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Advances in research on treatment of heart failure with nitrosyl hydrogen

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Abstract
Heart failure is the end stage of various heart diseases such as ischemic heart disease, dilated cardiomyopathy, valvular heart disease, congenital heart disease, and hypertensive myocardial damage. It is characterized by a decrease in myocardial contractility, but there is currently no ideal treatment. Nitroxyl hydrogen (HNO) is considered to be a protonated form of NO. It has special chemical properties compared to other nitrogen oxides. In the body of organisms, HNO can participate in all aspects of the occurrence and development of heart failure (HF) and react with some proteins closely related to cardiac activity, changing its spatial structure and exerting cardioprotective effects. In recent years, studies have shown that HNO can inhibit cardiomyocyte hypertrophy, reduce inflammation, enhance myocardial contractility, dilate coronary arteries as well as peripheral blood vessels in early heart failure, and protect the heart against heart failure. This paper, combined with the latest research results at home and abroad, clarifies that nitrosyl hydrogen exerts cardioprotective effects through various processes that occur in the development of heart failure.

Keywords Nitrosyl hydrogen · Heart failure · Sulfhydryl · Calcium cycle

Introduction

Nitroxyl hydrogen (HNO) is considered to be a protonated form of NO [1]. It has special chemical properties compared to other nitrogen oxides. In the body of organisms, HNO can participate in all aspects of the occurrence and development of heart failure (HF), and react with some proteins closely related to cardiac activity, changing its spatial structure and exerting cardioprotective effects [2, 3]. Like NO, HNO also significantly expands the capacity of blood vessels and resistance vessels [4, 5], but HNO does not have unpaired electrons. Therefore, HNO should not be scavenged by reactive oxygen species (ROS) [6], which can be stably present in depleted hearts and exert special biological effects. This has sparked interest in the treatment of HF with HNO.

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Mechanism of the occurrence of heart failure

HF is the end stage of various heart diseases such as ischemic heart disease, dilated cardiomyopathy, valvular heart disease, congenital heart disease, and hypertensive myocardial damage, and it is one of the leading causes of death. When various harmful factors act on the body, these factors can cause partial myocardial cell damage, reduce effective ejection of the heart, reflexively induce compensatory hypertrophy of normal cardiomyocytes, and enhance cardiac function, which is accompanied by sympathetic nerves, renin-angiotensinus activation of the aldosterone system, and acute and chronic oxidative stress responses [7]. As the disease progresses, the heart function will gradually decompensate, and local myocardial fibrosis and inflammatory reaction will increase, eventually leading to cardiac systolic dysfunction, which makes it difficult to meet the physiological needs of the body and develops heart failure.

The calcium cycle of cardiomyocytes is the basis of systolic and diastolic function. When the normal myocardium is repolarized, the ATPase (SERCA2) of the sarcoplasmic reticulum in the cardiomyocytes is activated, and the inverse concentration difference of calcium ions in the cytoplasm is taken

up into the sarcoplasmic reticulum (SR) for storage. Another part of the calcium ion is transported outside the cell, and the concentration of calcium ions in the cytoplasm of the cardiomyocyte decreases, leading to myocardial relaxation. When the myocardium is depolarized, SR releases calcium ions into the cytoplasm through the Reynolds Receptor (RyR2). At the same time, new calcium ions flow from the outside of the cell to the cytoplasm, and the concentration of calcium ions in the cardiomyocytes increases, thereby causing the heart muscle to contract. In hypertrophic cardiomyocytes, SERCA2 activity is reduced. During the myocardial repolarization, SR intake and storage of calcium ions decreased; when the myocardium is depolarized, SR released calcium ions into the cytoplasm also decreased, so the intracellular calcium concentration decreased, which is an important cause of myocardial contractile function decline [8, 9]. While the SR takes up less calcium ions, mitochondria increase calcium ion uptake. However, mitochondria release calcium ions to the cytoplasm at a slower rate during myocardial depolarization, which is another important cause of the decrease in cytosolic calcium concentration. In addition, increased calcium ions in mitochondria can cause oxidative phosphorylation decoupling, resulting in insufficient energy production, promoting cardiomyocyte degeneration, and reducing cardiac function [10]. Therefore, calcium dysfunction is the molecular basis for the occurrence of heart failure [11].

Medical treatment of heart failure

The current clinical fields still lack the ideal drug for the treatment of heart failure. Traditional beta-adrenergic receptor agonists and phosphodiesterase inhibitors enhance the contractile function of the heart by increasing cAMP levels in the cardiomyocytes. But, at the same time, they will increase the sympathetic tone, and long-term use may further worsen the heart function [12, 13]. Digitalis drugs enhance myocardial contractility by inhibiting Na^+-K^+-ATPase function and promoting Na^+-Ca^{2+} exchange to increase Ca^{2+} concentration in cardiomyocytes. But, at the same time, they will reduce the concentration of K^+ in the cells, which is easy to cause digitalis poisoning. The new calcium ion sensitizer, levosimendan, can enhance the calcium-reducing ability of calcium-related proteins without increasing myocardial oxygen consumption [14] and enhance myocardial contractility. However, it does not increase the dissociation rate of Ca^{2+} and troponin C, and has no protective effect on myocardial diastolic function. Long-term use does not improve the prognosis of patients. Therefore, it is particularly important to find new drugs that improve heart function.

HNO is widely used as a novel compound in the therapeutic basis and clinical trials of HF [2–5, 15]. A large number of experiments have shown that HNO can inhibit early myocardial hypertrophy in HF [16, 17], reduce the expression of pro-inflammatory factors [18], and exert anti-myocardial remodeling [19]. Tests such as Tocchetti [3] have shown that HNO can improve myocardial contraction and diastolic function by improving the activity of calcium cycle-related proteins and increasing the sensitivity of myofin to calcium ions. When constant pressure perfusion of isolated blood vessels and heart, it was found that HNO has dilated blood vessels and increased the effect of coronary blood flow [20]. These physiological effects can be applied to various stages of HF development and play a cardioprotective role.

Basic properties of HNO

HNO has redox activity and can exert different biological effects in organisms [21]. It can act as a reducing agent in combination with the metal reaction centers of some important proteins in the body [22]. For example, it can react with Fe^{3+} in oxygenated hemoglobin, reduce it to Fe^{2+}, and reduce Cu^{2+} in superoxide dismutase to Cu^+, etc., change their biological effects, exert anti-oxidation, and inhibit myocardial remodeling. It can be used as an oxidizing agent to react with sulfhydryl groups in the body to oxidize it to N-hydroxylated sulfinamide (RSNHOH) [23]. If other sulfhydryl groups are present near the thiol group, disulfide bonds [24] can be formed to alter the protein conformation, resulting in changes in protein function. These modifications are reversible and can be reversed by intracellular thioredoxin and glutathione [25].

The high affinity of HNO allows it to oxidize without changing the overall sulfhydryl redox state (e.g., the ratio of reduced glutathione to oxidized glutathione, GSH/GSSG) [26, 27] cardiomyocyte Ca^{2+} cycle-associated proteins or specific thiol groups on calcitonin (such as RyR2 and SERCA2a) to enhance systolic and diastolic function [26–30]. These effects persist with the presence of HNO. Tests such as Tocchetti [3] showed that a 6% increase in intracellular GSH inhibited 57% of sarcomer shortening caused by HNO. This suggests that HNO does not react with all sulfhydryl groups but has sulfhydryl selectivity [31], more specifically, negatively charged sulfhydryl or thiolate [31]. Studies have shown that cysteine-reactive sulfhydryl groups on calcium cycle-related proteins are important structures for redox reactions [26] and important groups involved in oxidative modification under physiological conditions. HNO promotes calcium release by increasing the Ca^{2+} channel opening probability as well as Ca^{2+} spark frequency of RyR2 and modulates SERCA2a/PLN (phosphoprotein) changes [30] to promote faster SR Ca^{2+} reabsorption, thereby improving systolic and diastolic function. These effects caused by HNO were significantly attenuated after the addition of the thiol reducing agent dithiothreitol [32], indicating that HNO targets the cysteine-active sulfhydryl groups on these channels. By identifying these specific

cysteine-modified subprotein structures, HNO induces changes and exerts biological effects. Although there is currently no way to detect whether HNO will be synthesized in organisms, the selective nucleophilic action of HNO suggests that it may be a signaling molecule in organisms [33].

HNO is a transient substance that is prone to dimerization to form secondary nitric acid (H2N2O2), which is subsequently decomposed into N_2O and H_2O [34]. Therefore, pharmacological studies often use its donors for testing. Classical HNO donors include Angeli's salt (AS, $Na_2N_2O_3$) [35], isopropylamine-NO (IPA-NO) [36], 1-nitrosocyclohexanoic acid (NCA) [37], and the like. However, they are all short-acting drugs, and they also produce other vasoactive substances when they are decomposed to produce HNO. In contrast, the new drug CXL-1020 is considered a pure HNO donor [2]. It decomposes in the body to produce HNO and CXL-1051. CXL-1051 has no biological activity and can be excreted through the kidneys. Its t1/2 is approximately 2 min and is therefore widely used in animal and clinical trials.

Anti-cardiac hypertrophy of HNO

Cardiomyocyte hypertrophy is the main pathological change in the early stage of HF. It is the initial compensatory response demonstrated when the factors such as myocardial cell injury and increased cardiac afterload stimulate the body to secrete angiotensin (Ang II), endothelin (ET1), and other cell hypertrophy-related factors in cardiomyocytes. Pathological hypertrophy of cardiomyocytes is not only closely related to the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase Nox2 subunit, peroxide production, and phosphorylation of mitogen-activated protein kinase (p38MAPK), but also intracellular phosphorylation of Akt kinase and its downstream glycogen synthase kinase-3β (GSK-3β), as well as phosphorylation of extracellular regulated protein kinase (ERK1/2) [38]. Continued progression of cardiac hypertrophy can lead to failure to meet the normal physiological needs of the body, resulting in decreased ventricular contraction and diastolic function, ultimately leading to heart failure [39]. Some current treatments, such as drugs that inhibit the renin-angiotensin system, can inhibit ventricular remodeling to a certain extent and prevent heart enlargement but cannot reverse cardiomyocyte hypertrophy [16]. The patient will eventually die from the enlarged heart. HNO can activate the cGMP system in the body, reduce the expression of p38 MAPK in the pre-cardiac hypertrophic signaling pathway, inhibit the expression of NADPH oxidase, and reduce the formation of peroxide [19], thereby exerting anti-cardiac hypertrophy.

The role of the cGMP system in the inhibition of cardiac hypertrophy by HNO

The cGMP system is a powerful anti-cardiac hypertrophy system in the heart. Various stimulation signals cause an increase in cGMP levels in the body to activate cGMP-dependent protein kinase (cGK-I), reduce reactive oxygen species production, and increase MAPK phosphatase-1 (MKP-1) activity. MKP-1 can dephosphorylate p38MAPK [40], thereby inhibiting cardiac hypertrophy caused by cell hypertrophy-related factors such as AngII and ET-1. Lin [19] and other experiments showed that HNO donor AS can inhibit the cardiac hypertrophy effect of isolated rat cardiomyocytes induced by AngII. When the sGC selective inhibitor H-[1,2,4]oxadiazol [4,3-A]quinoxalin-1-one (ODQ) was added, the anti-cardiac hypertrophy was significantly attenuated. This suggests that HNO exerts anti-cardiac hypertrophy by activating the sGC/cGMP system. Nitrate drugs, as NO donors, are thought to exert physiological effects by activating the cGMP pathway, but their anti-cardiac hypertrophy caused by depleted hearts is very limited [40]. First, NO can react rapidly with reactive oxygen species (ROS) to form a peroxynitro group, which attenuates the bioavailability of NO [40]. Secondly, long-term use of nitrate drugs can cause nitrate resistance. HNO has no unpaired electrons and is not easily removed by ROS. Even in the presence of ROS, it can exert physiological effects and does not cause drug resistance.

Activation of p38MAPK is a key site for a variety of neurohumoral factors mediating pathological cardiomyocyte hypertrophy [41, 42] and is the main cause of aggravation of myocardial lesions. Through the cGMP/cGK-I pathway, HNO can selectively inhibit AngII-induced phosphorylation of p38MAPK and exert anti-cardiac hypertrophy. When downstream cGK-I is present, MKP-1 immediately dephosphorylates p38MAPK [40–42], inhibiting cardiomyocyte hypertrophy. HNO can reduce the phosphorylation of p38MAPK by increasing MKP-1 activity and exert anti-cardiac hypertrophy [19]. In addition to causing p38MAPK activation, AngII also induces phosphorylation of threonine kinase (Akt) and ERK1/2. Akt can promote physiological hypertrophy and prevent apoptosis, and ERK1/2 has a similar effect in myocardial cell survival and physiological hypertrophy [41]. Although AngII and ET1 can significantly induce ERK1/2 activation in cardiomyocytes in vitro, activation of ERK1/2 in vivo does not lead to pathological hypertrophy of cardiomyocytes [43]. After HNO donor intervention, the phosphorylation levels of Akt and ERK1/2 increased, but the expression of myocardial cell volume and cardiac hypertrophy-related genes did not increase significantly. This may be because HNO has no significant effect on the effects of physiological hypertrophic signals such as Akt and ERK1/2.

HNO inhibition of the production of reactive oxygen species

NADPH oxidase is one of the main sources of ROS production in cardiomyocytes and is one of the important factors triggering cardiomyocyte hypertrophy [44]. In the depleted heart, Ca^{2+} is increased by mitochondria in the cytoplasm, and calcium overload in the mitochondria leads to oxidative phosphorylation of cells, which leads to increased ROS production [10]. In addition, when HF occurs, the expression of NADPH oxidase subunit Nox2 is up-regulated, which is also an important cause of increased reactive oxygen species [16]. HNO can selectively act on calcium cycle-related proteins such as phosphoprotein (PLN), SERCA2a, and RyR2 in cardiomyocytes, enhance Ca^{2+} release and reabsorption in cardiomyocytes, and reduce mitochondrial calcium overload. In addition, HNO can down-regulate the protein content of NADPH oxidase subunit Nox2 in cardiomyocytes, thereby reducing oxidative stress [19].

HNO inhibition of inflammatory response

The JAK-STAT (signal transducer and activator of transcription) signaling pathway is an important signaling pathway in the heart and plays an important role in cardiac inflammation and cardiomyocyte apoptosis [45]. The STAT protein is the most important functional segment in the SH2 domain and may be the site of action of HNO. Zgheib et al. [18] used HNO donors to intervene human microvascular endothelial cells (HMEC-1) and neonatal rat cardiomyocytes. They found that HNO inhibits leukemia inhibitory factor (LIF)-induced STAT3 activation and blocks the expression of downstream inflammation-related genes (such as intercellular adhesion molecule 1, CCAAT/enhancer binding protein δ, etc.). However, it has no significant effect on the catalytic activity of JAK but only slightly affects JAK-induced phosphorylation of LIF receptor. Therefore, the sulfhydryl group on JAK is not the target of HNO. When human recombinant STAT3 was treated with HNO, they found a significant decrease in free sulfhydryl groups and an increase in STAT3 dimers. Therefore, STAT3 is the main target of HNO action. HNO can oxidize sulfhydryl groups on STAT3, promote STAT3 dimer formation, inhibit JAK-catalyzed phosphorylation of STAT protein, and reduce genes such as proinflammatory cytokine intercellular adhesion factor (ICAM-1) and enhance the expression of CEBPD. It plays a role in inhibiting cardiac inflammatory response and anti-cardiomyocyte apoptosis in failing hearts.

Improvement of HNO on cardiac function

In a failing heart, a decrease in SERCA2 expression, phosphorylation of PLN, and leakage of Ca^{2+} in RyR2 can cause a decrease in Ca^{2+} storage, resulting in a decrease in Ca^{2+} in SR and an increase in Ca^{2+} in the cytoplasm, causing myocardial diastolic dysfunction. When the myocardium is depolarized, the release of Ca^{2+} from the cytoplasm is reduced, and the sensitivity of myofin to Ca^{2+} is reduced [46], which ultimately leads to a decrease in myocardial contractile function. HNO can selectively reversibly combine with sulfhydryl groups on PLN, SERCA2, and RyR2 to change its molecular structure, thereby regulating SERCA2/PLN changes, promoting SR reabsorption of Ca^{2+}, increasing Ca^{2+} storage in SR [47], reducing Ca^{2+} content in the cytoplasm during diastole, and promoting myocardial relaxation. During systole, it can increase RyR2 open frequency and Ca^{2+} spark, and enhance myocardial cell contractile function.

Under physiological conditions, the body triggers and activates the release of Ca^{2+} through the cAMP/PKA mechanism, resulting in contraction of the myofilament, increasing cardiac contractility, and causing relaxation by accelerating the uptake of Ca^{2+} by the sarcoplasmic reticulum. However, alteration of the cAMP/PKA signaling pathway may cause chronic ventricular remodeling and heart failure, and is ineffective for long-term treatment of heart failure. HNO can alter the redox state of SERCA2 and RyR2 independently of the cAMP/PKA pathway [26, 30], promote SR reabsorption and re-release of Ca^{2+} to increase calcium transients, and improve systolic and diastolic function [28–32]. HNO can increase SR Ca^{2+} release under the condition that the total amount of SR Ca^{2+} is constant by improving the function of RyR2 [30]. These effects are completely different from NO donors, beta receptor agonists, and caffeine.

PLN is a regulatory protein of SERCA2 that regulates the function of SERCA2 through phosphorylation. In intact cardiomyocytes, HNO forms a disulfide bond inside the PLN, stabilizes the PLN dimer structure, reduces the presence of PLN free monomers [48], and enhances SR to Ca^{2+} reabsorption [49]. Sivakumaran's [30] studies have shown that the function of HNO to increase myocardial contractility, calcium transients, SR reabsorption, and release of Ca^{2+} depends on PLN-regulated SERCA2 conformational changes. Replacing the three cysteines in the transmembrane domain of the PLN with an alanine residue eliminates the stimulatory effect of HNO. It can be seen that HNO can modify these residues of PLN to interact with SERCA2a, so PLN plays an important role in HNO in improving calcium circulation [49]. In the endoplasmic reticulum with normal PLN expression, HNO can increase its reabsorption capacity for Ca^{2+}; however, in the endoplasmic reticulum with missing PLN expression, it does not promote Ca^{2+} reabsorption. Using spectra to study the expression of SERCA2/PLN in insect cell microsomes,

the researchers found that HNO can only increase Ca^{2+} reabsorption through changes in SERCA2 conformation in the presence of PLN. Therefore, the presence of PLN is required for HNO to improve calcium circulation and enhance myocardial contractility [30].

The mechanism by which HNO improves cardiac function has no significant relationship with the phosphorylation of various excitatory contraction-coupled proteins (such as RyR2, PLN) [3]. First, blocking the PKG and PKA pathways had no significant effect on HNO-induced myocardial contraction [3]. Second, HNO does not alter the content of cAMP [3, 38]. Third, the addition of sulfhydryl-removing substances (substances that can react with sulfhydryl groups) can rapidly attenuate the effects caused by HNO [32]. These phenomena are not observed if it is primarily related to the phosphorylation mechanism. Fourth, in the study of HNO intervention of recombinant RyR2 membranes against phosphokinase-induced phosphorylation, the researchers obtained the same results as calcium sparks in intact cells [30]. Finally, HNO enhances cardiomyocyte contractile response that is independent of the β-adrenergic receptor effect and cannot be inhibited by beta blockers [3].

HNO induces a disulfide bond between actin-tropin and myosin heavy chain and increases the sensitivity of myosin light chain myofin Ca^{2+} [37]. When directly acting on free myocardium, HNO can enhance the sensitivity of myofilament to Ca^{2+} and increase myocardial contractility than whole-cell calcium transients, indicating that HNO can also act as a Ca^{2+} sensitizer. Altering the redox conditions in the cells and adding dithiothreitol can attenuate the positive inotropic effect of HNO, which also demonstrates the theory that HNO targets thiol groups [50].

Previous studies have shown that HNO interacts with sulfhydryl groups independently of the cAMP/PKA, cGMP/PKG signaling pathways [3, 16], increasing the activity of intracellular Ca^{2+}-related proteins and improving cardiac function. Therefore, the researchers proposed the idea that HNO exerts a cardiac effect through a cGMP-independent pathway. This conclusion was mainly due to the lack of techniques for detecting trace changes in cGMP in vivo and the lack of sensitive ODQ [3]. Moreover, previous researchers have studied the role of cGMP in the improvement of systolic and diastolic effects in HNO donors by isolating cardiomyocytes rather than intact hearts, using a HNO donor concentration (1 mmol/L) far exceeding the concentration of ODQ (10 μm/L). Recent studies have shown that HNO may improve systolic and diastolic function of intact heart LV through the sGC/cGMP pathway [20]. Jennifer et al. [16] found that HNO donor isopropylamine-NO (IPA-NO) increased sGC activity by a factor of three and increased cGMP in cardiomyocytes by a factor of 3.5. When the sGC selective inhibitor ODQ was used, the dose-response curve of HNO-induced systolic and diastolic effects was significantly shifted down but did not completely disappear. Therefore, HNO may partially improve LV contraction and diastolic function through the sGC/cGMP signaling pathway [20].

Early studies have found that HNO improves cardiac function accompanied by an increase in calcitonin-related gene peptide (CGRP) and suggests a role that CGRP may play in the role of HNO in cardioprotection, at least in part to its mechanism [22]. However, no significant cardiac function changes were observed after intervention with the CGRP receptor antagonist CGRP8-37. Later studies [51] confirmed that this effect is a sympathetic stimulatory effect that can be inhibited by beta blockers rather than by CGRP. Compared with HNO, CGRP itself relies on positive muscle strength and relaxation effects mediated by cAMP/PKA/L-type calcium channel signaling, which are dependent on β-adrenergic signaling, whereas the mechanism of action of HNO is independent of β-adrenergic receptors. Therefore, HNO does not improve systolic and diastolic effects through CGRP [51].

Vasodilator effect of HNO

Zhu et al. [5] used HNO donor CXL-1020 to intervene in rat blood vessels, isolated aorta, and mesenteric vessels; all of which showed different vasodilator effects. After the addition of the sGC inhibitor ODQ, the vasodilating effect was significantly attenuated [52] and even disappeared. However, ODQ can not only oxidize the heme in sGC to inhibit its function but also modify other heme-containing proteins such as hemoglobin, nitric oxide synthase, and cytochrome p-450, all of which can affect vasodilation effect. Subsequently, they used gene knockout technology to remove the rat sGC-β subunit (sGCKO), which led to the complete loss of sGC, and then intervened with HNO donors again. This time, it did not show vasodilation. Therefore, HNO exerts a vasodilating effect in vivo through the sGC-dependent pathway [5].

Studies have shown that under certain conditions (such as in the absence of oxygen), NO can be produced when the concentration of HNO donor AS is higher than 10 μmol/L. It may be the oxidation of HNO to NO by intracellular or extracellular Cu^{2+} or Cu^{2+}-containing enzymes [53, 54]. However, experiments by Lin et al. [19] have shown that HNO does not oxidize extracellularly, and no NO is detected even under 30 μmol/L. In addition, the vasodilation effect caused by HNO can be significantly attenuated (about five times) by the selective HNO inhibitor L-cysteine [52] but is completely unaffected by NO inhibitors. Therefore, the vasodilator effect of HNO is not related to NO but exerts a vasodilating effect through a thiol interaction with cysteine activity on the blood vessels [52].

Under physiological conditions, activation of potassium channels (including voltage-dependent potassium channel Kv and inward rectifier potassium channel K-ATP) plays an

important role in vasodilation. Previously, it was suggested that HNO donor AS mediates mesenteric vasodilation through Kv channels to some extent [55]. Andrews [52] et al. used a voltage-dependent potassium channel Kv inhibitor 4-AP to inhibit AS-induced brachial artery dilation, but Chin [20] et al. did not have significant AS-induced vasodilation effects with 4-AP. This may be due to the difference in the distribution of K^+ channel subtypes at different sites. Although the K^+-ATP channel may play a role in the function of AS in vasodilation [56], there is currently no way to verify this conclusion. Therefore, the role of K^+ channel activation in HNO-mediated vasodilation remains to be further studied.

HNO donor AS has a strong cardiovascular effect. Even at relatively low doses (e.g., from 10 nmol/L), this effect is evident, and it increases vasodilation with increasing dose [3]. However, when 1 μmol/L was reached, the vasodilation effect ceased, and the increased left ventricular systolic and diastolic function induced by AS increased with increasing HNO dose [3]. Previous reports have shown that the vasodilator effect of AS at relatively low concentrations (e.g., 0.1 μmol/L) is more pronounced than the high concentration required for cardiomyocyte contraction (e.g., 500 μmol/L) [3, 56], which is possibly because AS exerts vasodilatation at low concentrations and exhibits myocardial contraction at higher concentrations.

Clinical study of HNO

Sabbah [2] et al. first performed hemodynamic assessment before cardiac transplantation or clinical I-II trial of HNO in patients requiring hemodynamic testing in HF decompensation. They selected patients with a cardiac index ≤ 2.5 L/min and an average pulmonary capillary wedge pressure > 20 mmHg. The HNO donor CXL-1020 was given an intravenous dose of 1–20 μg/kg min for 6 h and a placebo control group was established. Finally, experiments have shown that CXL-1020 can reduce end-diastolic pressure without changing heart rate, appropriately reduce peripheral vascular resistance, increase cardiac output, and improve cardiac function. These effects are consistent with previous animal experiments [20, 50]. At the same time, clinical studies have also found that a dose of 10–20 μg/kg min is safe for hemodynamic stability [2].

Outlook

HNO can play a role in inhibiting cardiac hypertrophy, enhancing myocardial contractility, and improving hemodynamics during the development of HF. It protects the failing heart. Studying these biological effects of HNO can provide a theoretical basis for the clinical treatment of HF and bring new ideas for the development of new drugs for HF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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