decreased NO production. This imbalance weakens vascular relaxation, enhances vascular contractility, and contributes to hypertension.

Persistently elevated blood pressure leads to premature EC senescence, which increases its turnover rate and thus leads to endothelial dysfunction [92]. Abnormal purine catabolism in endothelial cells is also involved in endothelial cell dysfunction during the development of hypertension. Xanthine oxidoreductase (XOR) catalyzes the oxidation of hypoxanthine to xanthine and then xanthine to uric acid (UA), which is associated with EC dysfunction and hypertension [93]. UA inhibits eNOS phosphorylation and NO production through the PI3K/Akt pathway [94]. Furthermore, UA inhibits NO release and directly reacts with NO in an irreversible manner, leading to NO consumption.

A key TCA cycle enzyme, fumarase (FH), can effectively balance NO and ROS. FH-related metabolites regulate the blood pressure through changing the NO content, especially the NO synthesis substrates [95]. Comparing to salt-insensitive consomic SS with the Dahl salt-sensitive (SS) rat, a model of salt-sensitive hypertension, which exhibits

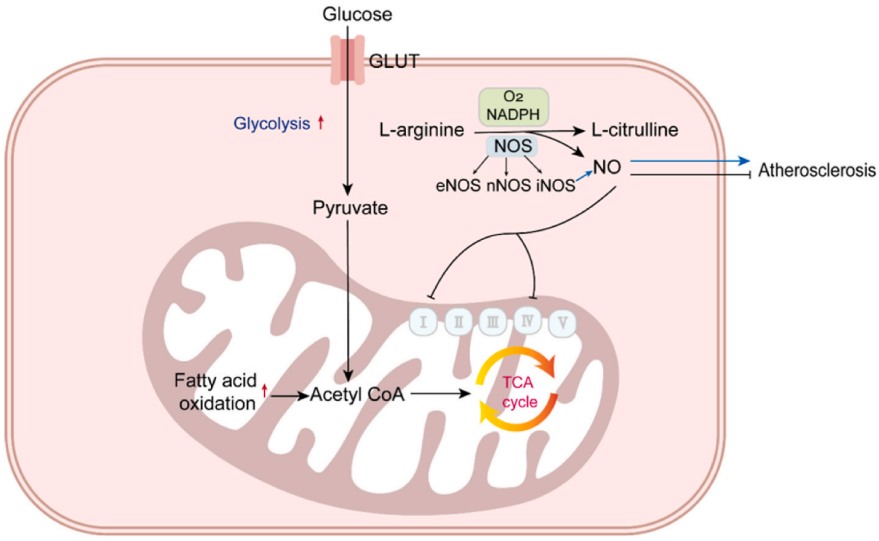

Fig. 4. NO mediates mitochondrial metabolism in atherogenesis. Oxidative stress and mitochondrial dysfunction participate in inflammatory reaction and promote atherosclerosis. NO produced by iNOS has a dual effect on glycolysis based on the degree of inflammation. In addition, high concentration of NO will change fatty acid metabolism and affect atherosclerosis.

fumarase insufficiencies. Research has shown that fumarase insufficiencies and lower levels of malate result in decreased levels of aspartate, to decreased L-arginine regeneration and NO production and contributing to hypertension [96]. As a potent vasodilator, NO is synthesized as a byproduct in the conversion of L-arginine to L-citrulline, a major intracellular source of cellular NO, which is catalyzed by nitric oxide synthase (NOS) [14]. Though FH is not directly involved in NO synthesis, the production of NO can be limited by the capacity of the kidney to regenerate L-arginine through the citrulline-NO pathway. The reduction of L-arginine and aspartate, the key NO synthetic intermediates in arginine-citrulline-NO pathway, suggested the NO content decreased and final contributed to hypertension [97].

Mitochondrial targeted compounds can be combined with potential adjuvant therapy for hypertension and related diseases. MitoQ can prevent the development of hypertension by targeting mitochondria and increasing the bioavailability of endothelial nitric oxide [98]. In spontaneously hypertensive rats, the combination of MitoQ and low-dose losartan alleviated the development of hypertension and reduced left ventricular hypertrophy [99]. NO inhibits the respiratory chain and affects cardiovascular function, indirectly leading to hypertension, but there is currently no drug strategy targeting this mechanism.

4.3. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is characterized by progressive increase in pulmonary vascular resistance, leading to right heart failure and death. Hyperproliferation and dysfunction of vascular endothelial cells are the main features of pulmonary arterial hypertension.

In PAH, reduced NO content in vascular endothelial cells is a prominent feature, often linked to elevated levels of arginase II [100]. Arginase II competes with eNOS for the substrate L-arginine, resulting in decreased NO production. Additionally, a deficiency of NO synthase in pulmonary vascular endothelial cells further reduces NO production, adversely affecting vascular tone and other cellular activities in the vessel wall [101]. PAH endothelial cells metabolize more glucose and produce less NO from eNOS [102].

Low levels of NO donors decreased HIF-1α expression in normoxic IPAH-ECs, and with HIF-1α knockdown, mitochondrial numbers increased in IPAH-ECs [103]. Chronic inhibition of ETC is sufficient to induce sustained pulmonary vasoconstriction, increased vascular edema, and a glycolytic metabolic shift in healthy female rats [104]. It has been demonstrated that in isolated pulmonary artery endothelial cells from fetal lambs with persistent neonatal pulmonary hypertension, HIF-1α expression and its downstream glycolysis are increased, but VEGF levels and angiogenesis are impaired. Inhibition of HIF-1α signaling downregulated glycolytic enzymes and improved VEGF levels as well as angiogenesis [105].

4.4. Abdominal aortic aneurysm

An aneurysm is a localised dilatation of the arterial wall, in other words a gradual loss of the ability of the arterial wall to support its haemodynamic load, which may lead to a rupture of the arterial wall [106]. Abdominal aortic aneurysm (AAA) can be diagnosed when the diameter of the abdominal aorta exceeds 3 cm or increases by more than 50 % compared with the normal value [107]. Currently, AAA treatment completely depends on surgical treatment, including open repair and intravascular repair [108,109]. Due to limited understanding of AAA pathogenesis, effective pharmacological treatments remain unavailable.

eNOS deficiency can promote the occurrence of aneurysm. Early studies found that the ratio of aortic aneurysm and atherosclerotic plaque in ApoE/eNOS double knockout mice was increased compared with ApoE knockout mice [110]. In addition, Cav-1 can inhibit the production of NO after binding with eNOS. Inhibiting the combination of eNOS and Cav-1 can increase NO, inhibit the level of oxidative stress and upgrade endothelial dysfunction [111]. Therefore, regulation of eNOS expression is of great significance for cardiovascular protection and intervention of cardiovascular disease.

Dihydrofolate reductase (DHFR) plays a significant role in folate metabolism [112]. Studies have demonstrated that DHFR deficiency causes reduced BH4 bioavailability and the uncoupling of endothelial nitric oxide synthase (eNOS), thus leading to the development of vascular disease [113,114]. Increased eNOS uncoupling activity in DHFR-het-KO mice, followed by mitochondrial dysfunction, and the emergence of persistent oxidative stress, leading to impaired vasodilatation and excessive vascular remodeling, thereby promoting hypertension and AAA [115]. In addition, it has been proved that restoring the expression of DHFR in endothelium and recoupling eNOS with folic acid (FA) can effectively treat AAA [116].

4.5. Heart failure

Heart failure (HF) is a complex syndrome caused by structural or dysfunctional ventricular filling (diastolic dysfunction) or blood ejection (systolic dysfunction), known as heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced blood fraction (HFrEF) [117]. A critical feature of HF is the loss of peripheral and coronary vascular NO activity. Endothelial dysfunction in HF patients is associated with reduced eNOS expression and reduced NO bioavailability [118]. Enhanced NO regulation can prevent the development of HF by increasing eNOS/nNOS pathway activation and reducing ROS generation. Conversely, iNOS activity and expression are elevated in heart failure. Under healthy conditions, cardiac ATP primarily derives from fatty acid oxidation (FAO), with glucose metabolism contributing less [119].

Studies have shown that in advanced heart failure, FAO decreases while glycolysis and glucose oxidation increase. Respiratory chain activity declines, and mitochondrial oxidative flux reserve is compromised [120]. It is now confirmed that the oxidation of fatty acids increases or decreases in the heart, depending on the type of heart failure [121]. For example, in heart failure associated with diabetes and obesity [122], myocardial fatty acid oxidation increases, while in HF associated with hypertension or ischemia, myocardial fatty acid oxidation decreases. Changes in glycolysis and mitochondrial oxidative metabolism during heart failure are due to the transcriptional changes of key enzymes involved in these metabolic pathways, as well as changes in redox status (NAD^+ and NADH levels) and metabolite signals. Impaired cardiac branched chain amino acid catabolism and insulin signaling occur in HF, and enhanced branched chain amino acid oxidation improves cardiac function in failing mouse hearts [123].

HFpEF induced by a high-salt diet showed a gradual increase in glycolysis with hypertrophy and diastolic dysfunction developing without unaltered glucose oxidation. A mismatch between early glycolysis and glucose oxidation may cause heart failure with preserved ejection fraction [124]. A reduction in FAO was not observed in heart failure episodes with ejection fraction retention, but only at later stages. In HFpEF, the intermediates of the TCA cycle play a key role in macrophage expansion and polarization, and can determine the changes in the expression of genes involved in inflammatory pathways [125].

The traditional drugs for treating HF mainly include beta blockers, angiotensin-converting enzyme inhibitors, vasodilators, and diuretics, which mainly work by reducing the workload of the failing heart. Recently, various mitochondrial drugs have emerged [126]. Mitochondrial targeted therapy focuses on enhancing mitochondrial function to improve cardiac contractility in HF patients and more effectively address energy issues.

4.6. Ischemia-reperfusion injury

Under hypoxic conditions, mitochondrial respiration is compromised, leading to a reduced capacity of cytochrome *c* to bind oxygen.

This results in electron accumulation and subsequent ROS formation, contributing to endothelial dysfunction. In the early stage of ischemia and reperfusion, endothelial-dependent coronary dilatation impairment, NO synthesis disorder, and myocardial leukocyte infiltration and myocardial cell necrosis appear. Thus, reduced NO synthesis in coronary endothelial cells is a critical pathological factor in ischemia-reperfusion injury. Ischemia also results in increased hypoxia-inducible transcription factor 1 (HIF-1) activity, and increased glycolysis in ECs upon hypoxia or HIF-1 overexpression [127]. After myocardial ischemia-reperfusion, fatty acid oxidation shows fast recovery while glucose oxidation rates remain depressed [128].

In ischemia/reperfusion (I/R) injury, stress conditions alter systemic substrate levels, affecting metabolic responses and leading to the accumulation of metabolic intermediates during ischemia. The depletion of oxygen and respiratory substrates inhibits pyruvate and fatty acid β-oxidation, as well as oxidative phosphorylation in mitochondria [129].

In the ischemic heart, the switch from oxidative phosphorylation to anaerobic glycolysis results in a marked increase in glucose-6-phosphate (G6P) and lactate concentrations [130]. During cardiac arrest, mitochondrial dysfunction and some changes in intracellular signaling pathways are associated with downregulation of FA metabolism and accumulation of long-chain FA in the cytoplasm [131]. Mitochondrial metabolism is limited mainly due to lack of oxygen as an electron acceptor. Furthermore, in ischemic mitochondria, restricted mitochondrial metabolism was also associated with TCA cycle intermediates and free CoA. Thus, alterations in mitochondrial function increased levels of TCA cycle intermediate succinate and FA metabolic intermediates acylcarnitine and acyl-CoA (acyl-CoAs). Selective accumulation of succinate is considered a pervasive metabolic feature of ischemia and is thought to be a major metabolite of mitochondrial ROS generation during reperfusion [132].

5. Conclusion

There is no doubt that nitric oxide plays a key role in the regulation of cardiovascular system, but the mechanism of nitric oxide treating cardiovascular diseases by regulating cell metabolism remains unclear. Therefore, it is necessary to deeply understand the relationship between nitric oxide and cell metabolism. The role of nitric oxide synthase subtypes, key metabolic enzymes, mitochondrial ETC components, cytokines, etc. is the mechanism of nitric oxide biological activity transduction when the cardiovascular system undergoes metabolic changes.

The current research focuses more on the regulation of nitric oxide on glycolysis and mitochondrial electronic respiratory chain, and the regulation of other metabolic substrates still needs to be further explored. Therefore, it is necessary to propose new strategies to improve the bioavailability of nitric oxide and study various aspects of cell metabolism to enhance its metabolic potential in disease treatment. Further research is needed to reveal the relationship between complex metabolic pathways and discover new metabolic pathways that regulate cell life activities. In addition, there have been many attempts to target the NO signaling pathway in cardiovascular therapy. However, there is still a lack of exploration and clinical trial research on the mechanism of improving diseases through direct or indirect NO donor targeted mitochondrial therapy. Further experimental studies are needed to provide important information on its safety, efficacy, and mechanism of action, in order to provide information for future clinical trials of cardiovascular patients. The intervention of NO drugs targeting mitochondria may be an effective treatment strategy, indicating a broad direction for the development of new drugs for the treatment of cardiovascular diseases in the future.

With the wide application of metabonomics, single cell sequencing and bioinformatics technologies, there will be greater breakthroughs in the analysis of cell metabolic heterogeneity and targeted cell metabolic therapy of different diseases in the future. Future efforts to reveal the role of NO as a mediator of cardiovascular metabolic phenotype will accelerate the development of NO based treatment strategies to combat cardiovascular disease.

CRediT authorship contribution statement

Haoqi Li: Writing – original draft. **Zijie Cheng:** Writing – original draft. **Dan Wu:** Writing – review & editing, Supervision, Funding acquisition. **Qingxun Hu:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Ethics approval and consent to participate

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All authors gave their consent for publication.

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No novel data were created in the writing of this review article.

Declaration of competing interest

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

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Data availability

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

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