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REVIEW

Controlled Delivery of Gasotransmitters for Cardiovascular Therapy: Molecular Mechanisms, Engineered Platforms, and Translational Perspectives

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Abstract: Gasotransmitters, including nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) exert broad cardioprotective effects by regulating vascular function, inflammatory signaling, oxidative stress, mitochondrial homeostasis, and myocardial remodeling. However, their short half-lives, rapid diffusion, and narrow therapeutic windows limit their clinical translation, making controlled delivery a central challenge for gas-based cardiovascular therapy. This review integrates recent mechanistic insights with advances in delivery engineering to provide a delivery-centric synthesis that links gasotransmitter biology, delivery strategies, and cardiovascular disease applications. We summarize the regulatory roles of NO, CO, and H_2S in cardiovascular pathophysiology and critically evaluate three delivery strategies designed to address the distinct and competing requirements of gas therapy. Localized in situ platforms improve lesion retention and reduce systemic exposure, systemic nanocarriers enhance donor stability and myocardial accumulation through passive or active targeting, and stimuli-responsive systems enable trigger-regulated gas release in response to pathological cues or external stimuli. Despite these advances, major translational barriers remain, including long-term biosafety, scalable manufacturing, complex pharmacokinetic behavior, and regulatory uncertainty. By integrating disease-stage requirements, release kinetics, myocardial or vascular specificity, and clinical feasibility, this review provides a delivery-centered framework for the rational design and translation of next-generation gasotransmitter therapies for cardiovascular diseases.

Keywords: gasotransmitters, molecular mechanisms, controlled release, localized delivery, systemic delivery, stimuli-responsive delivery, cardiovascular therapy

Introduction

Cardiovascular diseases remain the leading cause of global mortality and continue to impose a substantial burden on the healthcare system.[1] Despite considerable advances in revascularization, pharmacotherapy, interventional procedures, and regenerative medicine, current therapeutic strategies remain insufficient to precisely regulate the local myocardial and vascular microenvironment.[2] Most established interventions focus primarily on restoring blood flow, and maintaining cardiovascular function. However, their capacity to promote myocardial repair, stabilize local hemodynamics, and modulate specific pathological pathways remains limited. In particular, sustained inflammation, oxidative stress, endothelial dysfunction, impaired tissue repair, and adverse cardiac remodeling are often incompletely controlled.[3] These challenges highlight the need for complementary therapeutic strategies capable of targeting the cardiovascular lesion microenvironment with defined mechanisms, high specificity, and controllable therapeutic activity.[4]

Gasotransmitters have attracted increasing attention as endogenous signaling molecules with considerable therapeutic potential in cardiovascular diseases. The NO, CO, and H_2S can freely traverse biological membranes and regulate a wide range of physiological and pathological cardiovascular processes, including vascular tone, inflammatory signaling, oxidative stress, mitochondrial homeostasis, angiogenesis, cardiomyocyte survival, and myocardial remodeling.[5,6] Unlike conventional therapeutics that usually target discrete receptors or pathways, gasotransmitter-based strategies act

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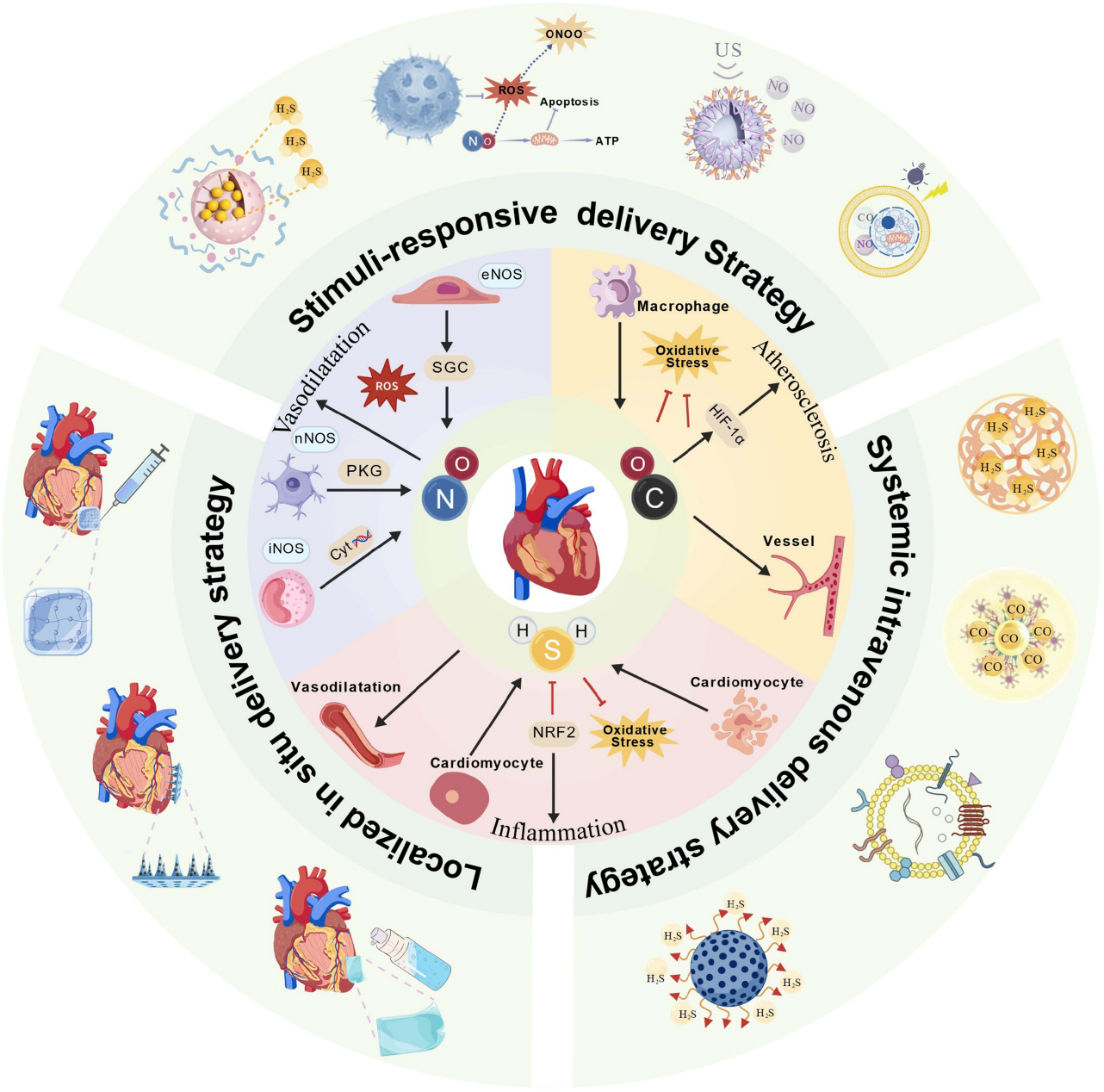
Graphical Abstract



through endogenous signaling networks and can simultaneously modulate multiple cell types and pathological events within the cardiovascular microenvironment. This multitarget regulatory capacity makes gaseous mediators attractive candidates for cardiovascular therapy, particularly in complex diseases such as myocardial ischemia-reperfusion injury, myocardial infarction, heart failure, and atherosclerosis.[7,8]

Despite these therapeutic advantages, gasotransmitters with inherent physicochemical limitations, such as short half-lives, poor in vivo stability, high diffusivity, and narrow therapeutic windows, severely restrict their clinical translation.[9,10] These limitations make it difficult to maintain therapeutic gas concentrations at diseased sites while avoiding systemic toxicity or off-target effects. This challenge is particularly enhanced in the heart, which is characterized by continuous

mechanical motion, high perfusion, pronounced redox heterogeneity, and disease-stage-dependent therapeutic requirements.[11,12] Therefore, effective cardiovascular gas therapy requires delivery systems that can coordinate gas release with both the spatial features of lesions and the temporal dynamics of disease progression.

Clinically, inhaled NO has been approved for the treatment of neonatal pulmonary hypertension and is widely used in perioperative cardiac and intensive care settings, demonstrating that gas-based therapies can achieve established clinical utility under specific indications.[13,14] However, gasotransmitter-based therapeutics still face several critical translational challenges, including precise dose control, potential off-target effects and safety concerns related to long-term exposure. In addition, regulatory complexity and the difficulty in standardizing delivery systems further limit their broader clinical adoption. These limitations have stimulated the development of advanced gas-delivery platforms based on materials science, nanoengineering, and biomedical technologies. Representative strategies include localized in situ delivery systems, systemic nanocarriers, and stimuli-responsive platforms, each designed to improve gas stability, tissue retention, controlled release, and therapeutic safety.

Although these delivery platforms have substantially expanded the therapeutic potential of gasotransmitters, several challenges remain before these approaches can be translated into clinical applications.[15] For local delivery systems such as hydrogels, microneedles, and spray-adhesive platforms, issues including limited delivery uniformity, insufficient coverage of large pathological regions, and potential long-term tissue reactions may restrict therapeutic efficacy.[16–18] Systemic intravenous delivery strategies, including passive and active targeting approaches, face challenges associated with rapid clearance, limited targeting efficiency, and significant interpatient variability in biodistribution.[19,20] Stimuli-responsive systems, while enabling precise spatiotemporal control of gas release, often rely on complex designs and external triggering devices, which may complicate reproducibility and clinical implementation.[21] Across all strategies, scalable manufacturing, long-term biosafety, storage stability, pharmacokinetic characterization, regulatory classification, and integration into clinical workflows remain insufficiently addressed. In this review, we integrate the molecular mechanisms of NO, CO, and H_2S with recent advances in delivery engineering to establish a delivery-centered framework for cardiovascular gas therapy. This review focuses on the key biological roles of NO, CO, and H_2S in the regulation of vascular function, inflammatory responses, oxidative stress, mitochondrial homeostasis, and myocardial remodeling. Furthermore, this review critically evaluates localized in situ delivery, systemic intravenous administration, and stimuli-responsive delivery platforms. Particular attention is devoted to release controllability, cardiac targeting efficiency, biosafety, and translational feasibility. By linking gasotransmitter biology with delivery-system design, this review aims to provide practical guidance for the rational development and future translation of next-generation gasotransmitter therapies for cardiovascular diseases.

Mechanisms of Gasotransmitters in Cardiac Disease Therapy

Gaseous signaling molecules represent a critical class of endogenous regulators within the cardiovascular system that play an essential role in maintaining cardiac homeostasis and driving adaptive responses to stress-induced injury. Unlike conventional small-molecule drugs or protein mediators, NO, CO, and H_2S exhibit distinctive physicochemical properties, including low molecular weight, high membrane permeability, and diffusion-dependent signaling, which allow them to freely diffuse across biological membranes. These features allow them to rapidly and broadly influence vascular endothelial cells, cardiomyocytes, immune cells, and smooth muscle cells, thereby contributing to the precise regulation of cardiovascular pathophysiological processes.

Accumulating evidence has demonstrated that NO, CO, and H_2S exert multilevel cardioprotective effects in myocardial ischemia-reperfusion injury, acute myocardial infarction, heart failure, atherosclerosis, and inflammatory cardiomyopathies.[22] These beneficial effects are primarily mediated through modulation of vascular function, inflammatory signaling, oxidative stress, mitochondrial metabolism, and cell fate regulation. This section systematically reviews the molecular mechanisms of NO, CO, and H_2S in different cardiac diseases and provides a robust theoretical basis for their development as potential therapeutic targets (Figure 1).

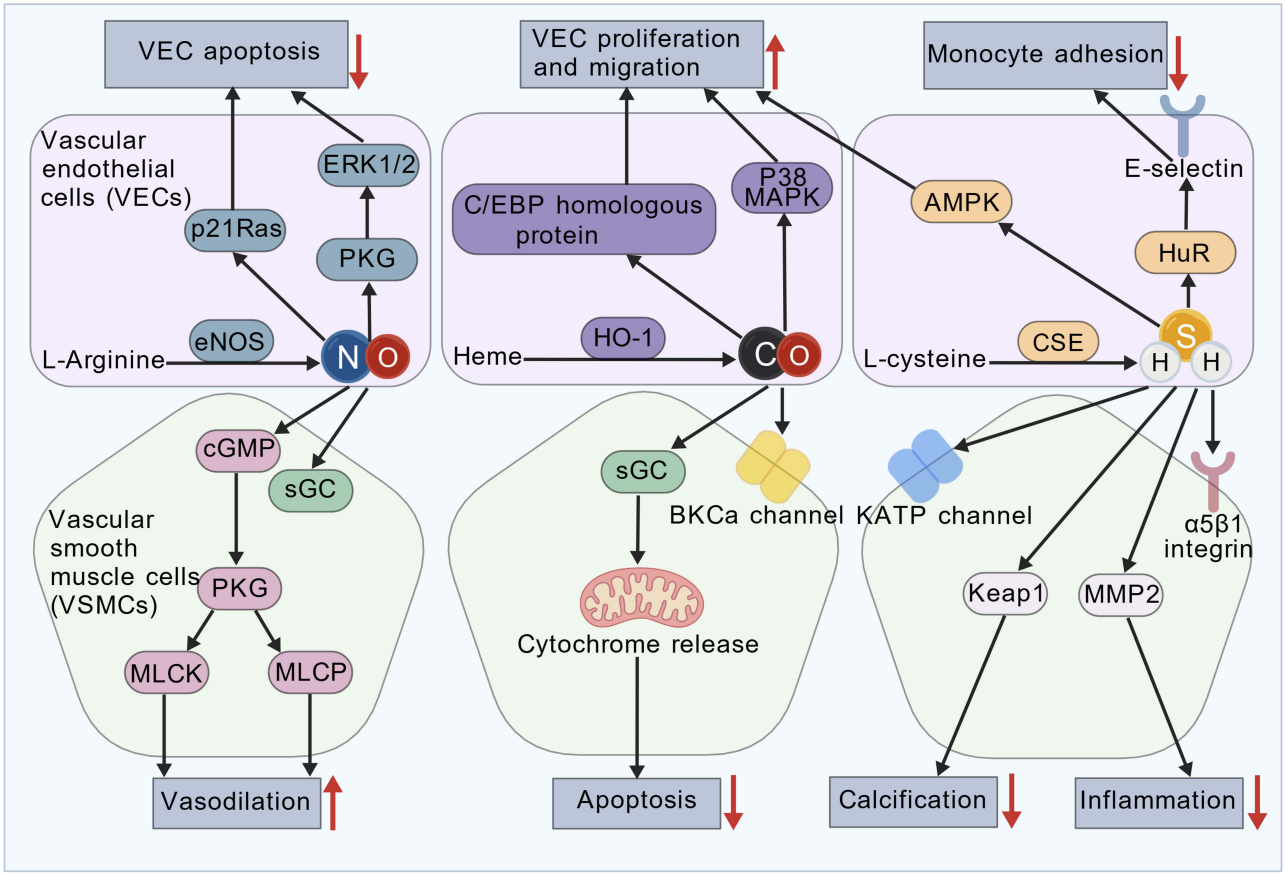


Figure 1 Schematic illustration of the regulatory roles of gasotransmitters in vascular function and atherosclerosis.
Notes: Arrows indicate the direction of signaling or functional regulation: black arrows represent activation or production in the signaling cascade; red upward arrows denote promotion or enhancement of biological processes; red downward arrows denote inhibition or reduction of biological processes.
Abbreviations: cGMP, cyclic guanosine monophosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; p21Ras, p21 Ras GTPase; ERK1/2, extracellular signal-regulated kinases 1/2; HO-1, heme oxygenase-1; CHOP, CCAAT/enhancer-binding protein homologous protein; p38 MAPK, p38 mitogen-activated protein kinase; BKCa channel, large-conductance Ca2+-activated K^+ channel; CSE, cystathionine γ-lyase; HuR, human antigen R; E-selectin, endothelial selectin; KATP channel, ATP-sensitive K^+ channel; Keap1, kelch-like ECH-associated protein 1; MMP2, matrix metalloproteinase-2; α5β1 integrin, α5β1 integrin receptor.

Nitric Oxide (NO)

NO is the first gaseous signaling molecule to be systematically elucidated with a defined physiological function. It plays a central role in maintaining vascular homeostasis and regulating myocardial function.[23,24] Endogenous NO is primarily generated by the nitric oxide synthase (NOS) family, including endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) isoforms,[25] which catalyze the conversion of L-arginine into L-citrulline using NADPH and tetrahydrobiopterin (BH_4) as cofactors.[26] Under ischemic or hypoxic conditions, the NOS-independent nitrite-nitrate-NO reduction pathway is activated to serve as a crucial compensatory mechanism for maintaining local NO bioavailability.[27]

Under physiological conditions, eNOS-derived NO is the key regulator of vascular tone and endothelial function.[28] Mechanistically, NO activates soluble guanylate cyclase (sGC), leading to increased cyclic guanosine monophosphate (cGMP) production and the subsequent activation of protein kinase G (PKG) (Figure 2A).[29,30] This signaling cascade induces vascular smooth muscle relaxation, reduces peripheral resistance, and enhances coronary perfusion.[31] In pathological conditions, such as myocardial ischemia, angina pectoris, and acute myocardial infarction, reduced endothelial NO bioavailability is recognized as a primary driver of vascular dysfunction. Restoration of NO signaling has been shown to significantly improve perfusion and alleviate myocardial workload.[32,33]

In addition to its role in vascular regulation, NO plays a critical role in modulating cardiac inflammation.[34] At physiological concentrations, NO inhibits the activation of the NF-κB signaling pathway, thereby suppressing the expression of pro-inflammatory cytokines, including TNF-α and IL-6.[35] Furthermore, NO attenuates the upregulation of adhesion

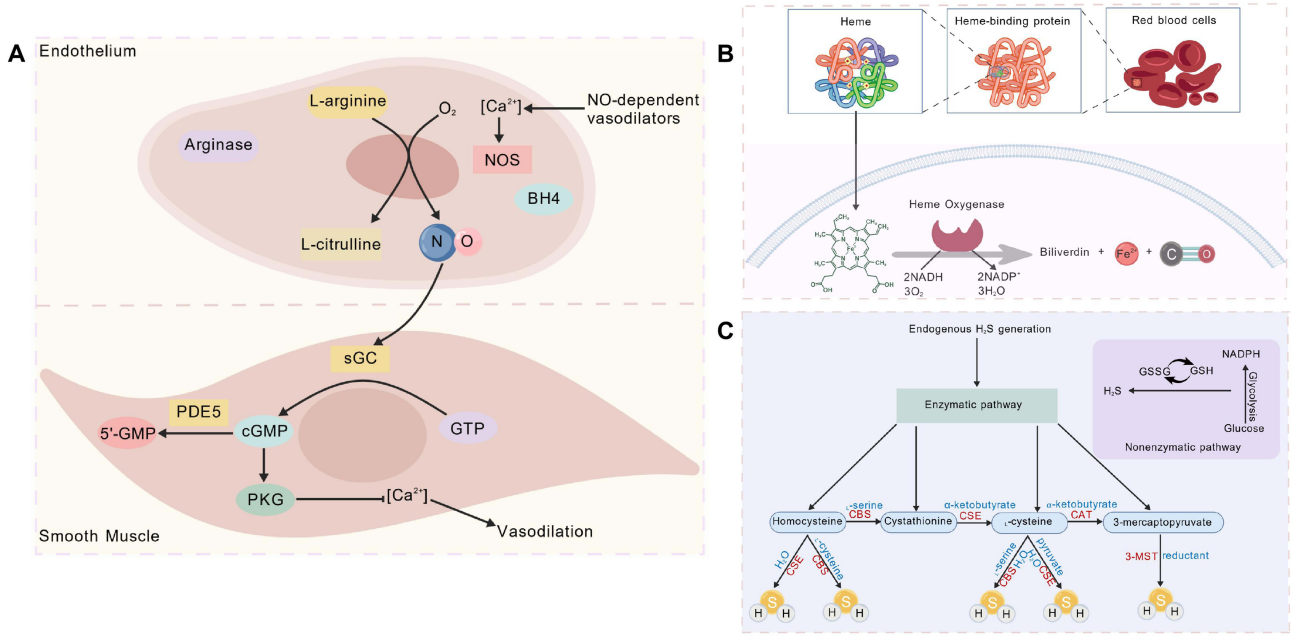


Figure 2 Schematic illustration of the endogenous biosynthesis and vascular signaling mechanisms of gasotransmitters (NO, CO, and H_2S). (**A**) NO production and signaling in endothelial cells: L-arginine is converted to NO by NOS in the presence of oxygen and the cofactor BH4. NO diffuses into adjacent smooth muscle cells and activates sGC, leading to cGMP generation, PKG activation, reduced intracellular Ca^{2+} levels, and subsequent vasodilation. (**B**) Endogenous CO generation: Heme is degraded by HO to produce biliverdin, Fe^{2+}, and CO. (**C**) Endogenous H_2S generation pathways: H_2S is produced through enzymatic pathways involving CBS, CSE, and 3-MST, as well as through non-enzymatic reactions dependent on NADPH.

Notes: Black arrows indicate catalytic reactions, molecular production, or signaling activation; the double arrow denotes a reversible redox cycle.

Abbreviations: NOS, nitric oxide synthase; BH4, tetrahydrobiopterin; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase 5; 5'-GMP, 5'-guanosine monophosphate; CBS, cystathionine β-synthase; CAT, cysteine aminotransferase; 3-MST, 3-mercaptopyruvate sulfurtransferase; GSSG, oxidized glutathione; GSH, reduced glutathione.

molecules, such as ICAM-1 and VCAM-1, effectively limiting the recruitment and infiltration of inflammatory cells into myocardial tissue.[36] In addition, NO influences macrophage polarization by promoting the transition from a pro-inflammatory M1 phenotype to a reparative M2 phenotype, thereby facilitating tissue repair and post-injury remodeling.[37,38]

Moreover, NO contributes to cardioprotection through context-dependent regulation of oxidative stress and mitochondrial function. On the one hand, it can directly scavenge ROS and enhance endogenous antioxidant defenses by upregulating enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT).[39] On the other hand, during ischemia-reperfusion injury, appropriate levels of NO reduce electron leakage from complex I of the electron transport chain and inhibit pathological opening of the mitochondrial permeability transition pore (mPTP), thereby preserving mitochondrial structural integrity and maintaining ATP production.[40]

In addition, NO directly regulates cardiomyocyte survival by activating the PI3K/Akt signaling pathway,[41] increasing the Bcl-2/Bax ratio, and suppressing the activation of caspase-3 and caspase-9, which collectively attenuates apoptosis.[42] Furthermore, NO mitigates calcium overload-induced mitochondrial dysfunction by maintaining intracellular calcium homeostasis.[43] Notably, NO exhibits potent pro-angiogenic activity by promoting endothelial cell migration and lumen formation through the upregulation of VEGF and FGF2.[44] These pro-angiogenic effects are crucial for improving local microcirculation during post-infarction cardiac remodeling.

The biological effects of NO are highly concentration-dependent, and its therapeutic activity is governed by a narrow spatiotemporal window.[45,46] Physiological NO concentrations generated by constitutive NOS isoforms (eNOS and nNOS) are typically maintained at low nanomolar levels and are sufficient to regulate vascular tone, endothelial homeostasis, and cytoprotective signaling.[47,48] Moderate increases in NO bioavailability, generally within the nanomolar to low micromolar range, have been associated with enhanced angiogenesis, attenuation of inflammation, and improved tissue perfusion in ischemic myocardium.[49] However, excessive NO production, particularly under pathological conditions involving iNOS overactivation, may elevate local NO concentrations to high micromolar levels. Such conditions

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favor rapid reactions with superoxide anions, resulting in excessive peroxynitrite generation and nitrosative stress, ultimately causing mitochondrial dysfunction, lipid peroxidation, and cardiomyocyte apoptosis.[50,51] Therefore, maintaining NO within an appropriate therapeutic window remains a key challenge for gas-delivery strategies designed for cardiovascular applications.

In summary, NO exerts fundamental cardioprotective effects by regulating vasodilation, suppressing inflammation, alleviating oxidative stress, preserving mitochondrial function, and promoting angiogenesis.[52,53] However, its biological efficacy is highly context-dependent and critically influenced by its cellular source, local concentration, and the surrounding redox microenvironment. Under severe pathological conditions, the rapid reaction between NO and superoxide anions generates peroxynitrite, a highly reactive species that exacerbates mitochondrial injury and induces apoptosis in cardiomyocytes.[54] In addition, the short half-life, rapid diffusion, and narrow therapeutic window of NO continue to limit the maintenance of stable and localized bioactivity in diseased cardiac tissues.

Carbon Monoxide (CO)

CO is an endogenous gaseous signaling molecule that has attracted increasing attention in cardiovascular research in recent years.[55] Although traditionally regarded as a toxic metabolic byproduct, physiological concentrations of CO play a critical role in maintaining cardiac homeostasis and mitigating pathological stress by modulating multiple intracellular signaling pathways.[56] Endogenous CO is primarily generated during heme degradation, a process catalyzed by heme oxygenase (HO). This NADPH- and O_2- dependent reaction produces CO, Fe^{2+}, and biliverdin, the latter of which is subsequently converted into bilirubin with potent antioxidant activity (Figure 2B).[57,58] Among the HO isoforms, inducible HO-1 is markedly upregulated in response to oxidative stress, inflammation, and ischemia, and serves as a key component of the endogenous cytoprotective system of the heart.[58,59]

CO exhibits pronounced immunomodulatory and anti-inflammatory effects in the cardiovascular system.[60] It suppresses the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, and MCP-1, primarily through inhibition of TLR4-mediated signaling and NF-κB activation.[61] As a result, inflammatory responses in myocardial tissues are effectively attenuated. In addition, CO promotes macrophage polarization toward the M2 phenotype, thereby enhancing anti-inflammatory signaling and tissue repair. These effects have consistently been observed in experimental models of myocardial infarction and ischemia/reperfusion injury.[62]

The regulation of oxidative stress represents another major cardioprotective mechanism of CO.[63] It activates intracellular antioxidant transcriptional pathways by facilitating the dissociation of Nrf2 from its inhibitor, Keap1, and promoting its nuclear translocation. This process induces the expression of downstream antioxidant genes including HO-1, NAD(P)H quinone dehydrogenase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), and ferritin.[64] Through these mechanisms, CO effectively enhances ROS scavenging capacity, attenuates ROS burst, reduces lipid peroxidation and DNA damage, and limits myocardial necrosis in acute ischemia-reperfusion injury.[65]

Mitochondria are central targets of CO-mediated cardioprotection.[66] At low concentrations, CO may interact with mitochondrial cytochrome c oxidase, resulting in a mild and transient modulation of mitochondrial respiration. This controlled inhibition triggers adaptive stress responses and activates cytoprotective signaling pathways, thereby increasing cardiomyocyte tolerance to ischemia and oxidative stress.[67] Moreover, CO suppresses mitochondrial calcium overload, limits mPTP opening, and preserves ATP production efficiency, ultimately reducing energy metabolism-related myocardial injuries.[68]

In cardiomyocytes, CO exerts strong anti-apoptotic effects.[69] It upregulates antiapoptotic Bcl-2 expression, suppresses proapoptotic Bax expression, and inhibits caspase-3 activation. Simultaneously, CO enhances cell survival under hypoxic conditions by stabilizing HIF-1α and promoting reparative responses in ischemic myocardium.[70,71] In addition, CO induces vasodilation in vascular smooth muscle cells, partly through the activation of large-conductance calcium-activated potassium (BK-Ca) channels, thereby improving coronary perfusion and reducing cardiac afterload.

Despite these beneficial effects, the therapeutic utility of CO is strongly constrained by its narrow therapeutic window.[72] Experimental studies suggest that low-dose CO exposure (typically 50–250 ppm inhaled CO or corresponding low carboxyhemoglobin (COHb) levels below approximately 10%) can activate cytoprotective signaling pathways without inducing overt toxicity.[59,73] In contrast, excessive CO exposure markedly increases COHb formation and impairs

oxygen delivery owing to the high affinity of CO for hemoglobin and myoglobin. Clinical manifestations of toxicity become increasingly apparent when COHb levels exceed approximately 15–20%, while severe poisoning and cardiovascular complications are frequently associated with COHb levels above 20–25%.[74,75] Moreover, patients with underlying cardiovascular disease may exhibit myocardial ischemia and arrhythmias even at lower COHb levels (approximately 2–6%).[76,77] Therefore, maintaining CO within a precise therapeutic range is essential, providing a strong rationale for the development of controlled and localized CO delivery systems for cardiovascular applications.

In summary, CO exerts substantial endogenous cardioprotective effects via the heme oxygenase pathway.[78] Its anti-inflammatory, antioxidant, anti-apoptotic, and mitochondrial-regulatory functions have been extensively validated in diverse cardiac disease models.[79] Compared with NO, CO displays a more moderate and sustained modulation of mitochondrial stress responses and cellular adaptation.[60] Nevertheless, its biological activity remains constrained by a narrow therapeutic window and dose-dependent toxicity, which complicate the maintenance of effective and safe concentrations in cardiac tissues. In addition, the precise regulation of CO bioavailability and spatial distribution remains challenging, limiting its therapeutic application in cardiovascular diseases.

Hydrogen Sulphide (H_2S)

H_2S is now widely regarded as the third endogenous gaseous signaling molecule, alongside NO and CO, with increasingly well-defined roles in cardiovascular physiology and pathology.[80] Endogenous H_2S is generated through three enzymatic pathways: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfotransferase (MST) (Figure 2C)[81] Among these enzymes, CSE is the predominant H_2S-producing enzyme in cardiovascular tissues, and is the primary source of cardiac H_2S.[82,83] At physiological concentrations, H_2S contributes to vasodilation, anti-inflammatory responses, antioxidant defenses, and energy metabolic homeostasis through coordinated modulation of multiple signaling pathways.[84,85]

H_2S markedly suppresses the activation of NF-κB and MAPK pathways, including ERK, p38, and JNK. This inhibition reduces the expression of pro-inflammatory cytokines and adhesion molecules, thereby limiting inflammatory cell recruitment and infiltration into myocardial tissue.[86] Beyond this, H_2S modulates immune responses by promoting macrophage polarization toward an anti-inflammatory M2 phenotype. This process effectively attenuates both local and systemic inflammatory responses in experimental models of myocardial infarction and atherosclerosis.[87]

H_2S also exhibits potent antioxidant activity.[88] It directly scavenges ROS, including $\cdot HO$, O^{2-}, and H_2O_2, while simultaneously strengthening cellular redox homeostasis. This is achieved through enhanced glutathione (GSH) biosynthesis and upregulation of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX).[89,90] A defining molecular feature of H_2S signaling is protein S-sulfhydration, a post-translational modification that regulates multiple signaling proteins and metabolic enzymes, thereby enhancing cellular antioxidant capacity and stress resistance.[91,92]

Mitochondria have emerged as preferential targets for H_2S-mediated cardioprotection, particularly under conditions of metabolic and ischemic stress.[93] H_2S preserves the mitochondrial membrane potential, regulates electron transport chain activity, and reduces electron leakage and excessive ROS production.[94,95] In addition, it suppresses abnormal opening of the mPTP to stabilize ATP generation.[96,97] In ischemia-reperfusion (IR) injury models, H_2S alleviates cardiomyocyte damage by improving mitochondrial energy metabolism and attenuating calcium overload. Notably, at moderate concentrations, H_2S also promotes mitochondrial biogenesis, suggesting a role not only in acute protection, but also in long-term metabolic adaptation of stressed cardiomyocytes.[98]

H_2S functions as a potent regulator of tone and perfusion by activating ATP-sensitive potassium channels in vascular smooth muscle cells.[99,100] The resulting membrane hyperpolarization reduces vascular resistance and improves myocardial perfusion, effects that have been demonstrated in experimental studies of hypertension and ischemic heart disease.[101,102] In addition, H_2S promotes autophagy by activating AMP-activated protein kinase and inhibiting the mTOR signaling pathway. This process facilitates the removal of damaged mitochondria and misfolded proteins, and contributes to cellular homeostasis.[103] Its anti-apoptotic effects are associated with an increased Bcl-2/Bax ratio, reduced caspase-3 activation, and upregulation of stress repair-related proteins, further consolidating its protective profile.

The biological actions of H_2S are highly concentration-dependent, and its therapeutic utility is constrained by a relatively narrow effective window.[104,105] Physiological circulating H_2S concentrations are generally reported within the nanomolar to low micromolar range, whereas low exogenous H_2S concentrations (typically within the range of approximately 10–100 μM in experimental studies) have been shown to exert cardioprotective effects through modulation of inflammation, oxidative stress, and mitochondrial function.[106,107] However, excessive H_2S exposure may result in mitochondrial dysfunction because H_2S acts as a potent inhibitor of cytochrome c oxidase at high concentrations, thereby impairing oxidative phosphorylation and ATP generation.[108,109] Concentrations exceeding several hundred micromolar have been associated with cytotoxic effects, including impaired cellular respiration, oxidative injury, and apoptosis.[110,111] Furthermore, because H_2S exhibits rapid metabolism and diffusion, maintaining local concentrations within a therapeutically beneficial range remains challenging. Therefore, precise spatiotemporal control of H_2S release has become an important consideration for cardiovascular therapeutic applications.

Collectively, H_2S has emerged as an important endogenous gaseous signaling molecule with diverse cardioprotective properties, including anti-inflammatory, antioxidant, vasodilatory, and mitochondrial protective effects.[101,112] By regulating inflammatory signaling, alleviating oxidative stress, and preserving mitochondrial energy homeostasis, H_2S shows significant therapeutic potential in diverse cardiac diseases.[113] Notably, protein S-sulfhydration provides a unique regulatory mechanism underlying H_2S signaling and new insights into its biological actions.[92] Nevertheless, the biological effects of H_2S remain highly dependent on its local concentration, release kinetics, and pathological context. In addition, the rapid metabolism and difficulties in maintaining sustained and localized H_2S bioavailability continue to limit its therapeutic application in cardiovascular diseases.

Taken together, NO, CO, and H_2S represent three key endogenous gaseous signaling molecules that exert substantial cardioprotective effects through multi-target and multi-pathway regulation. By convergently regulating inflammatory responses, oxidative stress, mitochondrial homeostasis, vascular function, autophagy, and cell fate decisions, these mediators form an essential endogenous defense network against stress-induced injury in the cardiovascular system. Despite differences in their biosynthetic pathways and signaling mechanisms, these gasotransmitters contribute through distinct biological functions to maintaining cardiovascular homeostasis and regulating disease progression. A comprehensive understanding of their mechanisms in cardiac diseases not only deepens the understanding of disease pathogenesis but also provides a solid theoretical basis for the development of more precise and safer therapeutic strategies.

Localized in situ Delivery Strategies to Enhance Myocardial Retention

In gas signaling molecule-based therapies for cardiac diseases, rational design of delivery strategies is a critical determinant of both therapeutic efficacy and safety. Gaseous mediators, including NO, CO, and H_2S, are characterized by their ultrashort half-lives, high diffusivity, and strict endogenous homeostatic regulation, which collectively impose substantial barriers to precise spatiotemporal control in vivo. Consequently, achieving effective accumulation and controlled release at cardiac lesion sites remains a major translational challenge. In recent years, a variety of delivery strategies integrating different administration routes with advanced material platforms have been developed for gasotransmitter therapy.[114,115] Based on the administration modes reported in previous studies, these approaches can generally be categorized into localized in situ delivery and systemic intravenous delivery. Localized in situ delivery is designed to maximize local bioavailability and prolong therapeutic exposure within the diseased myocardium, thereby minimizing the off-target effects. Previous studies have investigated stimuli-responsive delivery systems that exploit pathological signals within the cardiac microenvironment for regulated gas release.[116,117] Such systems may improve lesion specificity and spatiotemporal control of therapeutic delivery.

Localized in situ delivery strategies provide an effective means to overcome the intrinsic limitations of gaseous mediators.[115,118] By directly introducing gaseous signaling molecules or their corresponding donors into cardiac lesion sites, in situ delivery enables the establishment of relatively stable local concentration gradients and supports sustained and controllable gas release. This approach markedly enhances local bioavailability and substantially reduces systemic exposure and off-target toxicity.[119,120] Given the difficulty of maintaining stable therapeutic concentrations of NO, CO, and H_2S in vivo, in situ delivery exhibits distinct advantages in regulating the microenvironment of the ischemic myocardium. Accordingly, accumulating studies suggest that stimuli-responsive delivery systems may represent

a valuable approach for improving therapeutic precision in gas-mediated cardiac therapy.[121] Current in situ delivery systems include injectable hydrogel-based platforms, microneedle-assisted systems, and sprayable or tissue-adherent biomaterials. Collectively, these approaches have demonstrated encouraging therapeutic efficacy in myocardial infarction, I/R injury, and post-surgical cardiac repair.

In situ Delivery Based on Hydrogels

Hydrogels are uniquely suited for cardiac repair because of their good biocompatibility, injectability, and three-dimensional structure, which closely resembles the native extracellular matrix.[122] These features enable hydrogels to function as carriers for bioactive payloads such as stem cells, exosomes, and genetic materials. Hydrogels can also serve as controlled release systems for gaseous mediators such as NO, CO, and H_2S. Collectively, these attributes enable hydrogels to achieve stable local retention and spatiotemporally controlled release of gas donors within the injured myocardium.[115,123] With progress in chemical cross-linking methods, biodegradable material design, and stimuli-responsive systems, many hydrogel systems undergo in situ gelation following injection. This method can minimize surgical trauma and permit precise localized therapeutic intervention. Such minimally invasive in situ delivery strategies are increasingly regarded as particularly well-suited for clinical myocardial repair.[124]

Hydrogel-based cardiac patches have emerged as a promising therapeutic modality.[16,125] Importantly, well-designed hydrogels recapitulate the key features of the native myocardium, including appropriate elasticity, cell adhesion cues, and synchronous contractile behavior, thereby integrating mechanical support with biochemical signaling and immunomodulation.[126] In this context, gas-based hydrogels, particularly those incorporating H_2S, have attracted sustained interest because of the broad cardioprotective effects. Li et al developed a "drug–carrier homologation" cardiac patch (Fe@LA/LATS), in which lipoic acid (LA) and lipoic acid trisulfide (LATS) were crosslinked through an iron-mediated network to construct a sulfur-rich therapeutic matrix. Unlike conventional inert carriers, the carrier itself functions as a therapeutic component, where LATS serves as the H_2S source and Fe-mediated sulfur conversion enables gradual H_2S generation in the infarct microenvironment. This design achieved month-long localized H_2S release, thereby reducing oxidative stress and inflammation while promoting cardiac repair after myocardial infarction. The system was evaluated in a rodent myocardial infarction model in vivo following local patch implantation, demonstrating sustained therapeutic efficacy; however, its translation may still be limited by the need for surgical implantation, long-term material stability validation, and scalability of patch fabrication for clinical-grade production (Figure 3).[127] Similarly, epicardial hydrogel patches engineered for sustained NO release suppress cardiomyocyte apoptosis and inflammation while stimulating neovascularization, ultimately resulting in marked improvements in cardiac function (Figure 4A).[128,129]

Hydrogel-mediated gas delivery has also demonstrated pronounced efficacy in I/R injury. Deng et al developed a self-assembling supramolecular hydrogel for localized co-delivery of NO and curcumin in myocardial I/R injury treatment.[131] The hydrogel enabled sustained local release at the injured site, where NO contributed to vascular protection and curcumin exerted antioxidant and anti-inflammatory effects. Their synergistic action reduced ROS accumulation and suppressed the p38 MAPK/NF-κB pathway, thereby attenuating autophagy and apoptosis and ultimately alleviating myocardial I/R injury. The platform was evaluated in a myocardial ischemia/reperfusion animal model in vivo through local administration, demonstrating the feasibility of hydrogel-mediated sustained gasotransmitter delivery for cardiac protection. However, the study was primarily conducted in an acute preclinical setting, and further investigation into long-term biosafety, storage stability, reproducibility of hydrogel formation, and large-scale manufacturing feasibility is still required for clinical translation. Complementary H_2S-releasing hydrogels have demonstrated their capacity to alleviate microvascular obstruction, reduce fibrosis and inflammation, and preserve cardiac structure and function following reperfusion injury.[87] Notably, recent efforts have extended beyond single-function designs toward multifunctional cardiac patches that integrate gas delivery with ion-conductive or redox-active components. Zhao et al engineered a multifunctional cardiac patch (GMA@OSM) integrating an ion-conductive hydrogel with oxygen/strontium-releasing microspheres for myocardial infarction repair.[132] SrO_2 encapsulated within PCL microspheres enabled sustained release of oxygen and Sr^{2+}, thereby alleviating local hypoxia and promoting angiogenic activity. Meanwhile, the conductive matrix facilitated electrophysiological reconstruction. The platform was evaluated in a rat myocardial infarction model in vivo through epicardial patch implantation, where synergistic regulation of the infarct microenvironment promoted microcirculatory reconstruction,

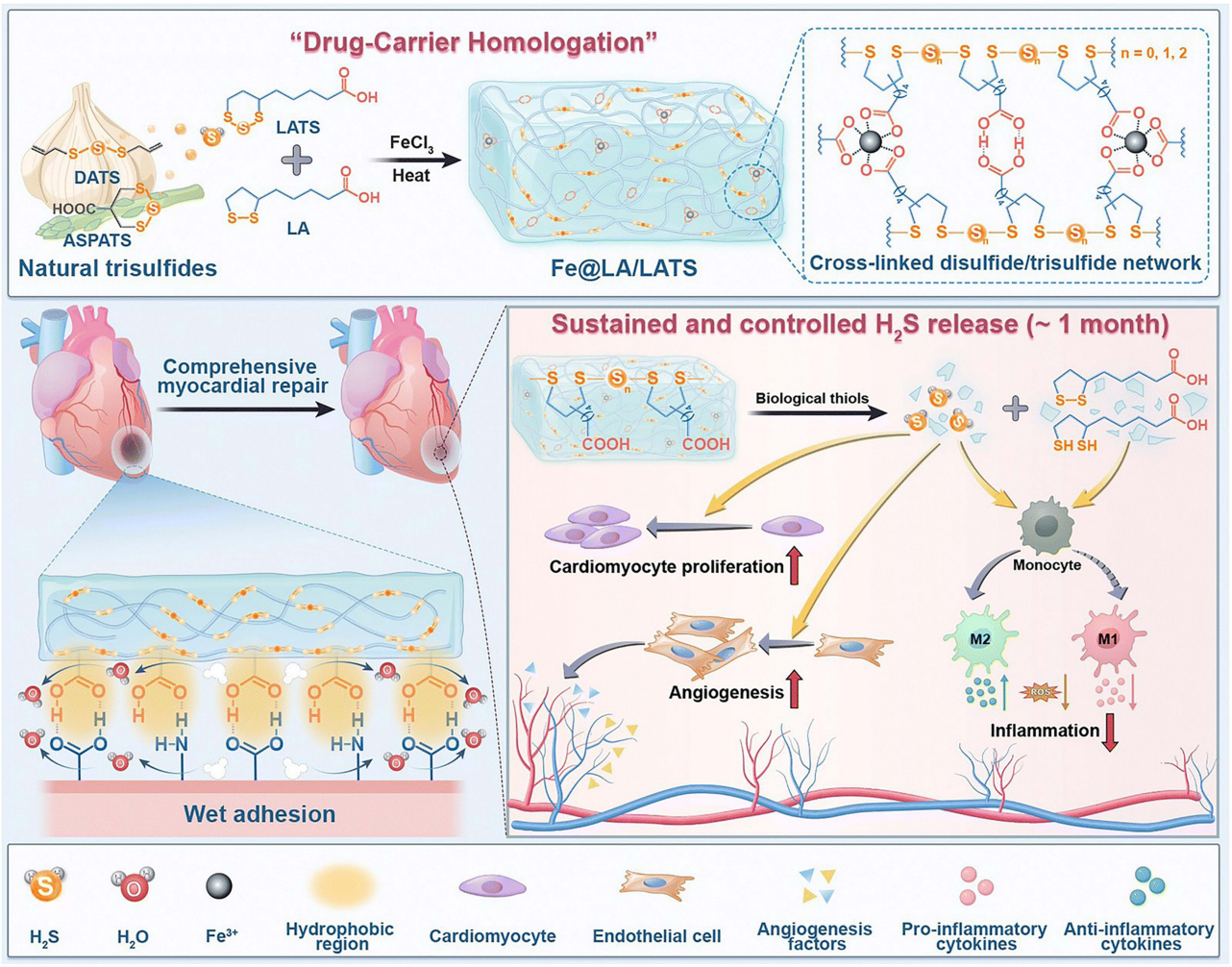

Figure 3 Schematic illustration of a "drug–carrier homologation" cardiac patch (Fe@LA/LATS) for myocardial infarction therapy through sustained H_2S release. Reproduced with permission from ref.[127] Copyright 2026, Royal Society of Chemistry.
Notes: Black arrows indicate reaction or process progression; yellow arrows denote H_2S-mediated biological effects. Red upward arrows mark promotion of cardiomyocyte proliferation and angiogenesis; red downward arrows mark anti-inflammatory effects.

protected cardiomyocytes, and improved cardiac function. Notably, the system provided localized and prolonged gas-related therapeutic modulation; however, long-term biosafety, storage stability, and large-scale manufacturing feasibility remain to be further investigated before clinical translation.

Overall, advances in hydrogel design and modification have rapidly expanded the therapeutic scope of gas-releasing biomaterials in cardiovascular applications. Hydrogel-based gas delivery has demonstrated robust cardioprotective efficacy against multiple diseases by reducing inflammation and cell death, increasing angiogenesis, and protecting against I/R injury. The integration of gas delivery with complementary modalities further amplifies therapeutic potential and shifts these systems closer to clinical relevance.

In situ Delivery Based on Microneedles

Microneedles (MNs) are a minimally invasive platform for in situ delivery of gas signaling molecules in cardiac diseases.[133] With micrometer-scale needle tips, MNs can precisely penetrate the epicardium or access the pericardial cavity, enabling targeted delivery with minimal tissue damage. This unique mode of access allows gas donors or gas-releasing systems to be placed directly on the myocardial surface or within epicardial regions, thereby achieving efficient local delivery.[134] Simultaneously, the ordered geometry of the MN arrays facilitates the establishment of stable, localized concentration gradients, supporting the sustained and spatially confined release of NO, CO, or H_2S. This feature provides

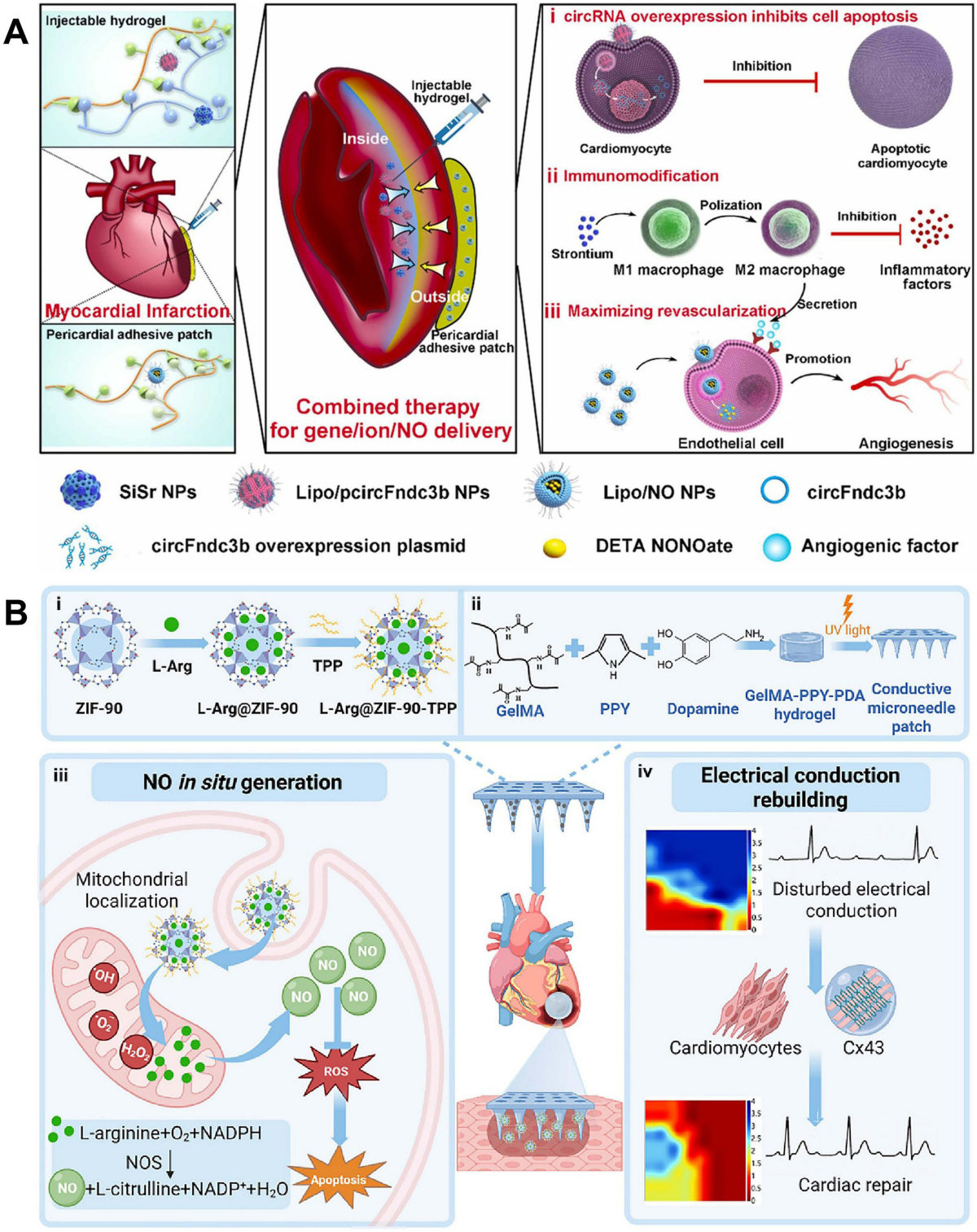

Figure 4 Schematic illustration of localized in situ gas-delivery biomaterial platforms for myocardial therapy. (**A**) Schematic of a combined strategy using an intramyocardial injectable hydrogel and a pericardial adhesive patch for localized, sustained delivery of genes, ions, and gaseous signaling molecules. Reproduced with permission from ref.[129] Copyright 2023, Elsevier. (**B**) Schematic of a conductive microneedle patch that generates mitochondria-localized NO upon penetrating the injured myocardium, thereby regulating mitochondrial function, reducing oxidative stress and inflammation, inhibiting cardiomyocyte apoptosis, and promoting repair after I/R injury. Reproduced with permission from ref.[130] Copyright 2025, Wiley-VCH GmbH.

Notes: In (**A**), black arrows indicate macrophage polarization, endothelial cell stimulation, and angiogenesis, while red bar-headed arrows indicate inhibition of cardiomyocyte apoptosis and pro-inflammatory factor release. In (**B**), black/blue arrows denote material fabrication processes, substance delivery, enzymatic reactions, and therapeutic signaling cascades. Blue bar-headed arrows indicate direct inhibition of pathological factors, such as ROS scavenging by NO.

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clear therapeutic advantages in the treatment of cardiac disease.[135] In addition, microneedle patches can be readily integrated with cardiac patches, injectable hydrogels, or exosome-based systems, greatly expanding their potential applications in myocardial infarction repair, I/R protection, and local angiogenesis.[134,136]

Microneedle patches (MNPs) are attractive tools for in situ cardiac therapy in bioengineered patch systems.[137] For example, Mao et al developed a conductive microneedle patch for mitochondria-targeted delivery of L-arginine, in which the conductive architecture facilitated localized bioelectrical signal transmission while mitochondria-localized NO generation enhanced mitochondrial function and reduced oxidative stress (Figure 4B).[130] The platform was evaluated in an in vivo ischemia–reperfusion injury model through localized epicardial administration, enabling spatially confined NO generation at the injured myocardium. This strategy promoted electrophysiological integration and improved cardiac repair after ischemia–reperfusion injury. Notably, the microneedle-based design provided localized and minimally invasive delivery; however, long-term biosafety, storage stability, and scalability of patch fabrication remain to be further investigated for clinical translation. We also developed a multifunctional MN patch based on gelatin methacryloyl (GelMA) to deliver a hybrid gas-nanozyme with antioxidant and anti-inflammatory activities.[138] On this platform, microfluidic-synthesized nanozymes exhibiting pH-responsive H_2S release synergized with enzymatic ROS scavenging to attenuate oxidative injury within the acidic post-infarction microenvironment. Additional designs include the incorporation of a porous metal-organic framework (MOF) for photothermal-triggered NO release to promote vasodilation and tissue repair.[139]

In addition, Liu et al developed a dual-layer microneedle system enabling temporally controlled O_2 and NO release for diabetic wound treatment.[140] The study was conducted in a diabetic wound model in vivo, with transdermal microneedle-based local administration. The upper layer rapidly generated O_2 to alleviate local hypoxia, while the lower layer provided sustained NO release to regulate the wound microenvironment. Through synergistic modulation of neurogenesis, angiogenesis, and immune responses, this sequential gas delivery strategy promoted neurovascular reconstruction and accelerated tissue regeneration. This platform demonstrates spatiotemporally programmed, layer-dependent gas release; however, its translation may still be limited by the complexity of fabrication and the need for standardized manufacturing for clinical-scale production. Yu et al designed a removable photocatalytic microneedle array based on a hydrogel matrix loaded with photocatalytic components, which enables in situ conversion of CO_2 into CO under light irradiation and sustained local gas release. The system allows minimally invasive transdermal administration with spatially controlled CO generation, providing a practical microneedle-based platform for precise gas therapy delivery. This study was demonstrated in vitro and further validated in a small-animal in vivo model, where localized transdermal administration was achieved in an acute experimental setting. The delivery is limited to superficial tissue penetration, and long-term stability and repeated administration frequency were not evaluated, which may affect its translational potential for chronic cardiovascular applications.[141] Although originally developed for tumor therapy, this microneedle-based CO delivery strategy may inspire future gas-delivery designs for cardiovascular applications.[142] Collectively, these studies confirm the feasibility of microneedle systems for localized gas delivery in cardiac therapy.

Overall, microneedle-based in situ delivery systems offer an innovative strategy for the precise application of gaseous signaling molecules in the treatment of cardiac diseases. Their minimally invasive, targeted, and spatially confined release characteristics enhance the local therapeutic efficacy and markedly reduce systemic adverse effects. By integrating conductive materials, nanozymes, metal–organic frameworks, and stimuli-responsive mechanisms, microneedle platforms have evolved into multifunctional systems capable of electrical integration, antioxidative protection, and pro-angiogenic regulation.

In situ Delivery Based on Spray-Applied Adhesion Systems

Injectable hydrogels and microneedle systems have shown considerable promise in localized cardiac therapy. However, the dynamic mechanical environment of the myocardium, including its complex geometry and continuous motion, presents challenges for the clinical translation of these systems.[12] Injection-based approaches may cause local mechanical injury and often fail to uniformly cover irregular or curved tissues. Microneedle systems are also limited by their procedural complexity and increased invasiveness. In response to these challenges, spray-applied bioadhesive delivery systems have attracted increasing attention as a more adaptable and practical surgical strategy for in situ cardiac treatment. Using low-viscosity precursor solutions, these materials can be sprayed directly onto the myocardial surface

and rapidly crosslink or undergo phase transition to form adhesive gels or thin films. These materials tightly attach to the myocardium, reduce mechanical damage, and maintain stable adhesion under continuous cardiac motion.[143,144] Therefore, this strategy offers clear advantages for the treatment of myocardial infarction and I/R injury.[145]

Spray-applied adhesive systems have been increasingly explored for the localized delivery of therapeutic agents in myocardial infarction and I/R injury.[146] For example, Zhao et al developed a sprayable ROS-responsive hydrogel coating incorporating a NO-releasing polymer (G-NO) and caffeic acid prodrug, which undergoes ROS-triggered degradation at injured vascular sites to enable on-demand NO release, thereby scavenging excessive ROS and preserving endothelial junction integrity (Figure 5A).[147] This system was evaluated in vitro and in vivo in vascular injury–related models, where spray-based local administration enabled site-specific deposition and spatiotemporally controlled NO release in response to elevated ROS levels. This study highlights the potential of spray-based systems to overcome the short half-life and rapid diffusion of NO into sustained lesion-restricted therapeutic effects; however, challenges related to standardized clinical application of spray delivery and reproducibility in large-area vascular lesions remain to be further addressed.

Building on this concept, gas-releasing spray or coating systems have been further integrated with implantable vascular devices to achieve long-term regulation of multiple pathological processes. For instance, Zhang et al developed an in situ H_2S-releasing stent based on a ROS-responsive coating strategy, in which the polymeric matrix is designed to degrade in the oxidative vascular injury microenvironment, enabling on-demand H_2S liberation.[149] The locally released H_2S modulates oxidative stress and inflammatory signaling while promoting endothelial regeneration, thereby improving vascular healing and reducing neointimal hyperplasia. This work highlights a stimuli-responsive stent platform that achieves spatially controlled gaseous mediator delivery in vascular injury settings. This system was evaluated in vivo in a vascular injury animal model via intravascular stent implantation, demonstrating its translational relevance for interventional cardiovascular therapy. However, the study primarily focused on short-term vascular healing outcomes, and long-term safety, material degradation stability, and potential variability in release kinetics under different hemodynamic conditions remain insufficiently addressed, which may limit direct clinical translation. Furthermore, multifunctional coatings capable of synergistic multiple gas regulation have been developed. A representative strategy employs a stabilized H_2S-NO synergistic coating constructed via covalent bonding and a multi-crosslinked network on device surfaces, which permits spontaneous or stimuli-responsive H_2S release while catalyzing endogenous NO production in an in vivo stent implantation model, enabling localized and long-acting gas release at the vascular interface (Figure 5B).[148] Mechanistically, this therapeutic synergy is mainly attributed to complementary regulation of oxidative stress and endothelial function, whereby H_2S reduces oxidative stress, while NO supports endothelial homeostasis. This dual-gas coordination concurrently achieves anti-inflammatory, anticoagulant, and endothelial repair-promoting effects, representing a new direction in the field toward integrated long-acting therapeutic coatings.

Spray-applied bioadhesive in situ delivery systems further extend this paradigm by offering a practical approach for localized and sustained delivery of gaseous signaling molecules in the myocardium. This inherent conformability allows intimate contact with the irregular geometry and dynamic pulsatile environment of the myocardium, which is a critical advantage over rigid or injection-based approaches.

Overall, in situ delivery strategies based on hydrogels, microneedles, and spray-applied adhesion systems offer complementary technical pathways for cardiac gas therapy. Hydrogels emphasize local retention and mechanical support, enabling minimally invasive and spatially confined delivery, whereas spray systems demonstrate distinct advantages in adapting to complex myocardial geometries and dynamic motion. Together, these approaches advance toward greater precision, controllability, and multifunctional synergy.

Systemic Intravenous Delivery Strategies to Improve Targeted Accumulation

Systemic intravenous administration remains the most clinically tractable route for gas signaling molecules delivery in cardiovascular disease therapy.[150,151] However, their therapeutic efficacy is significantly constrained by the short half-life of gas molecules, their non-specific distribution, and potential systemic toxicity.[114,152] To overcome these limitations, recent research has shifted from direct administration of conventional gas donors toward nanomaterial-based systemic delivery strategies. This section outlines the key design principles of systemic intravenous delivery, and summarizes the

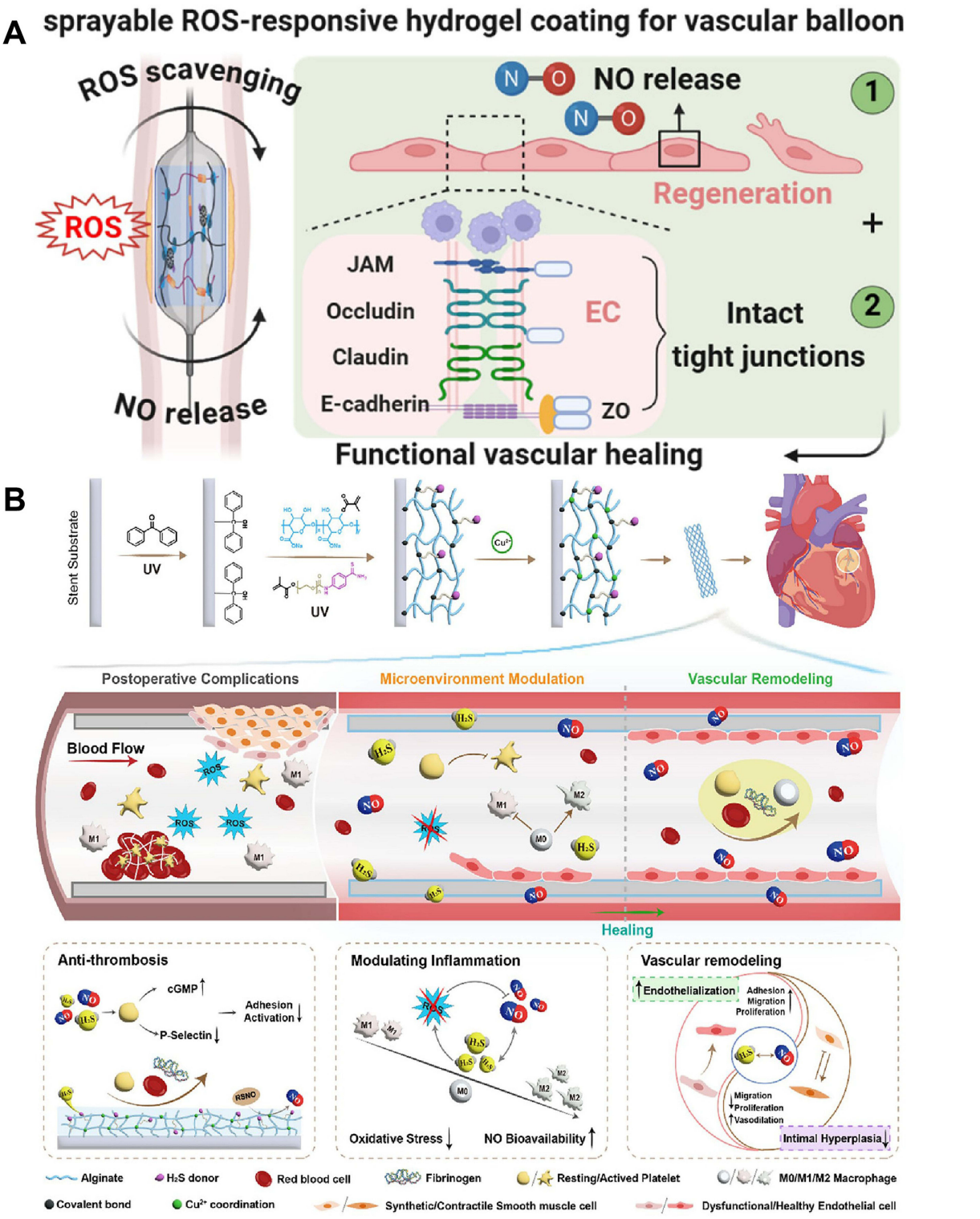

Figure 5 Schematic illustration of localized in situ gas-delivery biomaterial platforms for vascular healing in cardiac disease. (**A**) Schematic illustration of a sprayable ROS-responsive hydrogel coating that, upon application to damaged vascular tissue, responds to elevated ROS levels to restore endothelial barrier integrity, reduce inflammation, and promote functional vascular healing. Reproduced with permission from ref.[147] Copyright, 2025, American Chemical Society. (**B**) Schematic illustration of a spatiotemporally orchestrated H_2S/NO-releasing vascular stent that provides an early H_2S burst and sustained NO flux, thereby regulating vascular remodeling, reducing inflammation and SMC proliferation, promoting endothelial regeneration, and enhancing vascular healing and homeostasis. Reproduced with permission from ref.[148] Copyright 2025, Wiley-VCH GmbH.

Notes: In (**A**), black arrows indicate NO release, endothelial regeneration, and functional vascular healing, whereas circular/curved arrows indicate cyclic ROS scavenging by the hydrogel coating. In (**B**), black arrows indicate fabrication, gas release, and biological processes; red cross-out symbol indicate inhibition of pathological factors; upward/downward arrows denote enhanced or reduced biological responses.

research advances and inherent limitations of passive and active targeted nanodelivery systems for cardiac gas therapy. Collectively, these advances aim to move gas therapy toward precision and translational applications.

Among the various systemic delivery approaches, nanocarriers represent a central enabling platform for gas signaling molecule therapy due to their unique capability to bridge the gap between the intrinsic instability of gaseous mediators and the requirements of in vivo therapeutic delivery. By providing a protective microenvironment for gas donors, nanocarriers effectively mitigate rapid diffusion and premature degradation, thereby prolonging circulation time and enabling more controlled pharmacokinetics. In addition, their highly tunable physicochemical properties, including size, surface charge, and composition, allow for rational engineering of biodistribution behavior and lesion-specific accumulation. Importantly, nanocarrier systems also serve as versatile scaffolds for integrating both passive and active targeting strategies, as well as stimuli-responsive release mechanisms, making them a foundational component in the development of precision gas-based cardiovascular therapies. Despite these advantages, challenges such as large-scale manufacturing reproducibility, in vivo complexity, and long-term biosafety remain key barriers to clinical translation.

Passive-Targeted Nanomedicine Delivery

Passive targeted nanodelivery systems primarily exploit the size effect and intrinsic physicochemical properties of nanocarriers.[153] By leveraging the pathophysiological features of injured cardiac tissue, such as enhanced vascular permeability, inflammatory responses, and endothelial dysfunction, these systems achieve relative preferential accumulation within damaged tissues without specific targeting ligands.[154–156] Owing to their relatively simple structural design and high fabrication reproducibility, passive-targeting strategies represent an attractive and broadly applicable platform for the systemic delivery of gas-signaling molecules.[157,158]

For NO-based therapies, passive targeting may indirectly augment therapeutic efficacy by improving cellular functional states.[159,160] For example, Hao et al engineered mesenchymal stem cells (MSCs) with enhanced intracellular NO delivery by using a NO-releasing system, which improved cellular redox regulation and mitochondrial function under ischemic stress, thereby enhancing cell survival and paracrine pro-angiogenic signaling in a mouse MI model in vivo following MSC administration, representing an early-stage preclinical study with acute efficacy evaluation; key translational parameters such as dosing frequency, long-term safety, and manufacturing scalability remain unaddressed.[161] Similar concepts were extended to CO nanodelivery. Wu et al developed rhodium-based nanoparticles enabling ultrasound-triggered CO release for myocardial infarction therapy.[162] Following passive accumulation in ischemic myocardium this system was evaluated in vivo in a mouse myocardial infarction model, where external ultrasound irradiation was used to achieve spatiotemporally controlled, on-demand CO release. This strategy significantly reduced oxidative stress, suppressed inflammatory responses, and attenuated fibrotic remodeling, thereby improving post-infarction cardiac function. However, the study primarily demonstrated efficacy in an acute preclinical setting, and long-term safety, dosing frequency, and translational parameters such as repeatability of ultrasound activation and potential clinical scalability were not fully investigated.

H_2S, another endogenous gaseous mediator with potent cardioprotective effects, has been extensively explored for passive targeted delivery. Zhan et al developed H_2S-releasing nanoparticles with preferential accumulation in myocardial infarction tissue, achieving sustained and localized H_2S delivery through controlled release behavior (Figure 6A).[163] This system was evaluated in an in vivo mouse model of myocardial infarction, following systemic administration via intravenous injection, and demonstrated improved cardiac function recovery. Mechanistically, the nanoparticle system continuously modulated oxidative stress and inflammatory responses within the infarct microenvironment, thereby enhancing cardiomyocyte survival. However, this study was limited to acute preclinical small-animal models, and translational aspects such as long-term biodistribution stability, repeated dosing frequency, and formulation storage/shelf-life characteristics were not fully investigated. Consequently, it markedly enhances cardiac function recovery following myocardial infarction. Furthermore, Ma et al developed PLGA nanoparticles encapsulating sodium thiosulphate (STS) to achieve controlled and sustained H_2S release via polymer degradation.[164] This system enhances cellular uptake and preserves H_2S-mediated pro-angiogenic activity, supporting endothelial regeneration and highlighting the translational potential of biodegradable nanoparticle-based gas delivery. The study was primarily conducted in vitro using endothelial cell-based angiogenesis assays, and the release behavior was evaluated under controlled laboratory conditions. While the PLGA

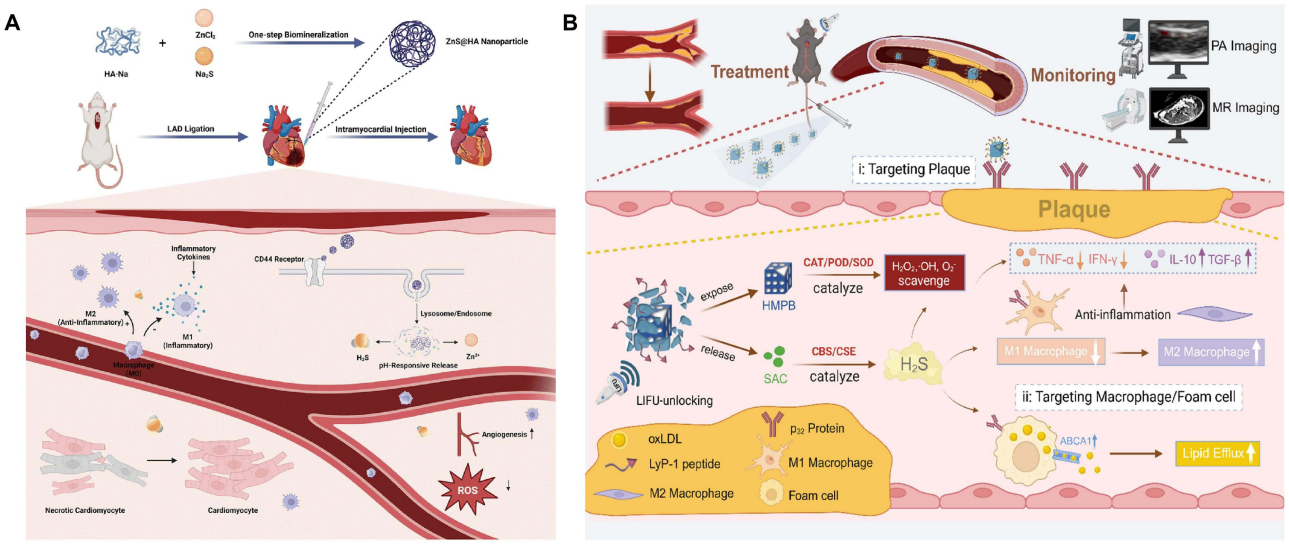

Figure 6 Schematic illustration of systemic intravenous nanomedicine delivery strategies for H_2S-based cardiovascular therapy. (**A**) Synthesis of HA@ZnS NP and their proposed therapeutic mechanism in myocardial infarction, involving H_2S release–mediated cardioprotective and microenvironment-modulating effects. Reproduced with permission from ref.[163] Copyright 2013, Royal Society of Chemistry. (**B**) Versatile nanoplatform integrating endogenous H_2S gas therapy with multienzyme-mimicking nanozyme activity, enabling synergistic regulation of oxidative stress and inflammation for the treatment of AS. Reproduced with permission from ref.[165] Copyright 2025, Elsevier.
Notes: In (**A**), black arrows indicate nanoparticle synthesis, disease modeling, delivery, and therapeutic progression. Black upward/downward arrows indicate Promotion of beneficial processes (angiogenesis, M2 polarization) or inhibition of pathological events (ROS, inflammation). In (**B**), Solid arrows indicate process progression (synthesis, targeting, catalysis, signaling); dashed represent ultrasound-triggered release or indirect regulation; upward arrows denote upregulation of beneficial processes (eg, anti-inflammatory cytokines, lipid efflux); downward arrows denote downregulation of pathological factors (eg, pro-inflammatory cytokines, oxidative stress).

platform offers favorable biodegradability and potential for systemic administration, the lack of in vivo validation limits assessment of biodistribution, pharmacokinetics, and therapeutic efficacy in physiologically relevant disease models.

Overall, passive targeting systems benefit from a simplified fabrication process, good reproducibility, and favorable scalability, making them a crucial foundational strategy for systemic intravenous gas delivery. Collectively, current studies suggest that the performance of passive-targeted systems may depend on pathological features of cardiac tissues, with targeting efficiency potentially varying across disease stages and individuals.[166] Therefore, although passive-targeted nanomedicine provides a feasible strategy for systemic gas therapy, further optimization may be needed to improve delivery precision and therapeutic consistency.

Active Targeted Nanomedicine Delivery

Active targeted nanodelivery systems achieve precise localization to cardiac tissues or specific cellular populations through rational surface functionalization of nanocarriers or incorporation of exogenous regulatory mechanisms, thereby significantly enhancing delivery efficiency and therapeutic safety.[167,168] Representative active targeting strategies include guidance from external physical fields, biomimetic surface modifications, ligand-specific recognition, and cell-mediated delivery. These approaches effectively overcome the intrinsic limitations of the non-specific distribution associated with systemic administration.[169]

In recent years, representative studies have reported the potential advantages of active targeting strategies in gas-based cardiovascular therapies.[34,170] For instance, Navati et al developed magnetically guided paramagnetic S-nitrosothiol-coated nanoparticles to achieve field-directed accumulation and on-demand NO release in ischemia/reperfusion (I/R)-injured myocardium.[171] This study was performed in an in vivo murine I/R injury model, where nanoparticles were administered via systemic intravenous injection and guided by an external magnetic field to enhance local cardiac accumulation Beyond physical field-mediated active targeting, intelligent responsive delivery systems have been explored further depending on the characteristics of the lesion-specific microenvironment. Zhang et al developed a platelet membrane-mimetic CO nanogenerator that actively targets ischemic lesions and responds to elevated peroxynitrite ($ONOO^-$) in the injured microenvironment to trigger on-site CO release, thereby attenuating oxidative stress and

reducing myocardial ischemia–reperfusion injury in a mouse myocardial ischemia–reperfusion (I/R) model in vivo.[65] Such designs illustrate the potential of endogenous lesion sites to drive precise gas delivery without continuous external intervention, although their translational evaluation remains limited to acute small-animal models and long-term pharmacokinetics and safety have not yet been fully established.

Active targeting strategies have also been extended for H_2S gas delivery. An et al developed a LyP-1-modified liposomal nanoplatform ($^{LyP-1}$Lip@H_2S) co-loading an H_2S donor and a nanozyme, enabling tumor/lesion-targeted delivery and ROS-responsive H_2S release. The system was evaluated in vivo in an atherosclerosis mouse model, where it was administered via intravenous injection, achieving preferential accumulation at lesion sites and enhanced spatiotemporal control of gas release under oxidative stress conditions. The incorporated nanozyme further catalyzed endogenous ROS scavenging, thereby synergistically enhancing anti-inflammatory, antioxidant, and lipid metabolism regulatory effects. However, the study remains at the preclinical small-animal stage, and aspects such as long-term storage stability, repeated dosing feasibility, and large-animal validation were not addressed, which may limit translational potential for clinical cardiovascular application (Figure 6B).[165]

Furthermore, Ma et al engineered mesenchymal stem cells (MSCs) as living carriers for H_2S delivery by leveraging their intrinsic inflammatory tropism to ischemic myocardium. This cell-based platform enables targeted accumulation of H_2S at injury sites, where released H_2S suppresses cGAS–STING–mediated inflammatory activation, thereby enhancing myocardial protection in ischemia–reperfusion injury (Figure 7).[172] Notably, this study was conducted in an in vivo myocardial ischemia–reperfusion (I/R) mouse model, representing an acute preclinical injury setting. The MSC-based system relies on systemic administration with inflammatory homing to damaged cardiac tissue, enabling spatiotemporally localized gas delivery; however, the therapeutic effect is largely demonstrated in short-term experimental conditions. From a translational perspective, limitations remain regarding cell manufacturing scalability, long-term engraftment behavior, dosing standardization, and model relevance to chronic human cardiovascular disease, which may hinder direct clinical translation. Collectively, active targeted nanodelivery strategies have achieved precise localization and controlled release of gas within cardiovascular lesions, resulting in significant enhancement of therapeutic efficacy and safety.

In summary, passive and active targeting nanodelivery systems are complementary strategies for the cardiovascular gas therapy. Passive targeting structures are simple and readily scalable, but rely heavily on the pathological microenvironment, whereas active targeting strategies enhance spatial precision and therapeutic efficacy via ligand modification, physical fields, or cellular mediation. The rational integration of these two modalities, together with the systematic evaluation of their long-term safety and clinical feasibility, will be critical for accelerating the translational development of gas-based nanotherapeutic platforms.

Stimuli-Responsive Delivery Strategies to Enable on-Demand Gas Release

Although in situ and systemic intravenous delivery has partially improved the local bioavailability of gaseous signaling molecules, the inability to achieve precise spatiotemporal control over gas release remains a major barrier to clinical translation.[173] Stimuli-responsive delivery platforms convert endogenous pathological conditions or external physical signals into controllable release triggers, thereby enabling on-demand gas release with enhanced therapeutic precision and fewer adverse effects.[174] This section systematically summarizes the principal stimuli -responsive strategies employed in cardiac gas therapy, with an emphasis on their mechanistic advantages and translational constraints within complex cardiovascular pathological environments.

Endogenous Stimuli-Responsive Gas Delivery Platform

Endogenous stimuli-responsive delivery platforms primarily exploit characteristic physiological or pathological microenvironmental alterations within cardiac lesion sites to achieve selective release of gaseous signaling molecules.[175] Under pathological conditions of myocardial injury, the local myocardial microenvironment is typically characterized by intensified acidic metabolism, excessive oxidative stress, and sustained inflammation activation, providing a rational biological basis for establishing gas delivery systems.[176]

Among them, pH-responsive delivery systems represent the most mature category of endogenous stimuli-responsive strategies.[177] Liu et al developed a platelet membrane-coated, pH-responsive H_2S nanodelivery system that exploits the

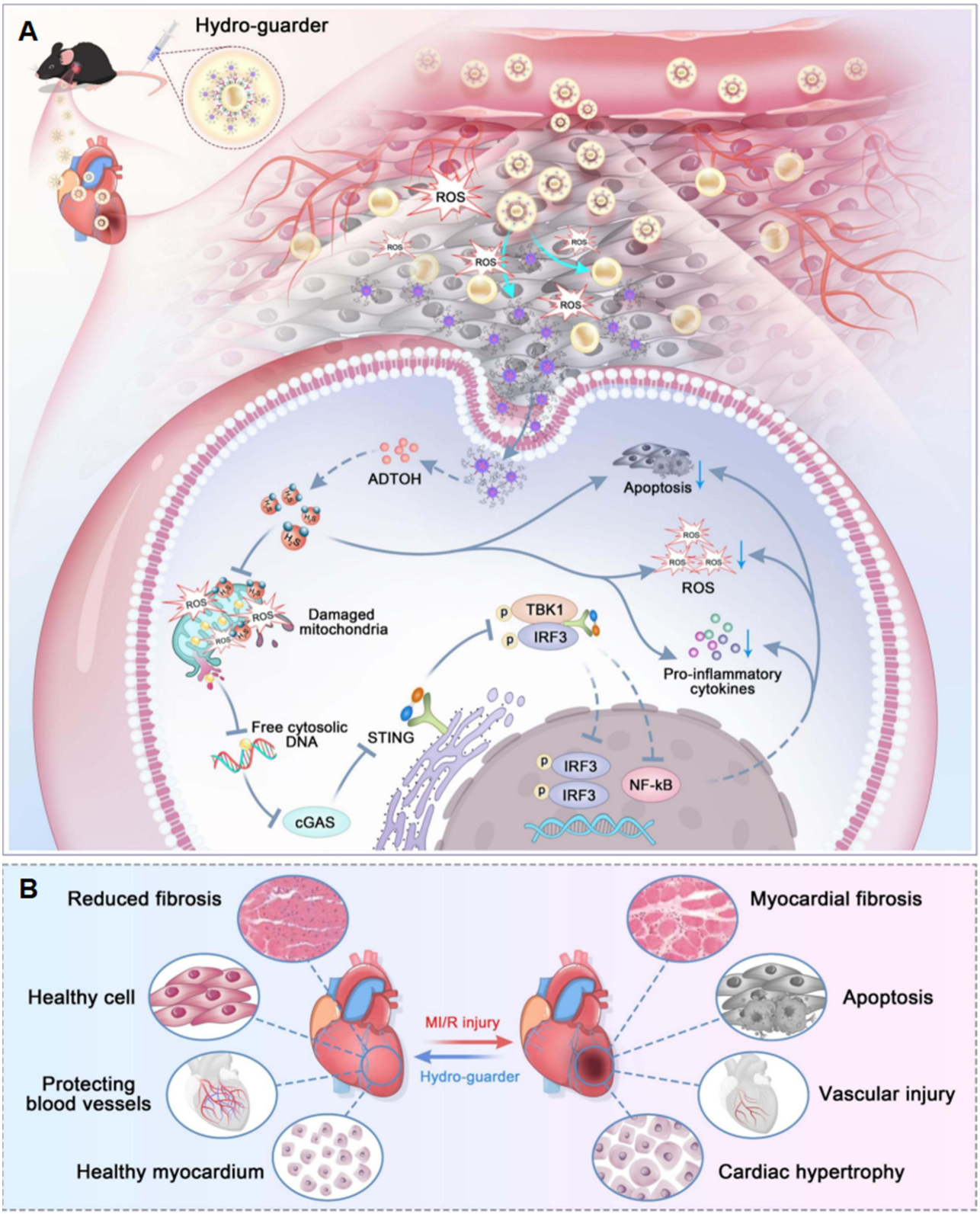

Figure 7 Schematic illustration of the "Hydro-guarder" bioorthogonally engineered MSCs system for targeted H_2S delivery and enhanced cardioprotection in MI/R injury. Reproduced with permission from ref.[172] Copyright 2026, Elsevier.

Notes: In (**A**), blue arrows indicate biological signaling pathways, process progression, and the inhibitory effects of Hydro-guarder on pathological processes. Cyan arrows denote the scavenging of ROS by Hydro-guarder nanoparticles. In (**B**), red arrows indicate the pathological consequences of MI/R injury. Blue arrows denote the protective effects of Hydro-guarder.

inflammatory and acidic microenvironment of ischemia–reperfusion (I/R) myocardium for targeted accumulation and on-site gas release. The system was evaluated in an in vivo mouse myocardial I/R injury model via systemic intravenous administration. The biomimetic platelet membrane enhances lesion homing, while acidic-triggered H_2S release alleviates oxidative stress and inflammation, leading to improved cardiac function after I/R injury (Figure 8A).[178] However, the study was limited to acute small-animal models, and long-term biodistribution, dosing frequency, and storage stability were not investigated, which may affect translational applicability.

Elevated ROS levels at lesion sites have also been used extensively as endogenous triggers for stimuli-responsive gas release. Lu et al developed mitochondria-targeted peptide–drug conjugates with ROS-responsive NO release capability,

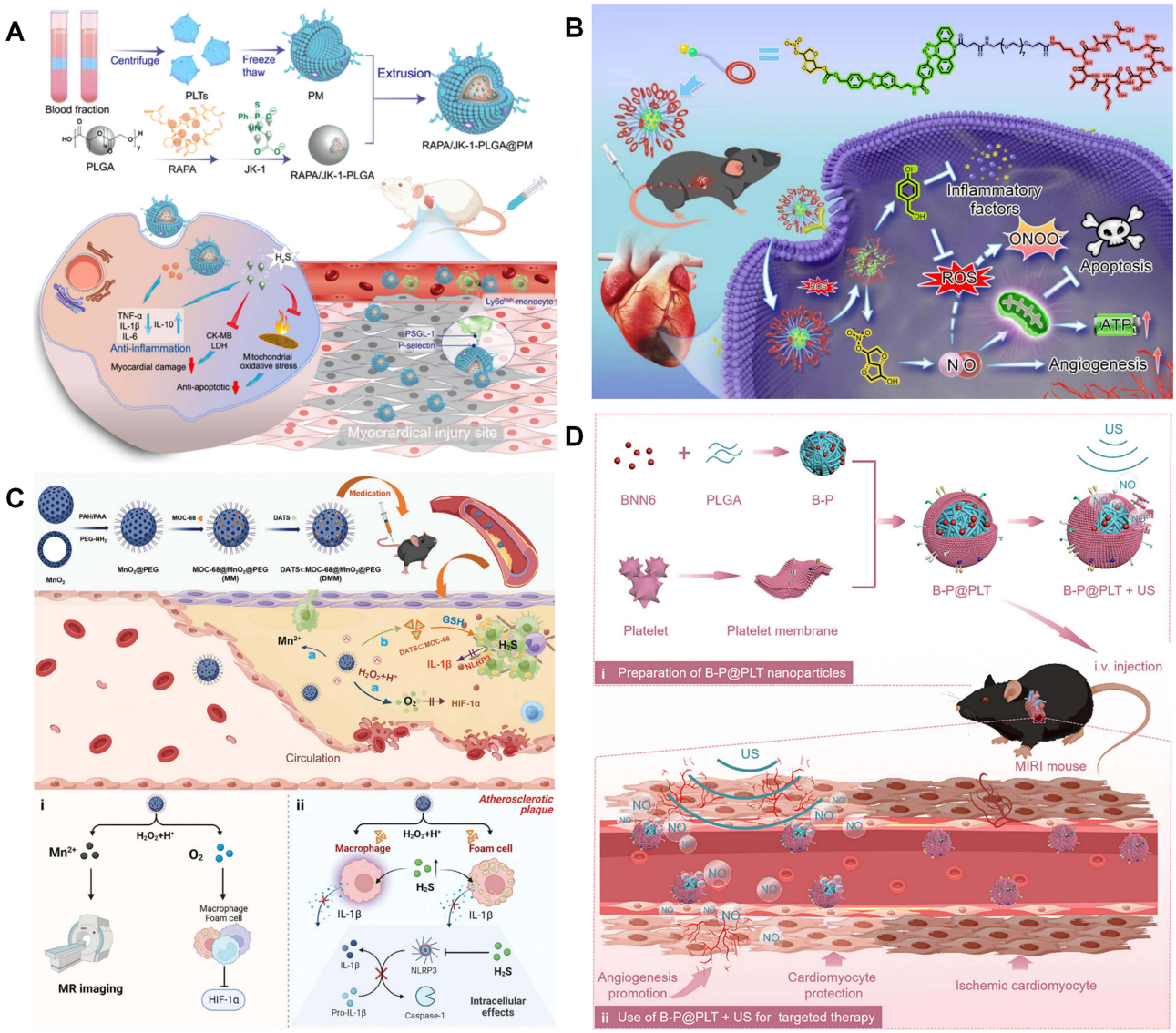

Figure 8 Schematic illustration of stimuli-responsive gas-delivering nanomedicine and biomimetic systems for cardiovascular therapy. (**A**) Myocardial injury–targeting nanoparticles enabling pH-responsive CO delivery of H_2S donor and rapamycin for gas therapy of myocardial ischemia–reperfusion injury Reproduced under the terms of the CC-BY 4.0 license from ref.[178] Copyright 2024, Biomaterials Research. (**B**) ROS-responsive and ROS-scavenging peptide–drug conjugates (PDCs)–mediated gas therapy for myocardial infarction. Reproduced under the terms of the CC-BY 4.0 license from ref.[179] Copyright 2025, Journal of Nanobiotechnology. (**C**) Synthesis and therapeutic delivery of MOC-68–based MnO2@PEG nanoparticles enabling MRI-visible dual-gas (H_2S and O_2) release for atherosclerosis therapy. Reproduced with permission from ref.[180] Copyright 2024, Wiley-VCH GmbH. (**D**) Platelet membrane–functionalized black phosphorus nanosheets (B-P@PLT) enabling magnetic targeting and ultrasound-triggered NO release MIRI therapy.[181] Copyright 2023, Small Structures.

Notes: Black/blue/pink arrows indicate nanoparticle synthesis, delivery, cellular uptake, and therapeutic signaling progression; red T-shaped arrows or crosses denote inhibition of pathological processes (eg, inflammation, ROS, apoptosis, myocardial damage); blue/green upward arrows indicate promotion of beneficial effects (eg, anti-inflammatory cytokines, angiogenesis, ATP production); specific process arrows (labeled a/b) represent catalytic reactions or release pathways, while US (ultrasound) symbols indicate external stimuli-triggered drug release.

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enabling on-demand NO liberation in oxidative stress–rich myocardial infarction microenvironments to restore mitochondrial homeostasis and improve cardiac function. This system was evaluated in vivo in a mouse myocardial infarction model following systemic administration (intravenous injection), demonstrating therapeutic efficacy in acute preclinical settings. However, the study remained limited to small-animal models, and long-term pharmacokinetics, dosing frequency, and formulation stability were not investigated, which may constrain its translational potential (Figure 8B).[179] Similarly, Li et al developed a ROS-responsive nanoplatform that simultaneously scavenges excessive reactive oxygen species while triggering on-demand NO release under oxidative stress conditions. This dual-function design not only alleviates ROS-induced endothelial and vascular injury, but also improves NO bioavailability by protecting NO from rapid oxidative inactivation. Mechanistically, the system further suppresses endoplasmic reticulum stress, thereby enhancing endothelial homeostasis and amplifying the overall vasoprotective efficacy of NO therapy. This system was evaluated in vitro under oxidative stress–induced endothelial cell injury models and further validated in vivo in a rodent vascular disease model via systemic intravenous administration, demonstrating acute therapeutic efficacy; however, long-term dosing frequency and storage stability were not investigated.[182] Furthermore, Li et al designed a multifunctional nanomedicine capable of synchronizing exogenous H_2S and in situ O_2 generation under acidic or ROS-rich conditions in atherosclerotic plaques. This strategy suppressed inflammatory responses and alleviated local tissue hypoxia (Figure 8C).[180] The system was evaluated in an in vivo atherosclerosis mouse model, where it responded to the inflammatory plaque microenvironment to achieve spatiotemporally controlled and on-demand gas release, thereby suppressing inflammatory activation and alleviating plaque progression. The platform was administered via systemic intravenous injection, enabling plaque-targeted accumulation through enhanced permeability and retention–like effects. However, the study remains at the preclinical stage, and further evaluation of long-term safety, dosing frequency, and pharmacokinetics is still required for potential clinical translation.

In addition to pH and ROS, abnormal expression of lesion-associated enzymes also provides highly specific triggers for endogenous stimuli-responsive release. Liu et al developed an enzyme-responsive hybrid NO–H_2S prodrug designed for sequential gas release in heart failure therapy.[183] The system incorporated β-galactosidase-sensitive galactose moieties as the primary trigger and a carbonyl sulfide (COS)-generating unit for H_2S production. Upon β-galactosidase-mediated cleavage, the prodrug underwent structural activation, resulting in NO release together with the generation of COS, which was subsequently converted into H_2S by endogenous carbonic anhydrase. This cascade enzyme-responsive strategy enabled controlled dual-gas delivery within the pathological microenvironment and produced significant therapeutic benefits in a post-myocardial infarction heart failure model, including improved cardiac function and enhanced cardioprotective efficacy arising from the synergistic actions of NO and H_2S.

Collectively, endogenous stimuli-responsive gas delivery platforms demonstrate significant advantages in enhancing therapeutic efficacy and safety by coupling gas release with pathological signals at the cardiac lesion sites, including acidity, oxidative stress, and abnormal enzyme expression.

Exogenous Stimuli-Responsive Gas Delivery Platform

Exogenous stimuli-responsive delivery platforms enable remote and non-invasive regulation of gas release through externally applied physical signals, including ultrasound, light, and magnetic fields. Compared with endogenous pathological cues that vary considerably among disease stages and individuals, exogenous triggers provide superior spatiotemporal control over gas release by allowing external modulation of release timing, dosage, and localization.[121,184] Such controllable systems have emerged as promising strategies to improve the precision and safety of gas-based cardiovascular therapy.

Among these approaches, ultrasound-responsive platforms have attracted considerable attention because of their deep tissue penetration, non-invasive characteristics, and adjustable acoustic parameters.[162,185] Ultrasonic stimulation can induce cavitation, mechanical oscillation, localized heating, or microbubble destruction, leading to carrier destabilization and subsequent gas release.[186,187] Xu et al developed ultrasound-responsive biomimetic nanoparticles (BNN6-loaded and cell membrane-coated) for targeted delivery of NO to ischemic myocardium. In this study, the system was evaluated in an in vivo murine myocardial ischemia–reperfusion (I/R) injury model, where ultrasound-triggered cavitation induced controlled decomposition of BNN6, enabling spatiotemporally controlled NO release upon external ultrasound

stimulation. The treatment was administered via systemic intravenous injection, followed by localized ultrasound activation at the ischemic region. The results demonstrated attenuation of oxidative stress, improved microvascular perfusion, and reduced cardiomyocyte apoptosis. However, the study was limited to an acute preclinical small-animal model, and long-term safety, dosing frequency, and translational parameters such as storage stability and repeated administration feasibility were not reported (Figure 8D).[181] Similarly, Chen et al developed hydrogen sulfide-loaded microbubbles and achieved site-specific H_2S delivery via ultrasound-targeted microbubble destruction, in which acoustic cavitation triggered rapid microbubble rupture and localized gas release at ischemia–reperfusion regions.[188] This strategy was evaluated in an in vivo rat myocardial ischemia–reperfusion model and administered via systemic intravenous injection followed by external ultrasound triggering, enabling highly spatiotemporally controlled gas release at the target site. It significantly attenuated myocardial injury by reducing oxidative stress and inflammatory responses, thereby improving cardiac function after ischemic insult. However, this platform relies on external ultrasound equipment for activation and has primarily been demonstrated in acute preclinical models, which may not fully reflect chronic ischemic conditions or long-term translational performance.

Recent studies further expanded ultrasound-triggered H_2S delivery systems by integrating advanced carrier designs and multifunctional therapeutic mechanisms. Beyond serving as a trigger for on-demand gas release, ultrasound itself can directly modulate the biological effects of H_2S, as exemplified by a recent study by Agilė Tunaitytė et al.[189] They demonstrated that low-frequency (20 kHz) ultrasound significantly inhibits contractions induced by the H_2S donor GYY4137 in isolated human pulmonary arteries. Mechanistically, low-frequency ultrasound does not alter the release or degradation of H_2S; instead, it antagonizes the contractile effect of GYY4137 by reducing calcium mobilization (particularly via inhibition of the calcium sensitization pathway) in smooth muscle cells. This finding suggests that low-frequency ultrasound can not only serve as a trigger for gas delivery but also directly modulate H_2S-mediated vascular functions, providing a new regulatory direction for the interaction between ultrasound and H_2S signaling.

Beyond ultrasound-responsive systems, gas-generating delivery approaches based on distinct physical mechanisms have also been explored. For example, stimuli-responsive CO_2-generating carriers have been developed to produce gas bubbles in situ, providing an alternative strategy for enhancing local drug transport and therapeutic efficacy through gas-mediated physical effects.[190] Such approaches broaden the conceptual framework of stimuli-responsive gas therapy beyond conventional donor decomposition strategies.

Light-responsive delivery platforms primarily exploit photothermal or photochemical mechanisms, whereby irradiation at defined wavelengths induces gas donor decomposition or carrier structural changes.[191,192] Hou et al developed a photo-responsive dual-gas donor integrating gas-releasing moieties with a fluorescent reporter system. Light irradiation induced simultaneous NO and H_2S release through photochemical activation while generating fluorescence signals for real-time tracking of release behavior, thus enabling externally controllable and traceable gas delivery. This platform was primarily validated in vitro, demonstrating proof-of-concept spatiotemporal control of gas release under defined light conditions. However, its in vivo translational relevance remains to be confirmed, particularly regarding tissue light penetration depth, potential phototoxicity, and controllability in deep cardiovascular tissues. Moreover, clinically feasible light delivery routes, dosing frequency, and system stability under physiological conditions were not fully addressed, which may limit its direct application in cardiovascular clinical translation.[193] Although the current cardiovascular applications of photothermal-triggered gas delivery remain limited, photothermal nanoplatforms have shown promising capabilities for remotely controlled gas release in other biomedical fields and may represent an emerging direction for future cardiovascular gas therapy.

Magnetic-field-responsive systems offer another strategy by combining physical targeting with controlled release. Wang et al designed an Fe_7S_8@liposome nanocarrier integrating magnetic guidance with pH-responsive H_2S release.[194] The Fe_7S_8 core enabled external magnetic field-mediated accumulation at target sites, while the liposomal system remained relatively stable under physiological conditions but underwent accelerated H_2S release in acidic pathological microenvironments. This programmed dual-responsive strategy improved localized gas delivery and minimized off-target release. Importantly, this system was evaluated in vivo in a small-animal disease model (preclinical stage), demonstrating proof-of-concept magnetic targeting and pH-triggered release in a pathophysiological environment. However, the study primarily focused on acute biodistribution and short-term therapeutic effects, without assessment of long-term biosafety, formulation shelf stability, or repeated dosing feasibility, which remain important translational considerations for clinical cardiovascular applications.

To provide a systematic comparison of representative endogenous and exogenous stimuli-responsive gas-delivery systems for cardiovascular applications, the major platforms discussed in this section are summarized in Table 1. Collectively, endogenous and exogenous stimuli-responsive delivery systems provide complementary strategies for achieving disease-specific and spatiotemporally controlled gas release in cardiovascular therapy.

Overall, exogenous stimuli-responsive gas-delivery platforms provide an effective approach for achieving precise spatiotemporal control of gases by converting endogenous microenvironmental signals or exogenous physical stimuli into programmable release events. Endogenous systems rely on lesion-associated features, including acidic environments, oxidative stress, and abnormal enzyme expression to achieve selective release, whereas exogenous stimuli offer superior controllability and operational flexibility. The rational convergence of these strategies, along with the optimization of biosafety profiles and release kinetics, will be essential for advancing gas-based therapeutics toward clinical applications in cardiovascular disease.

As highlighted in the Introduction, therapeutic requirements for cardiac gasotransmitter delivery vary substantially across different stages of disease progression. Acute ischemic injury, subacute inflammatory responses, and chronic cardiac remodeling each present distinct pathological microenvironments and therapeutic objectives, thereby influencing the suitability of different delivery strategies. While localized in situ, systemic intravenous, and stimuli-responsive platforms have generally been discussed according to their engineering characteristics, their relative advantages may also depend on the temporal stage of cardiovascular disease. To provide a stage-oriented perspective, Table 2 summarizes the potential applicability, key advantages, and current limitations of gasotransmitter delivery platforms across different stages of cardiac disease progression.

Future Perspectives and Translational Challenges

To better structure the discussion of future directions and translational challenges, gas delivery platforms are further evaluated from the perspective of translational readiness. Future progress in gasotransmitter-based cardiovascular therapies will depend on overcoming several fundamental barriers that continue to hinder clinical translation. Despite substantial advances in localized, systemic, and stimuli-responsive delivery strategies, maintaining therapeutic gas concentrations within a narrow biological window remains challenging due to the rapid diffusion, short biological half-lives, and context-dependent effects of NO, CO, and H_2S. Moreover, the heterogeneous and dynamic nature of cardiovascular diseases imposes distinct therapeutic requirements across different pathological stages, suggesting that no single delivery platform is likely to be universally optimal. Collectively, these limitations highlight the need for a shift from isolated platform optimization toward disease-mechanism-guided integration of delivery strategies.

Although significant progress has been made in elucidating the cardioprotective roles of NO, H_2S, and CO, their clinical translation remains limited. As summarized in Table 3, NO-based therapies have achieved the most advanced level of clinical application, whereas H_2S- and CO-based interventions remain largely at early clinical or preclinical stages. Notably, although nanocarrier-based and stimuli-responsive delivery systems have demonstrated promising preclinical efficacy, they have not yet progressed into cardiovascular clinical trials. These observations highlight the substantial gap that still exists between preclinical innovation and clinical implementation.

Importantly, future delivery systems should increasingly account for physiological characteristics unique to the heart that distinguish cardiac gas therapy from other biomedical delivery applications. The continuous mechanical motion of the myocardium imposes substantial challenges for maintaining local material retention and delivery stability, particularly for injectable and implantable systems. In addition, the therapeutic window following myocardial infarction is often limited and dynamically evolves with disease progression, requiring delivery systems capable of temporally coordinated intervention. Cardiac pathological microenvironments exhibit substantial stage-dependent heterogeneity in oxidative stress, inflammatory activity, and metabolism, suggesting that static release systems may be insufficient to accommodate evolving therapeutic demands. Furthermore, achieving myocardial specificity after systemic administration remains challenging because of rapid systemic distribution and limited cardiac accumulation. Therefore, future delivery strategies should integrate adaptive release behavior, disease-stage-specific responsiveness, and enhanced myocardial targeting while preserving translational simplicity and clinical feasibility.

Table 1 Representative Stimuli-Responsive Gas-Delivery Systems for Cardiovascular Therapy Categorized by Gas Type, Trigger Modality, Delivery Vehicle, Disease Model, and Therapeutic Outcome

Gas Type	Trigger Modality	Delivery Vehicle	Cardiovascular Disease Model	Key Reported Outcome	Ref.
H_2S	pH-responsive	Platelet membrane-coated pH-responsive H_2S nanoparticles	Mouse myocardial ischemia–reperfusion injury	Targeted H_2S release reduced oxidative stress and inflammation, resulting in improved cardiac function after I/R injury	[178]
NO	ROS-responsive	Mitochondria-targeted peptide–drug conjugates	Mouse myocardial infarction	ROS-triggered NO release restored mitochondrial homeostasis, reduced myocardial injury, and improved cardiac function	[179]
NO	ROS-responsive	ROS-scavenging and NO-releasing nanoplatform	Oxidative stress-induced endothelial injury and vascular disease model	Improved endothelial function, suppressed ER stress, enhanced NO bioavailability, and promoted vascular protection	[182]
H_2S and O_2	ROS/pH-responsive	Multifunctional gas-generating nanomedicine	Atherosclerosis mouse model	Suppressed plaque inflammation, alleviated local hypoxia, and slowed atherosclerotic progression	[180]
NO and H_2S	Enzyme-responsive	β-Galactosidase-responsive hybrid NO–H_2S prodrug	Post-myocardial infarction heart failure	Sequential dual-gas release improved cardiac function and enhanced cardioprotection through synergistic signaling	[183]
NO	Ultrasound-triggered	Cell membrane-coated BNN6-loaded biomimetic nanoparticles	Murine myocardial ischemia–reperfusion injury	Reduced oxidative stress, improved microvascular perfusion, and attenuated cardiomyocyte apoptosis	[181]
H_2S	Ultrasound-triggered	H_2S-loaded microbubbles	Rat myocardial ischemia–reperfusion injury	Decreased oxidative stress and inflammation, reducing myocardial injury and improving cardiac function	[188]
H_2S	Ultrasound-mediated biological regulation	H_2S donor (GYY4137) combined with low-frequency ultrasound	Human pulmonary artery model	Ultrasound modulated H_2S-mediated vascular responses by inhibiting calcium sensitization and vascular contraction	[189]
NO and H_2S	Photo-responsive /Photochemical activation	Fluorescent dual-gas donor	In vitro proof-of-concept cardiovascular delivery model	Achieved controllable and traceable dual-gas release with precise spatiotemporal regulation	[193]
H_2S	Magnetic-field-guided and pH-responsive	Fe_7S_8@liposome nanocarrier	Small-animal cardiovascular disease model	Enhanced target-site accumulation and localized H_2S release while minimizing off-target exposure	[194]

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Table 2 Disease-Stage-Dependent Applicability of Cardiac Gasotransmitter Delivery Platforms Across in Situ, Systemic Intravenous, and Stimuli-Responsive Strategies

Delivery Platform	Localized in situ Delivery (Hydrogel/Microneedle/Spray Systems)	Systemic Intravenous Delivery (Nanocarriers/Biomimetic Systems)	Stimuli-Responsive Delivery (Endogenous/Exogenous Triggers)	Ref.
Acute myocardial infarction (ischemia/reperfusion)	Rapid, high local gas concentration; effective for limiting early ischemia–reperfusion injury and acute oxidative stress	Moderate efficacy; dependent on passive/active accumulation and perfusion status during acute ischemia	Very high suitability (especially exogenous systems such as ultrasound/light) enabling on-demand burst release during acute injury	[195–200]
Subacute inflammatory phase	Moderate utility; mainly supports local anti-inflammatory modulation and tissue repair initiation	High relevance; matches sustained inflammatory signaling and endothelial dysfunction phases	Very high suitability due to ROS/pH/enzyme-responsive release aligned with inflammatory microenvironment dynamics	[196,199,201,202]
Chronic remodeling/heart failure	Limited applicability due to invasiveness and need for implantation or repeated local administration	Highly suitable for long-term disease modulation, remodeling control, and repeated dosing regimens	Moderate to high suitability depending on trigger stability and device accessibility for chronic intervention	[199,202–204]
Key advantages in this stage	High local bioavailability; minimal systemic exposure; spatiotemporally confined release	Clinically feasible administration; scalable manufacturing; potential for repeated dosing and long-term therapy	Precise spatiotemporal control; on-demand release; adaptable across disease stages; high design flexibility	[199,202]
Major limitations	Invasiveness (hydrogels/patches), limited long-term deployment, poor suitability for chronic disease management, fabrication/implantation complexity	Poor targeting efficiency in early ischemia, rapid clearance, off-target distribution, variability in biodistribution	Dependence on trigger intensity or external equipment; potential signal attenuation; long-term safety and clinical device integration challenges	[197,199,205]

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Table 3 Current Clinical Translation Status of Gasotransmitter-Based Therapies for Cardiovascular Applications

Gasotransmitter	Representative Clinical Approach	Cardiovascular Indication	Development Stage	Delivery Modality	Reported Outcome/Current Status	Ref
NO	Inhaled nitric oxide (iNO)	Pulmonary hypertension, perioperative cardiovascular support, right ventricular dysfunction	Clinical use/ approved in selected indications	Inhalation	Effective pulmonary vasodilation and improvement of oxygenation; however, benefits in myocardial I/R protection remain inconclusive.	[14,206,207]
NO	Nitrite- or nitrate-based NO supplementation	Myocardial ischemia–reperfusion injury, heart failure	Early clinical studies	Oral or intravenous administration	Demonstrated biological activity and acceptable safety, but inconsistent cardioprotective efficacy has limited widespread clinical adoption.	[208–210]
H_2S	SG1002 and other H_2S-releasing compounds	Heart failure and cardiovascular dysfunction	Early-phase clinical evaluation	Oral administration	Increased circulating H_2S and NO bioavailability with favorable safety profiles; larger efficacy studies are still required.	[211]
H_2S	ATB-346 and related H_2 S donor drugs	Primarily non-cardiovascular indications	Clinical trials	Oral administration	Clinical development has demonstrated safety and pharmacological feasibility, but cardiovascular efficacy remains unconfirmed.	[212,213]
CO	Controlled inhaled carbon monoxide	Ischemia–reperfusion injury and inflammatory cardiovascular conditions	Early clinical investigation	Inhalation	Feasibility demonstrated under carefully controlled dosing; cardiovascular efficacy remains insufficiently established.	[214]
Stimuli-responsive gas delivery systems ($NO/H_2S/CO$)	Ultrasound-, light-, magnetic-, or microenvironment-responsive nanoplatforms	Myocardial infarction, I/R injury, atherosclerosis, heart failure	Preclinical only	Engineered nanocarriers	No registered cardiovascular clinical trials have been reported to date, representing a major translational gap.	[199,215]

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First, gas therapy is expected to evolve from single-gas administration toward multi-gas or gas-drug synergistic strategies, enabling the coordinated regulation of vascular tone, inflammation, redox balance, and mitochondrial function. Second, delivery systems should transition from static release profiles to microenvironment-adaptive and feedback-regulated platforms capable of dynamically responding to disease progression and therapeutic demands. Third, material design must prioritize translational simplicity, favoring scalable architectures with predictable biosafety over those with excessive structural or targeting complexity.

Beyond therapeutic performance, several translational hurdles require further consideration before clinical implementation can be realized. Scalable and reproducible manufacturing processes remain challenging for many multifunctional nanoplatforms because increasing structural sophistication often complicates quality control and batch-to-batch consistency. Long-term biosafety evaluation, including material degradation behavior, off-target accumulation, chronic toxicity, and pharmacokinetic profiles, remains insufficient in most preclinical studies. Moreover, current evidence is derived predominantly from short-term efficacy assessments in small-animal models, highlighting the need for large-animal validation, long-term therapeutic outcome studies, and clinically relevant safety evaluations. Regulatory approval pathways for multifunctional gas-delivery systems are also not yet well established because these platforms frequently combine features of drugs, biomaterials, and medical devices. Real-world implementation will additionally require compatibility with existing clinical workflows, cost-effectiveness, and practical administration strategies.

Given the diverse advantages and limitations associated with currently available delivery strategies, a systematic comparison is necessary to better understand their translational potential. Although localized in situ delivery, systemic intravenous administration, and stimuli-responsive delivery platforms have all demonstrated therapeutic promise, they differ substantially in terms of targeting precision, release controllability, invasiveness, biosafety, and clinical feasibility. To facilitate the identification of future development priorities, the major characteristics of these representative delivery paradigms are summarized in Table 4.

Table 4 Comparative Evaluation of Representative Gas Delivery Strategies for Cardiovascular Therapy

Evaluation Dimension	Localized in situ Delivery	Systemic Intravenous Delivery	Stimuli-Responsive Delivery	Ref.
Spatial Precision	Very high; direct administration into the myocardium or pericardial space enables localized drug deposition, although precision may depend on procedural expertise.	Low; therapeutics are distributed systemically, resulting in limited cardiac accumulation.	High; drug release is selectively activated by pathological cues such as acidic pH, elevated ROS levels, or disease-associated enzymes.	[216–222]
Temporal Controllability	Low; typically limited to single or infrequent administrations with minimal dynamic control over release kinetics.	Moderate; partial control can be achieved through repeated dosing or sustained-release formulations.	High; enables on-demand, pulsatile, or sustained release in response to specific stimuli.	[218,221,223]
Invasiveness	High; generally requires thoracotomy, catheter-based intervention, or intramyocardial injection.	Low; administered through routine intravenous injection.	Low to moderate; administration is typically intravenous, while stimuli-triggered release occurs noninvasively at the target site.	[221,224,225]
Cardiac Targeting Efficiency	High; achieves elevated local concentrations and strong site-specific retention.	Low; cardiac accumulation is generally limited and highly dependent on carrier design.	Moderate to high; integration of active targeting and stimuli-responsive release can enhance myocardial retention and local bioavailability.	[197,199,226]
Biosafety Profile	Moderate to high; risks include local inflammation, tissue injury, bleeding, and fibrosis, although systemic adverse effects are generally minimized.	Low to moderate; potential concerns include off-target toxicity, hepatic and splenic accumulation, and immune responses.	Moderate; reduced systemic exposure may improve safety, but long-term biocompatibility and degradation products require further evaluation.	[204,227,228]

(*Continued*)

Table 4 (Continued).

Evaluation Dimension	Localized in situ Delivery	Systemic Intravenous Delivery	Stimuli-Responsive Delivery	Ref.
Clinical Feasibility	Moderate; catheter-based and intramyocardial delivery approaches have been evaluated clinically, but invasive procedures remain necessary.	High; utilizes established administration routes with favorable translational potential.	Low to moderate; most platforms remain at the preclinical stage, with only limited stimuli-responsive systems advancing toward clinical evaluation.	[229–231]

As summarized in Table 4, localized in situ delivery provides superior spatial precision and myocardial retention but remains constrained by procedural invasiveness. Systemic intravenous delivery offers the greatest clinical practicality and scalability, although limited cardiac accumulation and off-target distribution remain major obstacles. Stimuli-responsive systems present an attractive intermediate strategy by integrating controlled release with enhanced targeting capability; however, their translational readiness is currently limited by manufacturing complexity, regulatory uncertainty, and insufficient long-term safety validation. Future platform development should therefore focus on combining the strengths of these approaches while minimizing their respective limitations.

From a translational perspective, gas delivery platforms should also be systematically evaluated beyond therapeutic efficacy. Key criteria include manufacturability under good manufacturing practice (GMP) conditions, regulatory feasibility based on material composition and system complexity, and validation in clinically relevant large animal models. In general, systems with simplified architectures such as hydrogel-based local delivery platforms and conventional nanoparticle formulations tend to demonstrate higher scalability and more established regulatory pathways, whereas highly engineered multifunctional or stimuli-responsive systems often face challenges in large-scale production, safety assessment, and unclear approval routes. In addition, the limited use of large animal models in current studies further restricts the predictive value of preclinical findings and remains a critical gap for clinical translation.

Future research priorities should therefore focus on balancing therapeutic sophistication with real-world applicability by integrating disease-specific mechanisms, adaptive delivery control, and clinically practical platform design. Rather than pursuing increasingly complex multifunctional systems alone, future efforts should emphasize reproducibility, standardized evaluation frameworks, and patient-oriented therapeutic strategies. Such advances may ultimately facilitate the realization of precision cardiovascular medicine through personalized and dynamically regulated gas-based interventions tailored to specific pathological conditions and disease stages.

Conclusions

Gaseous signaling molecules have emerged as a promising therapeutic mediators for cardiovascular diseases, offering potent cardioprotective and regulatory functions. However, their clinical translation remains fundamentally constrained by intrinsic physicochemical properties, including short biological half-lives, rapid diffusion, and narrow therapeutic windows. Controlled delivery has therefore become an essential strategy for converting gasotransmitter biology into effective and safer cardiovascular therapies.

Current gas delivery platforms can be broadly classified into localized delivery systems, systemic nanocarrier-based platforms, and stimuli-responsive delivery systems. These approaches are complementary rather than universally interchangeable. Localized delivery approaches, such as injectable hydrogels and implantable patches, enable high local gas retention and reduced systemic exposure, but their clinical applicability is restricted by invasiveness and limited accessibility to deep tissues. Systemic nanocarrier-based platforms offer improved circulation stability and compatibility with intravenous administration, yet their clinical translation is often hindered by suboptimal targeting efficiency, complex pharmacokinetics, and challenges in in vivo reproducibility. Stimuli-responsive systems further enable spatiotemporally controlled gas release in response to endogenous pathological cues or external triggers. Nevertheless, most

remain at an early preclinical stage, with limited validation in large-animal models and unresolved challenges in structural complexity, manufacturing scalability, and long-term biosafety.

From a translational perspective, a substantial gap still exists between preclinical innovation and clinical implementation. Among gasotransmitters, NO-based interventions have achieved the most advanced clinical use, particularly in inhalation-based and vasodilatory applications, whereas CO- and H_2S-related therapies remain largely confined to early clinical exploration or preclinical development. More sophisticated delivery systems, including multifunctional nanoplatforms and stimuli-responsive carriers, have not yet achieved clear cardiovascular clinical translation despite promising experimental efficacy. Future studies should therefore prioritize clinically adaptable platform design, standardized evaluation criteria, scalable manufacturing, regulatory feasibility, and validation in clinically relevant long-term and large-animal models. Rather than pursuing increasing platform complexity alone, the next stage of gasotransmitter therapy should focus on mechanism-guided, disease-stage-specific, and clinically practical delivery systems capable of supporting precision cardiovascular medicine.

Data Sharing Statement

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

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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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