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Nitric Oxide and Mitochondrial Dysfunction in Chronic Heart Failure: A Narrative Review

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Abstract

Chronic heart failure (CHF) remains a leading cause of hospital admission, disability, and cardiovascular death despite major advances in guideline-directed therapy. Beyond hemodynamic impairment and neurohormonal activation, CHF is increasingly understood as a disorder of endothelial dysfunction, nitroso-redox imbalance, mitochondrial injury, energetic failure, and regulated cell death. Nitric oxide (NO) signaling and mitochondrial homeostasis are interconnected components of this broader pathophysiologic network. Under physiologic conditions, endothelial NO synthase-derived NO contributes to vascular tone, coronary microvascular regulation, and myocardial signaling. In CHF, reduced endothelial NO bioavailability may coexist with increased formation of reactive nitrogen species, particularly in inflammatory and oxidizing conditions. The resulting nitroso-redox imbalance can interact with mitochondrial respiratory dysfunction, altered calcium handling, oxidative stress, and regulated cell death, although the relative contribution of these mechanisms varies across heart failure phenotypes and disease states. Guideline-directed therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, evidence-based beta-blockers, and mineralocorticoid receptor antagonists, improve clinical outcomes through established neurohormonal, renal, and hemodynamic mechanisms. Experimental and translational evidence suggests that some of these therapies may also influence endothelial, redox, metabolic, or mitochondrial pathways, although the clinical contribution of these secondary effects remains incompletely defined. These mechanistic observations have also motivated investigation of therapies that more directly target endothelial, redox, or mitochondrial abnormalities. Hypertril (1-(beta-phenylethyl)-4-amino-1,2,4-triazolium bromide) is an investigational compound with reported beta-blocking, NO-related, and metabolic effects in experimental models; however, the available evidence remains predominantly preclinical and does not establish clinical efficacy in human CHF. This narrative review examines NO dysregulation and mitochondrial dysfunction as interconnected components of CHF pathophysiology, considers their relationship to contemporary pharmacotherapy, and discusses the translational limitations and research priorities associated with targeting these pathways.

Categories: Pharmacology, Cardiology, Internal Medicine
Keywords: beta-blockers, chronic heart failure, mitochondrial dysfunction, nitric oxide, nitrosative stress, oxidative stress, pharmacotherapy, sodium-glucose cotransporter 2 inhibitors

Introduction And Background

Heart failure continues to impose a substantial clinical and socioeconomic burden worldwide. Contemporary epidemiologic reports consistently show high rates of hospitalization, recurrent decompensation, impaired quality of life, and premature mortality, particularly among older adults and patients with multiple comorbidities [1,2]. Over the past two decades, the clinical framework of heart failure has become more precise, with clearer phenotypic separation into heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction, and preserved ejection fraction, alongside staged concepts that recognize pre-heart failure and advanced disease [3-5]. At the same time, guideline-directed therapy has expanded from symptom control alone to disease modification through simultaneous targeting of the renin-angiotensin-aldosterone system, the sympathetic nervous system, congestion, and more recently the metabolic and renal axes [3-5].

Despite these advances, substantial residual clinical risk remains, with recurrent hospitalization, progressive functional limitation, and mortality continuing across the heart failure spectrum [1-5]. Established neurohormonal and hemodynamic mechanisms remain fundamental to heart failure pathophysiology and treatment. At the same time, persistent endothelial dysfunction, altered myocardial energetics, oxidative stress, and mitochondrial abnormalities have prompted investigation of complementary cellular pathways that may contribute to disease progression and residual dysfunction [6-9].

Nitric oxide (NO) signaling and mitochondrial homeostasis are among the cellular processes implicated in heart failure pathophysiology. Under physiologic conditions, NO contributes to vascular tone, coronary microvascular regulation, and myocardial signaling, while mitochondria provide adenosine triphosphate (ATP) for cardiac work and participate in calcium and redox homeostasis [6-12]. In chronic heart failure (CHF), reduced endothelial NO bioavailability can coexist with increased formation of reactive nitrogen species (RNS), particularly under inflammatory and oxidizing conditions [10-16]. These disturbances may interact with mitochondrial respiratory dysfunction, oxidative stress, and altered calcium handling, although their relative importance is likely to vary with heart failure phenotype, etiology, comorbidities, and disease stage [6-16].

This narrative review examines NO dysregulation and mitochondrial dysfunction as interconnected components of CHF pathophysiology and considers how these mechanisms relate to contemporary pharmacotherapy. Particular attention is given to the distinction between established clinical benefits of guideline-directed therapies and proposed endothelial, redox, or mitochondrial effects that remain mechanistically or translationally defined. Emerging strategies, including the investigational compound Hypertril (1-(beta-phenylethyl)-4-amino-1,2,4-triazolium bromide), are discussed in the context of their current evidence base and limitations. The objective is to integrate these mechanisms with, rather than substitute them for, established neurohormonal and hemodynamic frameworks of heart failure.

Review

Search strategy and scope

This article was prepared as a narrative review. The initial literature search was completed before manuscript submission in March 2026 and was updated during peer-review revision in October 2026 to incorporate relevant newly published evidence. International heart failure guidelines, randomized clinical trials, mechanistic studies of NO signaling and mitochondrial biology, and peer-reviewed articles indexed in PubMed or available through major journal platforms were prioritized. Additional relevant publications were identified from the reference lists of selected articles. No fixed lower publication-date limit was applied, allowing inclusion of older landmark and foundational studies where scientifically necessary. Priority was given to English-language publications directly relevant to CHF, endothelial dysfunction, oxidative and nitrosative stress, myocardial energetics, and relevant pharmacologic therapies. Because the objective was to provide a clinically oriented mechanistic synthesis rather than a systematic review, literature selection was intentionally broad, with emphasis on contemporary guidelines, major clinical trials, foundational mechanistic studies, and recent translational evidence.

Clinical and biologic context of CHF

CHF is a heterogeneous clinical syndrome arising from multiple structural and functional cardiac disorders, including ischemic heart disease, long-standing hypertension, cardiomyopathy, valvular disease, and toxic myocardial injury [1-5]. Although the initiating causes differ, disease progression commonly involves ventricular remodeling, neurohormonal activation, impaired hemodynamic reserve, and recurrent congestion [1-5]. Established neurohormonal and hemodynamic mechanisms remain fundamental to the clinical understanding of heart failure and to contemporary guideline-directed treatment [3-5]. Endothelial, metabolic, redox, and mitochondrial abnormalities should therefore be considered complementary components of heart failure biology rather than alternatives to established neurohormonal mechanisms.

Cardiometabolic disorders provide an important clinical context for heart failure. Hypertension, obesity, insulin resistance or diabetes mellitus, and dyslipidemia frequently coexist and are associated with vascular dysfunction, coronary artery disease (CAD), and adverse myocardial remodeling [17-19]. CAD can contribute to heart failure through myocardial infarction, recurrent ischemia, loss of viable myocardium, and chronic ventricular dysfunction, while cardiometabolic abnormalities may additionally influence inflammation, endothelial function, substrate utilization, and myocardial energetics [17,18]. These overlapping relationships support consideration of metabolic risk, coronary disease, and heart failure within an integrated cardiometabolic framework [17-19].

The healthy myocardium has a continuous requirement for ATP, generated predominantly through mitochondrial oxidative phosphorylation and flexible use of fatty acids, glucose, lactate, ketone bodies, and other substrates [8,9,20,21]. In heart failure, mitochondrial oxidative capacity and metabolic flexibility may become impaired, although the pattern and magnitude of these abnormalities vary with etiology, disease stage, and phenotype [7-9,20,21]. HFrEF is commonly associated with impaired myocardial energetics and altered substrate utilization, whereas cardiometabolic phenotypes of heart failure with preserved ejection fraction (HFpEF) may show prominent metabolic stress, systemic inflammation, and microvascular dysfunction [20,21]. Despite these differences, impaired metabolic flexibility and reduced energetic reserve may contribute to limited myocardial adaptation to increased workload across multiple heart failure phenotypes [9,20,21].

Endothelial dysfunction further connects vascular and myocardial abnormalities in CHF. Reduced vasodilator reserve and coronary or systemic microvascular dysfunction can impair tissue perfusion and

ventricular-vascular coupling [10-12]. These abnormalities are relevant across the heart failure spectrum, although their relative contribution varies with etiology, phenotype, comorbidities, and disease stage. In HFpEF, cardiometabolic inflammation and coronary microvascular dysfunction have been implicated in impaired myocardial relaxation and increased ventricular stiffness, whereas in HFrEF endothelial dysfunction may coexist with ischemic injury, ventricular remodeling, and neurohormonal activation [10-12,21].

Within this broader framework, dysregulated NO signaling and mitochondrial dysfunction represent interconnected mechanisms rather than a single unifying cause of CHF. Reduced endothelial NO bioavailability can impair vascular adaptation and cyclic guanosine monophosphate (cGMP)-dependent signaling, whereas inflammatory and oxidizing conditions may favor inducible NO synthase activity, NO synthase uncoupling, and formation of RNS [10-16]. Mitochondria can both sustain injury from this disturbed nitroso-redox environment and amplify oxidative stress when respiratory function becomes impaired [6-9,13-16,20-21]. The sections that follow examine these interactions while recognizing that their relative importance varies across heart failure phenotypes and that they operate alongside established neurohormonal, hemodynamic, ischemic, inflammatory, renal, and metabolic mechanisms.

Physiologic role of NO in the heart and vasculature

NO is generated in the cardiovascular system by nitric oxide synthase (NOS) isoforms, with endothelial NOS (eNOS) and neuronal NOS contributing to physiologic signaling. In the vascular endothelium, eNOS-derived NO activates soluble guanylate cyclase in adjacent smooth muscle cells, increases cGMP, and promotes vasodilation [10-12]. NO also contributes to coronary microvascular regulation and exerts antiplatelet, anti-inflammatory, and endothelial-protective effects [10-12].

Within the myocardium, NO participates in the regulation of excitation-contraction coupling, relaxation, calcium handling, adrenergic signaling, and redox-sensitive protein modification [10-12]. These effects are concentration-, source-, and context-dependent. Physiologic NO signaling can support myocardial adaptation and vascular homeostasis, whereas NO generated in an oxidizing environment may participate in potentially harmful nitrosative reactions.

Mitochondria are important downstream targets of NO signaling. At low concentrations, NO can reversibly modulate cytochrome c oxidase and thereby influence mitochondrial oxygen consumption and respiratory activity [14,15]. In contrast, when NO is generated in an environment with increased superoxide, rapid formation of peroxynitrite can promote protein nitration, mitochondrial enzyme dysfunction, and membrane injury [15,16,22]. Thus, the relevant abnormality in CHF is not simply an overall deficiency or excess of NO. Reduced bioavailability of protective endothelial NO can coexist with increased formation of RNS from other enzymatic or redox sources. The pathophysiologic consequence therefore depends on the source, localization, concentration, and redox environment in which NO is generated [10-16,22].

NO dysregulation in CHF

In CHF, NO dysregulation begins in part with impaired endothelial signaling. Reduced endothelium-dependent vasodilation and lower effective NO bioavailability have been documented in heart failure and may reflect neurohormonal activation, inflammation, metabolic abnormalities, altered shear stress, and increased superoxide production [10-12]. Because superoxide rapidly consumes NO, effective endothelial NO signaling may decline even when total NO production is not uniformly reduced. This distinction is important: NO bioavailability and total NO generation are not equivalent measures of nitroso-redox status.

Inflammation and NOS uncoupling can simultaneously shift NO biology toward nitrosative and oxidative stress. Inflammatory signaling may increase inducible NOS (iNOS) expression, producing sustained NO in an environment in which superoxide and other reactive oxygen species (ROS) are already elevated [16,22,23]. Under these conditions, increased NO generation does not necessarily restore physiologic endothelial signaling and may instead favor peroxynitrite and other RNS formation [15,16,22]. In parallel, depletion or oxidation of essential NOS cofactors can promote NOS uncoupling, causing the enzyme to generate superoxide rather than NO [10,12]. These mechanisms provide a biologic explanation for the coexistence of reduced endothelial NO bioavailability, oxidative stress, and increased nitrosative injury in CHF.

The downstream consequences involve both the vasculature and myocardium. Reduced endothelial NO bioavailability can impair systemic and coronary vasodilator reserve and ventricular-vascular coupling [10-12]. At the cellular level, increased peroxynitrite and related RNS can modify proteins involved in mitochondrial respiration, membrane integrity, calcium handling, and contractile function [15,16,22]. These abnormalities provide plausible mechanistic links between disturbed nitroso-redox signaling, impaired myocardial energetics, and reduced functional reserve; however, individual clinical manifestations of CHF cannot be attributed to this pathway alone.

The relative contribution of these mechanisms is unlikely to be uniform across heart failure phenotypes or disease stages. Endothelial NO deficiency may be particularly relevant in settings dominated by vascular or microvascular dysfunction, whereas inflammatory states may favor greater iNOS activity and nitrosative

stress [10-12,22,23]. In HFpEF, obesity, diabetes mellitus, hypertension, systemic inflammation, and coronary microvascular dysfunction can interact with impaired NO signaling, while HFrEF may additionally involve ischemic injury, ventricular remodeling, and neurohormonal activation [17-21,23]. These patterns overlap substantially and should not be interpreted as mutually exclusive phenotype-specific mechanisms.

This complexity also helps explain why therapeutically targeting NO signaling is challenging. Increasing NO availability alone may be insufficient when oxidative conditions continue to favor NO consumption and peroxynitrite formation, whereas suppressing a single source of NO or reactive species may leave endothelial, mitochondrial, inflammatory, and neurohormonal abnormalities unresolved. Accordingly, NO-directed approaches should be considered within the broader pathophysiologic network of CHF rather than as correction of an isolated NO deficiency.

Mitochondrial dysfunction and altered myocardial energy metabolism

Mitochondrial dysfunction is an important component of myocardial energetic impairment in heart failure [6-9,20,21]. The healthy myocardium depends on mitochondrial oxidative phosphorylation to maintain a continuous supply of ATP and must rapidly adapt energy production to changes in workload, oxygen availability, and substrate supply. In CHF, impaired oxidative capacity, altered substrate utilization, and reduced metabolic flexibility can limit energetic reserve, although the magnitude and pattern of these abnormalities vary across etiologies and heart failure phenotypes [7-9,20,21].

Several mitochondrial alterations may contribute to this energetic impairment. Dysfunction of the electron transport chain can reduce ATP generation while increasing electron leak and ROS production [6-9,20,24]. Abnormalities in mitochondrial biogenesis, fusion, fission, mitophagy, membrane integrity, and cristae organization may further reduce the capacity to maintain a functionally competent mitochondrial network [6,9,20,24]. These processes are interconnected rather than independent defects: impaired respiratory function can promote oxidative injury, while structural and quality-control abnormalities can further compromise oxidative phosphorylation [9,20,24].

Metabolic remodeling accompanies these mitochondrial changes. The healthy adult heart can use fatty acids, glucose, lactate, ketone bodies, and other substrates according to physiologic demand. In heart failure, substrate utilization becomes altered, and metabolic flexibility may decline, but these changes are heterogeneous rather than representing a uniform switch from one fuel to another [8,9,20]. Altered fatty acid oxidation, glucose utilization, ketone metabolism, and coupling between glycolysis and mitochondrial oxidation have all been described, with patterns influenced by heart failure phenotype, disease stage, substrate availability, and comorbid metabolic disease [8,9,17,20,21]. The clinically relevant concept is therefore loss of efficient metabolic adaptation rather than a single characteristic substrate preference.

Nitroso-redox stress can further impair mitochondrial function. Physiologic NO can reversibly modulate mitochondrial respiration, whereas excessive formation of peroxynitrite and other RNS in an oxidizing environment can modify respiratory proteins, impair oxidative phosphorylation, and promote membrane injury [14-16,22]. Mitochondrial respiratory dysfunction can in turn increase ROS generation, creating a bidirectional interaction between mitochondrial injury and disturbed NO-redox signaling [15,16,20,22,24]. This interaction is mechanistically important but should not be interpreted as evidence that NO dysregulation is the sole cause of mitochondrial dysfunction in CHF.

Altered mitochondrial calcium handling provides another link between energetic dysfunction and cellular injury. Mitochondrial calcium uptake and extrusion normally help coordinate oxidative phosphorylation with contractile demand [25,26]. In heart failure, oxidative and nitrosative stress may disrupt this regulation, resulting in insufficient metabolic signaling or mitochondrial calcium overload [16,22,25,26]. Excessive calcium accumulation can promote mitochondrial membrane depolarization, permeability transition, further ROS generation, and activation of cell-death pathways [25,26]. These mechanisms may contribute to impaired energetic adaptation and electrical instability, but their contribution varies with the underlying disease context.

Mitochondrial abnormalities also interact with neurohormonal activation, inflammation, ischemia, and metabolic disease rather than occurring in isolation [17,20,21,23,24]. Catecholamine and renin-angiotensin-aldosterone system activation can increase oxidative and metabolic stress, while inflammatory signaling can further impair endothelial and mitochondrial homeostasis [3-5,23,24]. At the organ level, reduced energetic reserve, altered calcium handling, and increased oxidative stress provide biologically plausible contributions to impaired contractile reserve, reduced adaptation to physiologic stress, and progressive remodeling. However, symptoms such as exercise intolerance and fatigue are multifactorial and also reflect hemodynamic, pulmonary, skeletal-muscle, renal, vascular, and autonomic abnormalities.

These observations have stimulated investigation of mitochondrial-directed therapies, including approaches targeting mitochondrial quality control, redox homeostasis, membrane integrity, calcium handling, and substrate metabolism [24,27]. However, translation of mitochondrial targets into effective heart failure therapies remains challenging. Mitochondrial abnormalities differ among heart failure

etiologies and phenotypes; many candidate mechanisms have been characterized primarily in experimental models, and improvement in a mitochondrial biomarker does not necessarily translate into better clinical outcomes [24,27]. Mitochondrial-targeted strategies should therefore be regarded as an active area of translational investigation that may complement, rather than replace, established guideline-directed therapy.

Oxidative stress, inflammation, and regulated cell death

Oxidative stress is an important component of heart failure pathophysiology and arises from multiple interacting sources, including dysfunctional mitochondria, nicotinamide adenine dinucleotide phosphate oxidases, uncoupled NOS, and neurohormonal or inflammatory signaling [13,23,28]. Excess ROS can impair proteins, membrane lipids, mitochondrial function, and cellular signaling. Oxidative and nitrosative stress are closely interconnected because superoxide can reduce NO bioavailability while promoting peroxynitrite formation [15,16,22]. Peroxynitrite and related RNS can then further impair mitochondrial respiration and cellular redox homeostasis, creating a potentially self-reinforcing cycle of oxidative, nitrosative, and mitochondrial injury [13,15,16,22,24].

Inflammation can amplify this redox imbalance. Proinflammatory signaling can promote endothelial activation, increase iNOS expression, alter mitochondrial function, and increase oxidative and nitrosative stress [23,28]. These interactions may be particularly relevant in heart failure phenotypes associated with obesity, diabetes mellitus, aging, or other inflammatory comorbidities, but inflammatory activation is not restricted to HFpEF and can also occur in HFrEF [17-19,21,23,28]. Thus, inflammation is best considered one component of a broader network linking systemic comorbidity, endothelial dysfunction, redox imbalance, and myocardial injury.

Endogenous antioxidant systems normally constrain reactive species, but redox homeostasis may become impaired in the failing myocardium [13,28]. Because oxidant production and antioxidant defenses are distributed across multiple cellular compartments, oxidative injury in CHF is unlikely to reflect a single abnormal molecule or pathway. This complexity has important therapeutic implications, as correcting one component of the redox network may not normalize the broader pathophysiologic environment.

Persistent oxidative, nitrosative, and energetic stress can activate regulated cell-death pathways that contribute to myocardial injury and remodeling [29,30]. Mitochondrial membrane dysfunction, calcium overload, ATP depletion, and release of pro-apoptotic signals can promote intrinsic apoptosis, while other regulated processes, including necroptosis, ferroptosis, and pyroptosis, are also under investigation in cardiovascular disease [25,26,29,30]. These pathways can overlap and are influenced by the underlying injury, metabolic state, and inflammatory environment. Although experimental evidence supports a mechanistic role for regulated cell death in heart failure progression, the relative contribution of individual cell-death programs in human CHF remains incompletely defined [29,30].

These observations also illustrate the challenges of therapeutically targeting oxidative stress. Reactive species participate in normal signaling as well as pathologic injury, arise from multiple cellular sources, and interact with inflammation, mitochondrial dysfunction, endothelial signaling, and neurohormonal activation [13,23,24,28]. Consequently, reduction of a circulating oxidative-stress marker or nonspecific suppression of reactive species cannot be assumed to produce clinical benefit. More targeted approaches directed toward specific sources of oxidant production, mitochondrial injury, or pathologic nitroso-redox signaling remain under investigation, but their clinical value in CHF has not yet been established [24,27,28].

Therapeutic implications for current pharmacologic management

Contemporary heart failure treatment is grounded in guideline-directed medical therapy supported by randomized clinical trials and international guidelines [3-5]. In HFrEF, disease-modifying pharmacotherapy includes renin-angiotensin system inhibition or angiotensin receptor-neprilysin inhibition, evidence-based beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, while diuretics are used primarily to control congestion [3-5]. The established clinical benefits of these therapies should be distinguished from proposed effects on endothelial, redox, metabolic, or mitochondrial pathways. Such secondary mechanisms may contribute to the broader biologic response to treatment, but for many drug classes their magnitude and clinical relevance remain incompletely established.

Renin-angiotensin system inhibition and angiotensin receptor-neprilysin inhibition

The clinical value of renin-angiotensin system inhibition in HFrEF is supported by landmark randomized trials. CONSENSUS demonstrated a survival benefit with enalapril in severe heart failure, and SOLVD subsequently established benefits of enalapril in a broader population with symptomatic left ventricular systolic dysfunction [31,32]. Angiotensin receptor-neprilysin inhibition was later shown in PARADIGM-HF to reduce the risk of cardiovascular death or heart failure hospitalization compared with enalapril in eligible patients with HFrEF [33]. These outcome benefits underpin the role of renin-angiotensin system and

angiotensin receptor-neprilysin inhibition in contemporary guideline-directed therapy [3-5].

Renin-angiotensin system inhibition may also influence endothelial and redox biology, but these effects should be considered secondary to its established neurohormonal actions. Angiotensin-converting enzyme (ACE) inhibition reduces angiotensin II formation and limits bradykinin degradation, mechanisms that can favor vasodilation and endogenous NO signaling [34]. Reduced angiotensin II activity may also decrease oxidant-generating signaling and thereby indirectly preserve endothelial function. Angiotensin receptor-neprilysin inhibition additionally augments natriuretic peptide signaling, although the extent to which its clinical benefits are mediated by direct correction of mitochondrial or nitrosative abnormalities remains uncertain. Accordingly, neither ACE inhibitors nor angiotensin receptor-neprilysin inhibitors should be characterized primarily as NO- or mitochondrial-targeted therapies.

SGLT2 inhibitors

SGLT2 inhibitors have demonstrated clinical benefit across a broad range of heart failure phenotypes. In HFrEF, DAPA-HF showed that dapagliflozin reduced the composite risk of worsening heart failure or cardiovascular death, including in patients without diabetes mellitus, while EMPEROR-Reduced demonstrated benefit with empagliflozin on cardiovascular death or heart failure hospitalization [35,36]. In patients with mildly reduced or preserved ejection fraction, EMPEROR-Preserved and DELIVER demonstrated reductions in composite heart failure outcomes with empagliflozin and dapagliflozin, respectively [37,38]. These trials support the incorporation of SGLT2 inhibitors into contemporary heart failure management across a broad ejection-fraction spectrum [3-5,35-38].

The mechanisms underlying these clinical benefits remain incompletely resolved and are likely multifactorial. Proposed effects include changes in natriuresis, renal hemodynamics, cardiac loading conditions, intracellular ion homeostasis, inflammation, and systemic or myocardial metabolism [39]. Experimental and translational studies have also suggested effects on mitochondrial function, oxidative stress, and substrate utilization, including altered ketone availability and oxidation [8,9,39]. These observations provide biologically plausible links between SGLT2 inhibition and myocardial energetics, but they do not establish that mitochondrial or NO-related effects are the principal mediators of the outcome benefits observed in randomized trials.

Accordingly, the strongest evidence for SGLT2 inhibitors in heart failure remains their demonstrated effect on clinical outcomes rather than any single proposed cellular mechanism [35-38]. Their potential effects on myocardial energetics, endothelial function, oxidative stress, and mitochondrial homeostasis remain relevant to mechanistic research, but the magnitude of these effects in human CHF and their contribution to clinical benefit require further clarification [8,9,39].

Beta-blockers

Evidence-based beta-blockers are a core component of guideline-directed therapy for HFrEF [3-5]. Randomized trials demonstrated reductions in mortality and heart failure morbidity with metoprolol CR/XL, bisoprolol, and carvedilol [40-42]. The SENIORS trial additionally demonstrated benefit with nebivolol in an older heart failure population [43]. The established clinical benefits of beta-blockade are primarily related to attenuation of chronic sympathetic activation and its adverse effects on heart rate, rhythm, ventricular function, and remodeling [3-5].

Beta-blockade may also indirectly influence redox and metabolic pathways by reducing chronic adrenergic stimulation. Catecholamine excess can increase myocardial oxygen demand, calcium-cycling requirements, and oxidative stress, providing a mechanistic rationale for secondary effects of beta-blockade on cellular energetics and redox homeostasis [23-25,28]. However, these effects should not be considered independent explanations for the established outcome benefits of beta-blockers, which were demonstrated clinically without requiring evidence of mitochondrial or NO-pathway modification [40-43].

Individual beta-blockers also differ pharmacologically. Carvedilol has additional vasodilatory and antioxidant properties, while nebivolol has vasodilatory actions associated with endothelial NO signaling. Comparative studies have reported differences in oxidative-stress or inflammatory biomarkers among beta-blockers, including carvedilol and bisoprolol [44]. These pharmacologic distinctions are mechanistically relevant, but current evidence does not establish that differences in NO, redox, or mitochondrial effects translate into superior heart failure outcomes for one evidence-based beta-blocker solely through these pathways. Drug selection should therefore remain grounded in clinical evidence, guideline recommendations, patient characteristics, and tolerability rather than mechanistic biomarkers alone [3-5,40-44].

In clinical practice, beta-blocker selection and titration remain guided by the evidence base, heart rate and rhythm, blood pressure, congestion status, comorbidities, and treatment tolerance [3-5]. Additional endothelial, antioxidant, or metabolic properties remain scientifically relevant areas of investigation, but they should be interpreted as complementary pharmacologic characteristics rather than established determinants of comparative clinical efficacy.

Diuretics and mineralocorticoid receptor antagonists

Diuretics are used primarily to relieve congestion in heart failure. Loop diuretics reduce signs and symptoms of fluid overload and remain important for management of pulmonary and systemic congestion, but their principal clinical role is symptomatic decongestion rather than direct modification of NO signaling or mitochondrial function [3-5,45]. Changes in ventricular loading conditions, renal congestion, or tissue perfusion may secondarily influence inflammatory and metabolic stress, but these effects should not be interpreted as established mitochondrial-targeted mechanisms. Mineralocorticoid receptor antagonists (MRAs), in contrast, are disease-modifying therapy in appropriate patients with HFrEF and are incorporated into contemporary guideline-directed treatment [3-5]. Their established therapeutic role is based on clinical outcome evidence and blockade of maladaptive mineralocorticoid signaling rather than demonstrated correction of mitochondrial dysfunction. Reduced aldosterone signaling may secondarily attenuate sodium retention, fibrosis, inflammation, and oxidative stress, providing plausible indirect links to the endothelial and redox pathways discussed in this review. These mechanistic links are complementary to, rather than the basis for, evidence-based use of MRAs [3-5].

Emerging NO-modulating and metabolic strategies: Hypertril as a preclinical example

Persistent endothelial, redox, and mitochondrial abnormalities despite contemporary heart failure therapy have motivated investigation of compounds designed to influence more than one cellular pathway. Such strategies remain investigational and should be distinguished from guideline-directed therapies with established clinical outcome benefits. One preclinical example is Hypertril, a 1,2,4-triazole derivative studied for beta-adrenergic, NO-related, and metabolic effects in experimental cardiovascular models.

In a preclinical study in spontaneously hypertensive rats, Mazur et al. reported antihypertensive and cardioprotective effects of Hypertril, including experimental comparisons with metoprolol [46]. Subsequent studies evaluated Hypertril or related beta-blocker comparisons in experimental doxorubicin-induced cardiac injury or CHF models, examining myocardial morphology, energy-metabolism indices, electrocardiographic and autonomic parameters, and markers related to myocardial NO signaling [47-50]. These studies provide mechanistic and proof-of-concept data but do not establish efficacy in human CHF.

Within these experimental models, Hypertril treatment has been associated with changes in several mechanistic endpoints. In a rat model of doxorubicin-induced CHF, Belenichev et al. reported effects on indices of myocardial energy metabolism during treatment with beta-blockers of different generations [49]. A separate experimental study reported changes in components of the myocardial nitrooxidergic system during doxorubicin-induced CHF and beta-blocker administration [50]. Other animal studies described morphologic, electrocardiographic, or autonomic findings [47,48]. Collectively, these observations support further investigation of possible metabolic and NO-related actions, but comparisons based on experimental biomarkers cannot establish clinical superiority over evidence-based beta-blockers.

The evidence base for Hypertril nevertheless remains limited. The published studies cited above are predominantly preclinical, rely heavily on rodent models, and arise from a relatively limited research base [46-50]. In particular, doxorubicin-induced cardiac injury is useful for studying oxidative, mitochondrial, and toxic myocardial damage but does not reproduce the full heterogeneity of human CHF, including ischemic and nonischemic HFrEF and the diverse cardiometabolic phenotypes of HFpEF. Experimental endpoints such as myocardial energy-metabolism indices, histologic findings, electrocardiographic measures, or markers of NO-related signaling cannot by themselves establish clinical efficacy or safety. The literature evaluated in this review does not provide randomized human outcome evidence demonstrating that Hypertril reduces mortality, heart failure hospitalization, symptoms, or impaired quality of life in patients with CHF.

Translation from experimental bioenergetic or redox effects to clinically useful heart failure therapy is challenging. Differences in pharmacokinetics, tissue exposure, safety, off-target effects, disease phenotype, and background treatment can all limit extrapolation from animal models to human CHF [24,27]. Moreover, any investigational agent would now need to demonstrate safety and incremental clinical value when added to contemporary guideline-directed therapy rather than when compared only with older or incomplete treatment regimens [3-5]. For Hypertril specifically, human pharmacokinetic, dose-ranging, safety, and efficacy data would be required before its role in heart failure treatment could be determined.

Hypertril can therefore be considered a preclinical example of a broader investigational strategy in which adrenergic modulation is studied together with endothelial, redox, or metabolic effects. Whether such multitarget pharmacology provides clinically meaningful advantages over established therapies remains unknown. Evaluation of this concept requires independent replication, characterization in disease models beyond doxorubicin-induced injury, and ultimately appropriately designed human studies with clinically relevant outcomes.

Limitations and future directions

Several limitations should be acknowledged. First, this is a narrative review rather than a systematic review or meta-analysis, and the literature selection was intended to provide a clinically oriented mechanistic synthesis rather than an exhaustive assessment of all available evidence. Second, a substantial proportion of the evidence linking NO dysregulation, oxidative or nitrosative stress, and mitochondrial dysfunction to heart failure derives from experimental models, ex vivo systems, or translational studies. These approaches are valuable for defining mechanisms but do not fully reproduce the complexity of human CHF. Third, heart failure is biologically heterogeneous. The relative contributions of endothelial dysfunction, inflammatory activation, altered NO signaling, mitochondrial energetic impairment, calcium dysregulation, and metabolic remodeling may differ between HFrEF and HFpEF, between ischemic and nonischemic etiologies, across comorbidity profiles, and across stages of disease [9,20,21,24,28]. Consequently, mechanistic findings from one phenotype or experimental model should not be assumed to apply uniformly across the heart failure spectrum.

Future research should determine which endothelial, redox, metabolic, and mitochondrial abnormalities are clinically relevant within specific heart failure phenotypes and which are primarily markers rather than mediators of disease. Human translational studies integrating molecular or metabolic measurements with well-characterized clinical phenotypes may help clarify these relationships. Candidate biomarkers of endothelial injury, nitrosative stress, or mitochondrial dysfunction also require prospective validation before they can be used to select patients for targeted therapy or to predict treatment response.

For investigational therapies, mechanistic plausibility should be followed by independent replication, pharmacokinetic and safety characterization, dose-ranging studies, and appropriately controlled human trials. Such studies should evaluate new strategies against contemporary guideline-directed therapy and should distinguish changes in mechanistic biomarkers from clinically meaningful outcomes. Where appropriate, clinical endpoints may be complemented by validated measures of endothelial function, myocardial energetics, or redox biology to determine whether modulation of these pathways accompanies - and potentially contributes to - clinical benefit [24,27,28].

Conclusions

CHF is a multifactorial syndrome in which neurohormonal activation, hemodynamic abnormalities, renal dysfunction, inflammation, endothelial dysfunction, metabolic remodeling, oxidative and nitrosative stress, and mitochondrial impairment interact to varying degrees across disease phenotypes. Within this broader network, dysregulated NO signaling and mitochondrial dysfunction represent interconnected contributing mechanisms rather than a single unifying explanation for CHF. Reduced endothelial NO bioavailability can coexist with increased RNS formation under inflammatory and oxidizing conditions, while mitochondrial dysfunction can both result from and amplify disturbed redox homeostasis. Contemporary heart failure treatment remains grounded in therapies with demonstrated clinical outcome benefits. Some established therapies may also influence endothelial, redox, metabolic, or mitochondrial pathways, but the contribution of these secondary effects to their clinical efficacy remains incompletely defined. Mitochondrial- and NO-directed approaches therefore remain complementary areas of mechanistic and translational investigation rather than alternatives to guideline-directed therapy. Preclinical studies of Hypertril illustrate one investigational approach combining beta-adrenergic modulation with proposed NO-related and metabolic effects, but the available evidence does not establish efficacy or safety in human CHF. Further independent translational and clinical studies are needed to determine whether targeted modulation of endothelial, nitroso-redox, or mitochondrial abnormalities can provide incremental clinical benefit within specific heart failure phenotypes.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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