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EDITORIAL COMMENT

Hydrogen Sulfide Therapy Promotes Beneficial Systemic Effects in Experimental Heart Failure*

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Heart failure is accompanied by a chronic systemic and local activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Local neurohumoral activation in the myocardium contributes, at least in part, to interstitial cardiac fibrosis, cardiomyocyte hypertrophy, oxidative stress, contractile dysfunction, and extracellular matrix remodeling leading to chamber dilatation (1). Systemic features of the heart failure syndrome, such as kidney dysfunction, vasoconstriction and endothelial dysfunction, and skeletal muscle fatigue, are also affected by neurohumoral activation (2). As such, the inhibition of the RAAS and SNS (e.g., with angiotensin-converting enzyme [ACE] inhibitors, mineralocorticoid receptor antagonists, and beta-blockers) is a cornerstone of modern heart failure therapy. Nevertheless, morbidity and mortality from heart failure remain high and there is a vital need for new therapies. Since the use of RAAS inhibitors may be limited by renal dysfunction, which is common in advanced heart failure, therapies that improve both cardiac and renal status are especially desirable.

In this issue of *JACC: Basic to Translational Science,* Li et al. (3) investigated the effects of a novel class of therapeutic agents, namely hydrogen-sulfide (H_2S)-based drugs. Although the efficacy of these agents has previously been studied immediately after pathological insults (e.g., experimental myocardial infarction and pressure overload) (4), here the focus was on a relatively delayed administration of an H_2S-donor, JK-1, in an attempt to more closely parallel the clinical setting. Li et al. (3) found that in a murine model of pressure overload-induced heart failure, the administration of JK-1 after the development of cardiac remodeling was able to significantly delay the progression of remodeling and contractile impairment. Moreover, they observed a significant improvement in renal dysfunction, endothelial dysfunction, and exercise tolerance compared with untreated animals, therefore achieving a combination of beneficial systemic effects.

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H_2S is an endogenous gasotransmitter that is reported to have pleiotropic cardiovascular effects including vasodilation, angiogenesis, and cytoprotection (5). The physiological production of H_2S is predominantly enzymatically controlled by enzymes involved in cysteine metabolism: cystathionine β-synthase, cystathionine γ-lyase, and 3-mercaptopyruvate sulfurtransferase (see **Figure 1**). All 3 enzymes are expressed in cardiovascular cells, including cardiomyocytes and endothelial cells (6). A key physiological action of H_2S is to mediate vasorelaxation (7,8), which may involve activation of the vascular smooth muscle K_{ATP} channel and/or an enhancement of endogenous nitric oxide (NO) signaling; NO itself is a central mediator of endothelium-dependent vasorelaxation. H_2S also has potent cytoprotective actions, including an ability to

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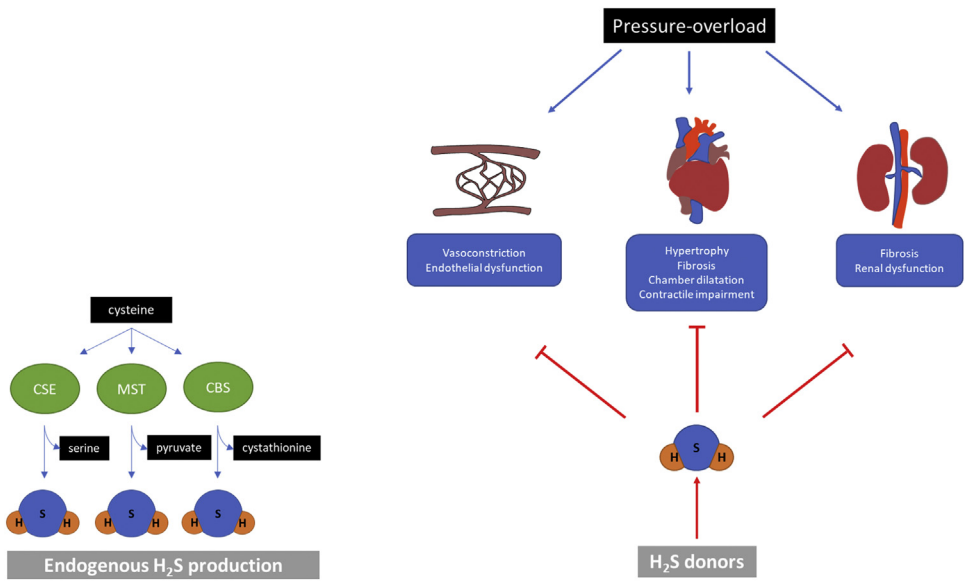
FIGURE 1 Schematic of Potential Effects of H_2S



The inset **(box)** shows pathways for endogenous production of hydrogen sulphide (H_2S). CBS = cystathionine β-synthase (CBS); CSE = cystathionine γ-lyase; MST = mercaptopyruvate sulfurtransferase.

inhibit apoptosis, promote angiogenesis, maintain mitochondrial function, and attenuate oxidative stress through activation of Nrf2-dependent pathways (9). The vasoactive and cytoprotective properties of H_2S therefore make it a promising adjunct to treat the deleterious local and systemic effects of RAAS and SNS activation in heart failure.

Developing "donors" of H_2S has focused on extending its half-life (seconds to minutes) and therefore its duration of action, and on achieving therapeutic concentrations without toxicity. JK-1 is a phosphorothioate synthetic compound that liberates H_2S in a pH-sensitive fashion in aqueous solutions (10). Its tolerability, dosing, safety, and efficacy have previously been established by this group in a mouse model of ischemia-reperfusion myocardial injury in which intramyocardial injections were used to deliver JK-1 (10). In the current study (3), the authors administered intraperitoneal injections of JK-1 commencing either 3 or 10 weeks after transverse aortic constriction (TAC). Although the early treatment had a greater magnitude of effect on LV ejection fraction and remodeling, treatment at 10 weeks also led to a significant delay of adverse heart failure phenotypes at 18 weeks compared with the untreated group. This included a reduction in chamber dilatation, significantly reduced cardiac fibrosis and diastolic dysfunction, reduced renal fibrosis and improved renal function, improved endothelial function, and a longer exercise duration. The authors confirmed that JK-1 significantly increased myocardial and renal H_2S levels as well as cyclic GMP levels (a readout for increased NO bioactivity), and reduced circulating markers of RAAS activity and BNP levels. The most interesting findings are that even relatively delayed treatment with JK-1 had substantial beneficial effects on renal and vascular function in this model, in addition to modest cardiac effects.

It is feasible that the effects of JK-1 observed by Li et al. (3) may involve local actions in the heart, vasculature, and kidneys. However, the study design does not exclude the possibility that some of the salubrious extracardiac effects might be secondary to improved cardiac function or related to reduction in SNS/RAAS activation. The authors reported that JK-1-treated mice had a similar systemic blood pressure to control untreated TAC animals, suggesting that its effects are not related simply to a reduction in blood pressure. Crosstalk between H_2S and NO is well recognized (6) and an enhancement in NO signaling could be another mechanism contributing to these effects.

This study highlights the potential of gasotransmitters with primarily vasoreactive properties

(H_2S, NO, and CO) as therapeutic targets in heart failure. NO has long been considered a promising target, although the major focus at present is on modulators of cyclic GMP production and signaling. Agents such as H_2S and NO that improve endothelial function are considered promising, at least in part because they act in multiple organs affected in heart failure. Li et al. (3) are to be commended for designing a study that investigates delayed treatment in an experimental heart failure model. In particular, their global analysis approach with the inclusion of renal function and exercise duration readouts goes beyond the common cardiocentric view of experimental heart failure in rodent models. However, there remain significant limitations in extrapolating these data to the clinical setting. TAC-induced heart failure is an imperfect model in many ways, and even 18 weeks of follow-up may be too short in comparison to human heart failure. More importantly, like most other investigators undertaking this type of work, Li et al. (3) performed their studies in young healthy mice and used an untreated control group. The key question from a clinical perspective for any potential new heart failure therapy is whether it has significant additive effects on top of standard anti-RAAS and anti-SNS drugs and whether it works in older age groups. These are challenging studies to undertake in rodent models, but the current work sets some of the groundwork for future studies, ideally in large animals or even in humans, to investigate the potential of H_2S donors as a heart failure therapy.

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