

# The cGMP Signaling Pathway as a Therapeutic Target in Heart Failure With Preserved Ejection Fraction

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**H**eat failure with preserved ejection fraction (HFpEF) is a growing public health problem that accounts for approximately half of all prevalent heart failure (HF).<sup>1,2</sup> Once believed to carry a favorable prognosis compared with HF and reduced ejection fraction (HFrEF), contemporary data suggest that both groups face similar outcomes in the community setting.<sup>1,3</sup> Although survival rates for patients with chronic HFrEF have improved in the last 2 decades with advances in drug and device-based therapies, there has been no such parallel progress in HFpEF management,<sup>4</sup> and treatment remains largely limited to the active recognition and treatment of comorbidities and the use of diuretics. The prevalence of HFpEF relative to HFrEF continues to rise at  $\approx 1\%$  per year, projecting it to be the more common form of HF over the next decade.<sup>5,6</sup> HFpEF is particularly common in the elderly and is associated with a significant risk of death, hospitalization and suboptimal quality of life. Thus, there remains an enormous unmet need for effective therapy for this group of patients.<sup>7,8</sup>

Augmentation of cyclic guanosine monophosphate (cGMP) signaling is recognized as a potential therapeutic strategy in

HFpEF based on several preclinical and clinical studies that have investigated various mechanisms and effects of cGMP enhancement.<sup>7,9–14</sup> However, the recent neutral result of the Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) trial with the phosphodiesterase-5 (PDE-5) inhibitor sildenafil has challenged this strategy.<sup>11</sup> Nevertheless, there are multiple pharmacologic strategies for cGMP pathway modulation and the effects of an intervention might vary with the mode and pathway site of action. In this article, we review the physiology and pathophysiology of the cGMP signaling pathway as it relates to HFpEF, discuss the various pharmacologic mechanisms for pathway modulation, appraise the current body of evidence for the multiple agents targeting cGMP enhancement, and outline future directions for drug development targeting cGMP enhancement as treatment for HFpEF.

## The cGMP Signaling Cascade

Guanylate cyclases represent a widely distributed family of enzymes that convert guanosine triphosphate to the second-messenger molecule cGMP.<sup>15</sup> The 2 primary forms are the transmembrane-associated particulate guanylate cyclase, which functions as a receptor for natriuretic peptides, and the soluble guanylate cyclase (sGC), which serves as a receptor for nitric oxide (NO) (Figure 1).<sup>16</sup> The physiologic actions of cGMP are mediated through intracellular effector molecules, namely, cGMP-dependent protein kinases, cGMP-gated ion channels, and cGMP-regulated phosphodiesterases.<sup>17,18</sup> cGMP contributes to the normal function of vital organs, and alterations in signaling have been implicated in derangements of multiple end-organ systems.<sup>15,19–24</sup>

## cGMP and HFpEF Pathophysiology

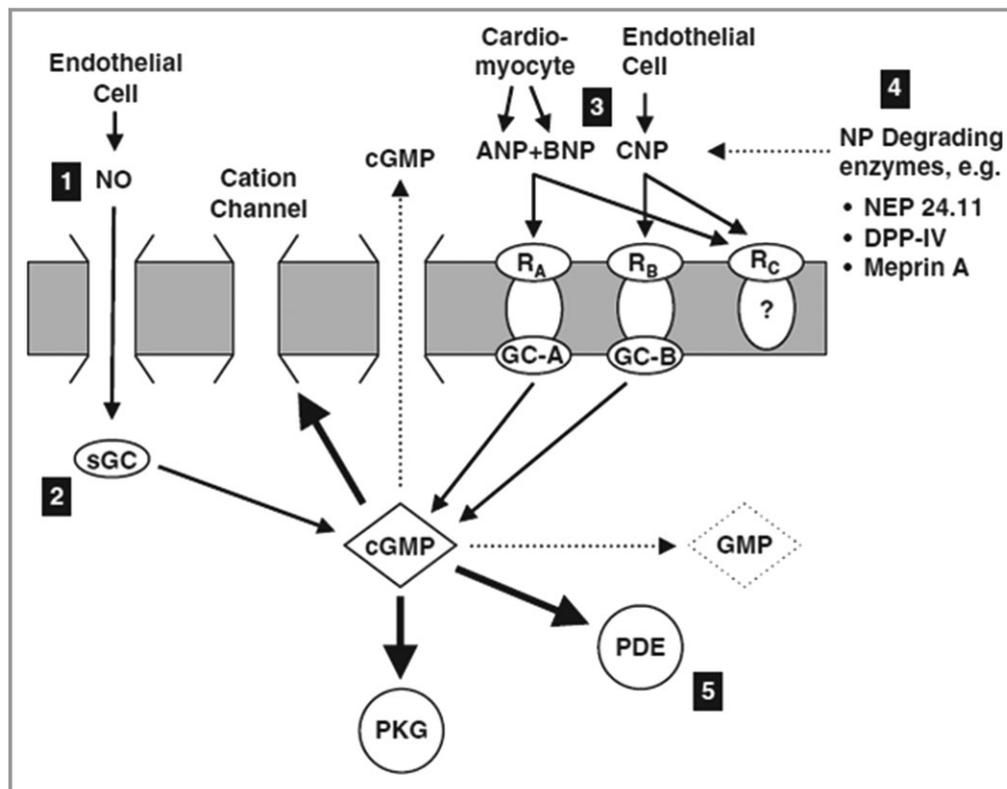
Once thought synonymous with diastolic dysfunction, HFpEF is now understood as a complex interplay between increased left ventricular (LV) and peripheral vascular stiffness, right and

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**Figure 1.** cGMP signaling pathways. cGMP is the second messenger of 2 distinct signaling pathways: (1) NO is produced by endothelial cells and binds to sGC in the target cell; and (2) ANP and BNP, derived primarily from cardiomyocytes, stimulate GC-A, whereas CNP, secreted by endothelial cells, stimulates GC-B. cGMP signaling may be augmented by (1) the use of NO mimetics such as nitrovasodilators; (2) sGC activators or stimulators; (3) increasing levels of natriuretic peptides; (4) by inhibiting natriuretic peptide degrading enzymes; and (5) inhibiting the activity of cGMP-hydrolyzing PDEs. ANP indicates atrial natriuretic peptide; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; DPP4, dipeptidyl peptidase IV; GC, guanylate cyclase; GMP, guanosine monophosphate; NEP, neutral endopeptidase; NO, nitric oxide; PDE, phosphodiesterase; PKG, protein kinase G; RA, natriuretic peptide receptor A; sGC, soluble guanylate cyclase. Adapted with permission from Boerrigter et al.<sup>16</sup>

LV diastolic and systolic dysfunction, and chronotropic incompetence that results in abnormal ventricular relaxation and elevated LV end-diastolic pressures.<sup>5</sup> This mechanistic understanding provides compelling rationale for targeting cGMP activity (Figure 2).<sup>25</sup>

### Diastolic Function

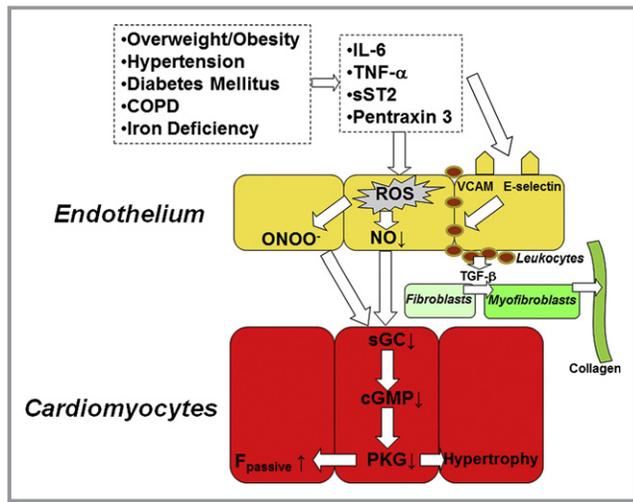
LV diastolic dysfunction is universally seen in HFpEF, and many patients have evidence of increased LV mass or relative wall thickness.<sup>26</sup> sGC may reduce myofilament calcium sensitivity and exert beneficial effects on cross-bridge detachment, consistent with the ability of the NO donor sodium nitroprusside to increase cGMP generation and hasten LV relaxation.<sup>27</sup> A more recently characterized mechanism may be activation of cGMP-dependent protein kinases, which have been shown to favorably influence ventricular hypertrophy, and diastolic relaxation and stiffness.<sup>13,28–30</sup>

### Systolic Function

Despite preserved LV ejection fraction, many HFpEF patients have concurrent systolic dysfunction.<sup>31</sup> Regional measures of systolic function with tissue Doppler may show depression of both longitudinal and radial ventricular contractile function.<sup>32–35</sup> Moreover, there is an elevation in end-systolic elastance and passive ventricular stiffening.<sup>31,36</sup> In the myocardium, sGC modulates contractility and attenuates adrenergic stimulation.<sup>37–43</sup> However, beyond these myocardial effects, reversal of cardiac endothelial dysfunction may improve ventricular performance secondary to improvement in coronary blood flow.<sup>44</sup>

### Structural Cardiac Changes

Many HFpEF patients have increased LV mass or relative wall thickness and may have concentric remodeling or hypertrophy. Total LV chamber size is typically normal or near normal, but the

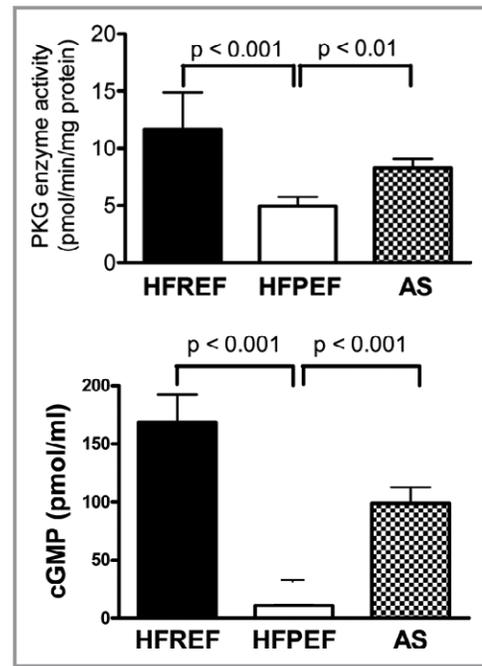


**Figure 2.** cGMP signaling and myocardial dysfunction and remodeling in HFpEF. Comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , soluble ST2 (sST2), and pentraxin 3. Coronary microvascular endothelial cells reactively produce reactive oxygen species (ROS), vascular cell adhesion molecules (VCAMs), and E-selectin. Production of ROS leads to formation of peroxynitrite (ONOO<sup>-</sup>) and reduced nitric oxide (NO) bioavailability, both of which lower soluble guanylate cyclase (sGC) activity in adjacent cardiomyocytes. Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. Low PKG activity increases resting tension ( $F_{\text{passive}}$ ) of cardiomyocytes because of hypophosphorylation of titin and removes the brake on prohypertrophic stimuli inducing cardiomyocyte hypertrophy. VCAM and E-selectin expression in endothelial cells favors migration into the subendothelium of monocytes. These monocytes release transforming growth factor  $\beta$  (TGF- $\beta$ ). The latter stimulates conversion of fibroblasts to myofibroblasts, which deposit collagen in the interstitial space. cGMP indicates cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction. Adapted and modified with permission from Paulus and Tschope.<sup>25</sup>

cardiomyocytes themselves may have increased diameter compared with HFREF.<sup>45</sup> Likewise, changes in the interstitial matrix, notably fibrosis, have been described. Experimental models of cardiac fibroblast activation have induced HF through generation of diffuse fibrosis,<sup>46</sup> which in turn is associated with diastolic dysfunction<sup>47</sup> and risk of arrhythmia or death.<sup>48–50</sup> Agents targeting cGMP signaling elicit antihypertrophic effects and may favorably influence cardiac remodeling at doses not affecting blood pressure<sup>51</sup> and attenuate cardiac fibrosis.<sup>52,53</sup>

### cGMP-Dependent Protein Kinase Phosphorylation

Novel molecular understanding of cardiac mechanotransduction in normal and failing myocardium has provided an added perspective on the role of cGMP and protein kinase G (PKG) in HFpEF. Titin, a protein anchored to the sarcomere Z-line that serves as a major determinant of myocardial passive tension



**Figure 3.** PKG activity and cGMP concentration in myocardial tissue from patients with heart failure with reduced and preserved ejection fraction and aortic stenosis. AS indicates aortic stenosis; cGMP, cyclic guanosine monophosphate; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; PKG, protein kinase G. Adapted and modified with permission from van Heerebeek et al.<sup>13</sup>

and stiffness, can be modulated via phosphorylation.<sup>54,55</sup> Although the ability of cAMP-dependent protein kinase A to phosphorylate titin had been well known, it was more recently discovered that PKG can mediate similar phosphorylation in both dog and human hearts.<sup>29,56</sup> This posttranslational modification promotes reduction in titin-based passive tension and thus may represent a promising therapeutic target for reducing myocardial stiffness. A study of myocardial biopsies among patients with HFpEF, HFREF, and aortic stenosis evaluated the relationship between cardiac PKG, cardiomyocyte resting tension, and upstream regulation with levels of cGMP, natriuretic peptides, and oxidative stress.<sup>13</sup> Of the 3 cohorts, HFpEF had significantly lower PKG and cGMP activity, high myocardial resting tension, and a higher degree of oxidative stress (Figure 3).<sup>13</sup> In vitro administration of PKG resulted in significantly greater improvement in resting tension among HFpEF patients relative to those with HFREF and aortic stenosis.

### Vascular Function and Stiffness

Patients with HFpEF have significantly impaired systemic vasorelaxation with exercise, limiting cardiac output reserve under stress,<sup>57–59</sup> and exhibit limited flow-mediated

vasodilation compared with healthy age-matched controls,<sup>58</sup> implicating the role of endothelial dysfunction. Moreover, endothelial dysfunction corresponds to the severity of HF symptoms, exercise capacity, and exertional intolerance.<sup>58</sup> NO-dependent regulation is a significant modulator of vascular tone, and decreased NO bioavailability in HFpEF favors vasoconstriction and vascular stiffness, amplifying afterload. Decreased NO bioavailability may also upregulate sympathetic drive and catecholamine release,<sup>60</sup> and enhance endothelin-1-induced vasoconstriction.<sup>61</sup>

## Pulmonary Hypertension

Among elderly patients with a normal LV ejection fraction, HFpEF is the most common cause of elevated pulmonary pressures.<sup>62</sup> Elevated pulmonary artery pressure is predictive of increased mortality in HFpEF.<sup>63</sup> High LV end-diastolic pressures can induce both a passive increase in pulmonary artery pressure via retrograde pressure transmission, and a reactive increase in pulmonary vascular resistance with elevations in the transpulmonary gradient out of proportion to the LV end-diastolic pressure.<sup>64</sup> Enhancement of cGMP in patients with pulmonary arterial hypertension improves hemodynamics, functional status, and exercise capacity.<sup>65</sup> Given the significant overlap between diastolic dysfunction and pulmonary hypertension, it has been hypothesized that cGMP modulating agents efficacious in pulmonary arterial hypertension would be beneficial in HFpEF, but this has yet to be definitively proven.<sup>11</sup>

## Renal Function

Preclinical data suggest a role for cGMP in regulation of renal function with possible mechanisms including hemodynamic-associated and hemodynamic-independent modulation of endothelial function and organ fibrosis. Direct stimulation of sGC in acute and chronic glomerulonephritis may attenuate renal dysfunction and limit progressive sclerosis and matrix deposition.<sup>23,66,67</sup> Long-term sGC activation prevented increases in blood pressure, preserved renal function, improved natriuretic peptide levels, reduced LV hypertrophy, and slowed progress of renal disease in a rat model of chronic renal failure.<sup>68</sup> In a canine HF model, pharmacologic targeting of cGMP increased renal blood flow and reduced mean arterial and pulmonary capillary wedge pressure without concurrent decreases in glomerular filtration rate or upregulation of the renin-angiotensin-aldosterone system.<sup>69</sup>

## Other Peripheral Effects

Endothelial dysfunction has also been associated with abnormal ergoreflex and metaboreflex actions, which lead to

excessive ventilation in HF patients with exercise.<sup>70</sup> Guazzi et al observed that treatment with the PDE-5 inhibitor sildenafil improved this ergoreflex activation and that the magnitude of improvement correlated with enhancement in flow-mediated arterial dilatation.<sup>70</sup> In addition, recent studies have shown that many patients with HFpEF display abnormalities in peripheral oxygen utilization, uptake, or distribution in skeletal muscle that contribute to functional disability and symptoms.<sup>71,72</sup> As NO is known to play a key role in the regulation of mitochondrial respiration, perfusion, and excitation-contraction coupling in skeletal muscle,<sup>73</sup> it is plausible that cGMP enhancement would carry additional benefits for HFpEF patients outside the heart and vasculature.

## Disturbed cGMP Signaling and Strategies for Enhancement

Recently, a novel paradigm has been proposed that supports the critical role of deranged cGMP signaling in HFpEF pathophysiology.<sup>25</sup> It is proposed that the various comorbidities common to HFpEF patients foster a systemic inflammatory state contributing to endothelial dysfunction, reactive oxygen species production, nitrosative stress, and depressed NO bioavailability. This decreased NO bioavailability results in poor cGMP-dependent PKG signaling, with consequent effects on cardiac hypertrophy, relaxation, and stiffness. Consistent with this paradigm, multiple preclinical and clinical trials have explored or are planning to study the role of novel therapeutic interventions at various levels in the cGMP-signaling pathway.

## Nitric Oxide Donors and Nitrates

NO sits at the most upstream location of the cGMP pathway, and multiple studies have investigated it as a therapeutic target in HFpEF. Exogenous NO exerts a negative inotropic effect at high doses with earlier ventricular relaxation<sup>74</sup> and leads to a rightward shift of the length-tension relationship.<sup>75,76</sup> Intracoronary infusion of nitroprusside results in a decrease in LV peak systolic pressure and increases in diastolic distensibility.<sup>77</sup> Aside from effects on inotropy and ventricular compliance, NO is a mediator of myocardial energetics through regulation of mitochondrial respiration, oxygen consumption, and substrate utilization.<sup>77</sup> However, tolerance is a well-recognized limitation of organic nitrates, and both oxidative stress and impaired bioactivation of NO in HF may blunt the long-term effects of nitrate therapy.<sup>78</sup> Furthermore, chronic treatment with nitrates may cause oxidative stress via increased expression of endothelin, hence potentially exacerbating endothelial dysfunction.<sup>79</sup> Also, HFpEF patients were found to be 4 times more likely than those with HFrEF to experience a reduction in stroke volume with nitroprusside, suggesting greater vulnerability to preload

reduction.<sup>80</sup> Thus, although NO donors may be helpful in reducing LV filling pressures, cGMP enhancement via other agents with different regional vasoactivity may be preferred to minimize the risk of tolerability-limiting preload and blood pressure reduction. The National Institutes of Health plans to perform a small pilot study with oral nitrates assessing exercise tolerance in HFpEF patients to further explore the effect of cGMP modulation via nitrates.

### Phosphodiesterase-5 Inhibition

An alternative approach is to inhibit catabolism of cGMP through PDE-5 inhibition. PDE-5 inhibition blunts adrenergic stimulation,<sup>40</sup> attenuates maladaptive myocardial remodeling,<sup>30</sup> improves endothelial function,<sup>81</sup> and enhances the renal response to natriuretic peptides.<sup>82</sup> Commonly used for pulmonary arterial hypertension,<sup>65</sup> several small studies have explored the use of sildenafil in HFrEF patients with favorable results.<sup>70,83–85</sup> In HFpEF, a single-center study of 44 patients found significant improvements in central hemodynamics, left and right ventricular function, and lung function with PDE-5 inhibition.<sup>10</sup> However, in the multicenter RELAX trial, which included 216 stable ambulatory HFpEF patients,<sup>11</sup> sildenafil failed to significantly improve peak exercise oxygen consumption, clinical status rank score, or 6-minute walk distance at 24 weeks. In addition, there were no hemodynamic effects, including changes in systemic vascular resistance, consistent with a study of the drug in HFrEF and secondary pulmonary hypertension.<sup>84</sup> Moreover, there were no significant differences in plasma cGMP levels between sildenafil and placebo groups. The investigators postulated that the lack of a positive trial result may be related to the relatively modest level of pulmonary hypertension and LV hypertrophy in the RELAX trial compared with the study by Guazzi and colleagues, in which right ventricular function was markedly impaired with baseline right atrial pressures of 23 mm Hg, mean baseline pulmonary artery systolic pressure >50 mm Hg, and LV mass index >160 g/m<sup>2</sup>.<sup>10</sup> An alternative explanation centers on the lack of significant increase in plasma cGMP with sildenafil, suggesting a failure to adequately test the cGMP enhancement hypothesis. Along these lines, upregulation of PDE-5 has not been definitively shown to be the underlying mechanism of reduced cGMP signaling in HFpEF, and it may be less important to inhibit this enzyme if decreased cGMP production is instead the predominant problem.<sup>13,30</sup>

### sGC Activation and Stimulation

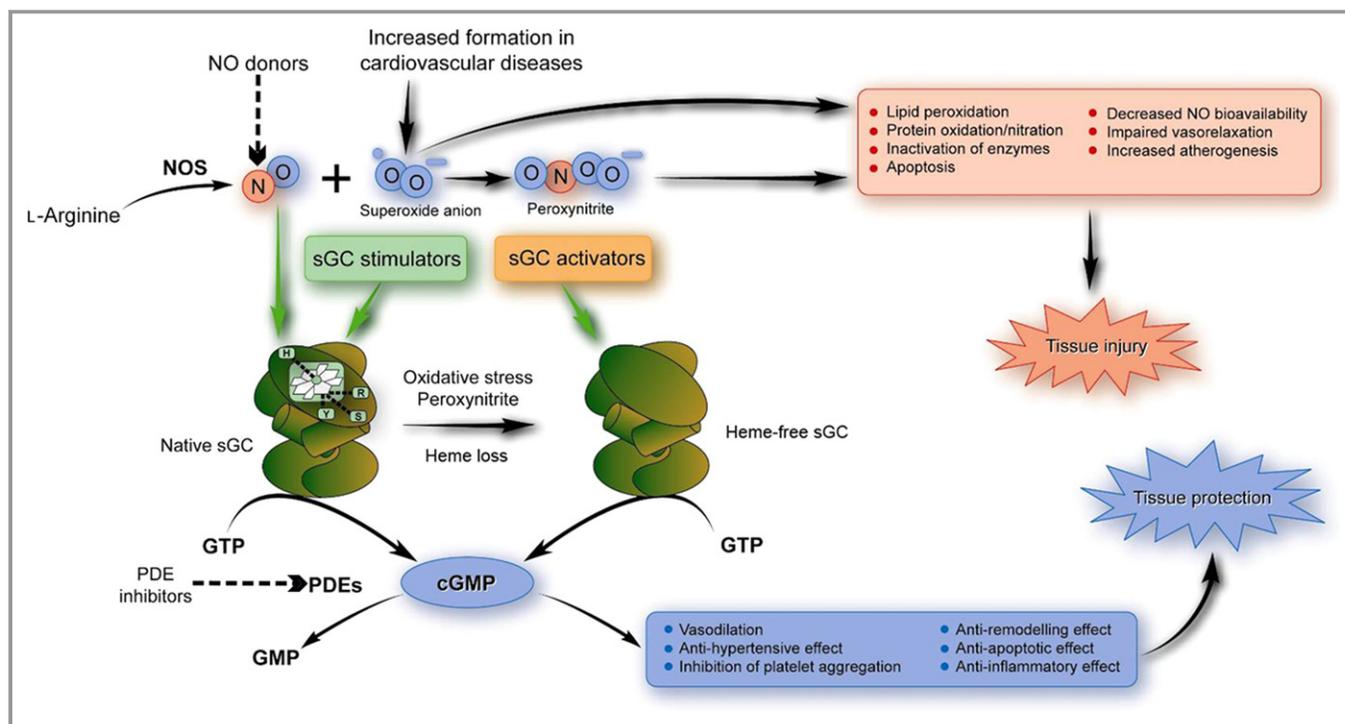
In the last 15 years, 2 classes of compounds have been discovered that are capable of modulating sGC in a NO-independent manner, the so-called sGC activators and sGC stimulators (Figure 4).<sup>86</sup>

In addition to reducing NO bioavailability, reactive oxygen species are capable of downstream cGMP pathway modulation via sGC inactivation. A reduced ferrous heme prosthetic group is required for sGC to facilitate NO-dependent cGMP stimulation. Oxidative stress shifts intracellular levels of native sGC toward the oxidized, dysfunctional, heme-free form that is unresponsive to both endogenous and exogenous NO.<sup>15,87</sup> This concept of NO resistance provides the rationale for sGC activators that bind to the unoccupied sGC heme-binding site, thereby favoring the active enzyme state.<sup>88</sup> The pharmacologic efficacy profile of cinaciguat, an intravenous sGC activator, has been explored in various in vivo models of myocardial infarction, chronic renal failure, and pulmonary hypertension. In a canine HF model, cinaciguat resulted in dose-dependent reductions in preload and afterload and a concomitant increase in cardiac output and renal blood flow without further neurohormonal activation.<sup>89</sup> To date, published studies with sGC activators in human HF have been restricted to HFrEF. Although these agents demonstrate the ability to attenuate remodeling at doses that do not affect blood pressure in rodent models,<sup>90</sup> a short-term infusion of cinaciguat in a phase II program of HFrEF had to be prematurely terminated partly because of excess hypotension.<sup>91</sup> Future studies are required to test if the vascular and myocardial benefits seen in animal models with sGC activators can be reproduced in HFpEF patients.

In comparison to activators, sGC stimulators stimulate the enzyme by mimicking NO, thus overcoming the relative NO-deficient state.<sup>88</sup> Preclinical models with these agents have demonstrated reductions in renal and cardiac fibrosis, decreased LV mass, and anti-inflammatory properties.<sup>53,92,93</sup> Recently, 2 placebo-controlled phase III trials were published demonstrating beneficial effects of the sGC stimulator riociguat on 6-minute walk distance, natriuretic peptide levels, and functional class in patients with WHO Group 1 and Group 4 pulmonary hypertension.<sup>94,95</sup> A phase IIb study in HFrEF patients testing riociguat failed to show a benefit for the primary end point of pulmonary artery pressure, but did show improvements in pulmonary and systemic vascular resistance, cardiac output, stroke volume, and quality-of-life scores.<sup>96</sup> To test this pathway further in HFpEF, a trial with a once-daily oral sGC stimulator, BAY1021189, is currently under way.

### Nepriylsin Inhibition

Natriuretic peptide levels are a strong predictor of prognosis in HF, irrespective of LV ejection fraction.<sup>97</sup> Natriuretic peptides stimulate diuresis, natriuresis, and vasodilation and may have antifibrotic and antiadrenergic effects.<sup>98,99</sup> These physiologic effects are mediated, in part, through 3 natriuretic peptide receptors, 2 of which are transmembrane



**Figure 4.** Schematic representation of the mechanism(s) by which NO-independent sGC stimulators and sGC activators fit into the NO/sGC/cGMP pathway. Oxidative stress—a risk factor for several cardiovascular diseases—is associated with increased formation of reactive oxygen species that are known to oxidize and inactivate many biomolecules, culminating in tissue damage. In particular,  $\text{ONOO}^-$  oxidizes sGC, resulting in loss of the heme group. Heme-free sGC is unable to respond to NO and can be regarded as a dysfunctional form of the enzyme (NO stimulates only the native form of sGC). Stimulators of sGC have a dual mode of action: they directly stimulate the native form of the enzyme and make it more sensitive to endogenous NO. Activators of sGC specifically activate dysfunctional or heme-free sGC. Stimulation of native sGC and activation of heme-free sGC both lead to increased formation of cGMP, which exerts a profound, multifaceted cytoprotective effect. cGMP indicates cyclic guanosine monophosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; NOS, nitric oxide synthase;  $\text{ONOO}^-$ , peroxynitrite; PDE, phosphodiesterase; sGC, soluble guanylate cyclase. Adapted and modified with permission from Hobbs and Stasch.<sup>86</sup>

guanylyl cyclases capable of catalyzing cGMP.<sup>99</sup> Neprilysin enzymatically degrades B-type natriuretic peptide (BNP), but not N-terminal pro-B-type natriuretic peptide (NT-proBNP), and compounds combining neprilysin inhibition with renin-angiotensin-aldosterone blockade are actively being tested in human HF. In HFrEF, omapatrilat, a combined neprilysin and angiotensin-converting enzyme (ACE) inhibitor, demonstrated similar effects on outcomes compared with ACE inhibitors alone, but excess angioedema halted further drug development.<sup>100</sup> Recently, LCZ696, a first-in-class angiotensin receptor/neprilysin inhibitor, was tested in 301 patients with HFpEF. Compared with valsartan, the study drug led to greater reductions in NT-proBNP at 12 weeks and was safely tolerated.<sup>12</sup> LCZ696 also significantly increased urinary cGMP/creatinine ratio at 12 and 36 weeks relative to valsartan (S.D. Solomon, MD, unpublished data, personal communication). Whether the observed favorable effect on NT-proBNP and cGMP will translate into improved clinical outcomes will be tested in a larger ongoing phase III program.

## Future Directions With cGMP Enhancement in HFpEF

The body of evidence surrounding cGMP enhancement provides compelling rationale for further investigation of this pathway in HFpEF. Although the initial phase III attempt with PDE-5 inhibition produced a neutral result, the hypothesis of cGMP upregulation in HFpEF remains to be definitively tested.

Although animal studies suggest low PKG activity in HFpEF stems largely from elevated PDE-5 activity,<sup>56</sup> the aforementioned study by van Heerebeek and colleagues does not support this notion.<sup>13</sup> In that study, although myocardial levels of PKG and cGMP were significantly reduced in patients with HFpEF compared with those with HFrEF and aortic stenosis, there was no difference in cardiac expression of PDE-5 between HFpEF patients and the other groups. Moreover, no differences in myocardial sGC level were observed, although it is unclear what fraction of the detected enzyme was optimally active.<sup>88</sup> Taken together, these results suggest that the cGMP and PKG deficiency seen in HFpEF

manifests from reduced upstream production and bioavailability of NO or inactivation of sGC and not largely from an increased rate of cGMP degradation via PDE-5. Although plasma cGMP levels may not completely reflect tissue status, it is nevertheless not surprising that plasma cGMP level did not rise in the RELAX trial, given that it might be inefficient to inhibit an enzyme that is not upregulated and likely not primarily responsible for the cGMP deficiency. Further evidence to this effect was seen in a preclinical study by Takimoto et al, in which sildenafil produced blunting of cardiac hypertrophy and fibrosis in mice but failed to increase cGMP level.<sup>30</sup> For a PDE-5 inhibitor to effectively increase cGMP expression it must rely on sufficient input at the start of the NO-sGC-cGMP pathway, and the deficiency in upstream pathway activity in HFpEF will likely limit drug efficacy. Indeed, preclinical studies in erectile dysfunction have shown the effect of sildenafil to be limited by low NO levels.<sup>101</sup> Moreover, and further complicating matters, when PDE-5 is inhibited, the activity of other phosphodiesterases may compensate for it.<sup>102</sup>

Given these experiences with sildenafil, interventions targeting reductions in NO bioavailability or sGC signaling are warranted to target the upstream arm of the cGMP pathway. The recently proposed novel HFpEF paradigm advocates for the central role of a systemic proinflammatory state favoring coronary microvascular inflammation and reduction in NO, cGMP, and PKG, with consequent increases in LV hypertrophy and stiffness.<sup>25</sup> Among already available therapies, this paradigm supports the use of statin therapy in HFpEF given the favorable cholesterol-independent effects on endothelial dysfunction, NO bioavailability, and LV hypertrophy, fibrosis, and diastolic dysfunction, although data on hard outcomes are limited.<sup>103,104</sup> Recent data suggest structured exercise training may be a practical means of improving peak oxygen consumption in HFpEF, perhaps through improved cGMP-mediated peripheral vascular and microcirculatory function.<sup>71,105</sup> Dietary nitrate and nitrate therapy may also have beneficial cardiovascular effects on endothelial function and platelet activity.<sup>106</sup>

Among investigational therapies, agents that target sGC, including sGC stimulators and activators and neprilysin inhibitors, represent promising alternatives to increase cGMP level in HFpEF. All have the advantage of an NO-independent mechanism that may circumvent problems with inflammatory-mediated NO resistance. In contrast, attenuation of cGMP catabolism with PDE5 inhibitors may facilitate increases in oxidative stress and inflammation via worsening renal function, as the high doses of sildenafil used in the RELAX trial resulted in significantly greater increases in creatinine and cystatin-C.

Clinical trials of drugs in HF have consistently shown dissociations between acute hemodynamic effects and long-

term outcomes.<sup>107,108</sup> In HFpEF, hemodynamic effects centered on vasodilation should not be a prerequisite for drug development, due in part to deficiencies in stroke volume reserve. Central hemodynamics in these patients are less volume dependent and more dependent on peripheral vasotone<sup>109,110</sup> Moreover, a subset of HFpEF patients display hemodynamic derangements primarily during exercise (ie, high filling pressures and inadequate cardiac output), whereas resting hemodynamics remain relatively normal. Applying pure vasodilator therapies in these patients may improve exercise hemodynamics at the cost of excessive vasodilation, hypotension, or azotemia in the resting state.<sup>59,111</sup> Thus, the ideal vasoactive agent would offer a modest dilatory effect and favor concurrent improvement in myocardial performance by decreasing ventricular stiffness and increasing stroke volume.<sup>110</sup> Accordingly, it will be important for future trials in cGMP enhancement to dose investigational agents with this goal in mind.

Unlike acute coronary syndrome, no short-term intervention, with 1 possible exception,<sup>112</sup> has been shown to offer long-term benefit in HF. Similar to HFrEF, future trials in HFpEF should focus on long-term outcomes and test therapies that are initiated during hospitalization and continued into the postdischarge period, when patients are at highest risk of poor outcomes. Likewise, future trials of cGMP augmentation should preferentially concentrate on development of oral therapies that can be used in both the hospital and outpatient settings. In this regard, focus on the upstream synthetic pathway for cGMP with use of sGC modulators and neprilysin inhibitors appears promising. Low-dose oral formulations initiated in stable hospitalized patients and continued in the ambulatory setting may be ideal to minimize the risk of hypotension and to explore long-term influences on mortality and HFpEF progression that may occur independent of any vasodilatory action. In addition, enrollment of hospitalized HF patients identifies a cohort of patients who have a more certain diagnosis and who are at high risk of subsequent events, thus improving power to detect a drug effect.

## Conclusions

HFpEF is a major public health problem that lacks effective evidence-based therapies. The cGMP pathway plays a central role in derangements integral to HFpEF pathophysiology. Improved characterization of cGMP signaling and its relation to cardiac function has revealed multiple options for targeted therapeutic intervention. To date, no large phase III HFpEF trial has definitively tested the effects of pharmacologically mediated increases in cGMP activity. Future prospective studies are needed to explore the effects of pharmacologically induced increases in cGMP cell signaling on HFpEF clinical outcomes.

## Disclosures

Dr Gheorghiadu has been a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer HealthCare AG, CorThera, Cytokinetics, DebioPharm S.A., Errekappa Terapeutici, Glaxo-SmithKline, Icaria, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda Pharmaceutical, and Trevena Therapeutics. Dr Borlaug receives research funding from the NHLBI, AtCor Medical, and Gilead and serves as a consultant for GlaxoSmithKline, Merck, Amgen, CardioKinetics, and Medscape. Dr Roessig is a full-time employee of Bayer Pharma AG. Dr Stasch is an employee of Bayer Pharma AG and holds multiple patent applications related to soluble guanylate cyclase stimulators and activators. Dr Solomon receives research support from Novartis (>\$10 000) and consulting support from Novartis and Bayer (<\$10 000). Dr Butler reports research support from the NIH and the European Union and is a consultant to Amgen, Bayer, BG Medicine, Celladon, Gambro, GE Healthcare, Harvest, Medtronic, Ono Pharma, Stemedica, and Trevena. The other authors report no conflicts.

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**Key Words:** cGMP • heart failure • phosphodiesterase 5 • preserved ejection fraction • soluble guanylate cyclase



## The cGMP Signaling Pathway as a Therapeutic Target in Heart Failure With Preserved Ejection Fraction

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