Cyclic GMP and PKG Signaling in Heart Failure

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Cyclic guanosine monophosphate (cGMP), produced by guanylate cyclase (GC), activates protein kinase G (PKG) and regulates cardiac remodeling. cGMP/PKG signal is activated by two intrinsic pathways: nitric oxide (NO)-soluble GC and natriuretic peptide (NP)-particulate GC (pGC) pathways. Activation of these pathways has emerged as a potent therapeutic strategy to treat patients with heart failure, given cGMP-PKG signaling is impaired in heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Large scale clinical trials in patients with HFrEF have shown positive results with agents that activate cGMP-PKG pathways. In patients with HFpEF, however, benefits were observed only in a subgroup of patients. Further investigation for cGMP-PKG pathway is needed to develop better targeting strategies for HFpEF. This review outlines cGMP-PKG pathway and its modulation in heart failure.

Keywords: NO, SGC, NPR, PGC, cGMP, PKG

INTRODUCTION

Heart failure is a major health problem, and its prevalence is increasing worldwide. The traditional guideline directed therapies target the renin-angiotensin-aldosterone system and the sympathetic nervous system, but recently, cyclic guanosine 3',5'-monophosphate (cGMP) and its downstream protein kinase G (PKG) signaling has attracted attention as a novel therapeutic target (Tsai and Kass, 2009). cGMP-PKG pathway regulates diverse cellular mechanisms to maintain cellular homeostasis and is activated by two different pathways. One is natriuretic peptide (NP)-NP receptor (NPR)-particulate guanylate cyclase (pGC) pathway, and the other is NO-soluble GC (sGC) pathway. cGMP-PKG pathway has been suggested to be blunted or dysregulated in patients with HFrEF or HFpEF (Paulus et al., 2013; Redfield et al., 2013). Increased plasma levels of inflammatory cytokines including TNF-α and IL-6 in HF are related to endothelial dysfunction with low NO-sGC-cGMP signaling in the heart and vasculature (Torre-Amione et al., 1996; Lommi et al., 1997), where its degradation by cGMP-PDEs might be enhanced. In HFpEF patients, myocardial homogenates from biopsy samples revealed low PKG activity and cGMP concentration compared with HFrEF and aortic stenosis patients (Van Heerebeek et al., 2012). Thus, the therapeutic strategy to recover blunted cGMP/PKG signaling in heart failure is very reasonable. Sacubitril/valsartan is the first agent in this class that has been approved for use in heart failure. It consists of the neprilysin (NEP) inhibitor and the angiotensin receptor blocker, and is described as an angiotensin receptor-neprilysin inhibitor (ARNi). NEP hydrolyzes several peptide hormones including NPs (ANP, BNP, CNP), adrenomedullin, glucagon, enkephalins, substance P, neurotensin, oxytocin, and bradykinin. Thus, its inhibition enhances NPs-pGC-cGMP. ARNi improved clinical outcomes in patients with HFpEF (McMurray et al., 2014; Velazquez et al., 2018) and also exhibited favorable outcomes in a particular sub-group (female) in HFpEF (Solomon et al., 2019; Pieske et al.,...
Phosphodiesterase and cGMP/PKG Signaling

Phosphodiesterase (PDE) has 11 superfamilies and more than 100 isoforms that hydrolyze cAMP or cGMP to their inactive respective 5'-monophosphate form. Seven PDEs (PDE1, 2, 3, 4, 5, 8, and 9) are currently known to be expressed in myocardium. PDE1, 2, and 3 hydrolyze both cAMP and cGMP, while PDE5 and 9 are selective for cGMP and PDE4 and 8 are selective for cAMP (Kim and Kass, 2017). PDEs are differentially localized within the cells, contributing to the compartmentalized regulation of cGMP and cAMP signaling in both space and time.

Inhibition of PDE1, a dual substrate esterase, demonstrates acute inotropic and lusitropic effects largely via cAMP pathway (Hashimoto et al., 2018), demonstrated in large animal models. PDE1A, one of the three isoforms of PDE1, modulates pathological hypertrophy via cGMP-PKG in rodent and cell models, while PDE1C, coupled with adenosine A2A receptor and TRPC3, hydrolyzes cAMP and regulates apoptosis in cardiac myocytes (Miller et al., 2009; Zhang et al., 2018).

PDE2 is also a dual substrate esterase and involved in the regulation of cardiac hypertrophy via cGMP. PDE2 specifically plays an important role in the crosstalk between cGMP and cAMP pathways because its activity is stimulated by cGMP (Zhang et al., 2018). PDE2 has three splice variants (PDE2A1, 2A2, 2A3), which are differentially localized: PDE2A1 in cytoplasm, PDE2A2 in mitochondrial matrix, and PDE2A3 at membrane (mostly PDE2A3) (Geoffroy et al., 1999; Lugnier et al., 1999; Mongillo et al., 2006; Weber et al., 2017). In the heart, in particular, PDE2A might be localized in both cytosolic and particulate fractions of cardiac ventricle, though it differs from species to species (Le Trong et al., 1990; Bode et al., 1991; Muller et al., 1992; Sugioka et al., 1994; Geoffroy et al., 1999; Mongillo et al., 2006). In humans, PDE2A3 is expressed in cardiomyocytes and vascular endothelial cells (Sadhu et al., 1999). Under the normal conditions, PDE2 is less abundant in cardiomyocytes than in fibroblasts and endothelial cells (Stephenson et al., 2009; Vettel et al., 2014), but under the pathological conditions, PDE2 expressions and cAMP-hydrolyzing activity significantly increase (Levy, 2013; Mehel et al., 2013). (Chen et al., 2016). Cardiac PDE2A expressions increase in rat cardiac hypertrophy and also in human ischemic or non-ischemic heart failure (Mehel et al., 2013). PDE2 can hydrolyze cGMP produced by either pGC (Stangherlin et al., 2011) and sGC (Mongillo et al., 2006) with the allosteric hydrolyzing ability activated by cGMP, but this might depend on the stress conditions and cGMP concentrations (Terasaki and Appleman, 1975; Prigent et al., 1988; Mery et al., 1993; Dittrich et al., 2001; Herring et al., 2001; Weber et al., 2017).

Vericiguat, an sCG stimulator that enhances (NO)-sGC-cGMP pathway independently of NO, was approved for the treatment of heart failure. Vericiguat is effective in patients with HFrEF (Armstrong et al., 2020a), but it failed to reveal clinical improvement in HfPEF (Armstrong et al., 2020b; Udelson et al., 2020) (Table 1). The clinical importance of cGMP-PKG pathway is clear; however, a better understanding of underlying mechanisms is necessary for the optimal therapeutic strategy with enhancement of cGMP-PKG signaling pathway. This review focuses on the regulatory mechanisms of cGMP-PKG pathway in heart failure.
AT1 receptor mice (Straubinger et al., 2015). Lukowski et al. showed that the deletion of cardiomyocyte-specific PKG had no effect on cardiac hypertrophy caused by pressure overload and isoproterenol administration (Lukowski et al., 2010). Patrucco et al. reported that the lack of PKG in cardiomyocytes, endothelial cells, or cardiac fibroblast did not augment hypertrophic response and sildenafil had modest effects on angiotensin II-induced cardiac hypertrophy (Patrucco et al., 2014). On the other hand, however, cardiomyocyte-specific overexpression of PDE5A recovered impaired cardiac functions from pressure overload (Zhang et al., 2010) and myocardial infarction (Pokreisz et al., 2009). Frantz and Kuhn et al. generated animals with cardiomyocyte-restricted deletion of PKG, and demonstrated the animals developed severe hypertrophy by chronic angiotensin II infusion or pressure overload (Frantz et al., 2013). Recently, we have consistently reported that sildenafil exhibited protective effects against cardiac hypertrophy via proliferator activated receptor γ co-activator-1α-PKG cascade (Zhu et al., 2021). Together it would be reasonable to conclude that cGMP-PKG signaling in cardiomyocyte would be important in cardiac hypertrophy and remodeling. With regard to the cardiac-specific role and regulation of PDE5, a tissue-specific conditional deletion model would be awaited.

sGC stimulators and sGC activators are direct modulators of sGC, increasing the production of cGMP: the former stimulates NO-sensitive (unoxidized) sGC, while the latter can activate NO-insensitive (oxidized) sGC. sGC stimulators have shown cardiac benefits in an HFpEF model (Wilck et al., 2018) as well as in an HFrEF model. Double-transgenic rats (dTGR) harboring the renin and angiotensinogen genes exhibit an HFpEF phenotype of diastolic dysfunction, preserved EF, systemic hypertension, cardiac hypertrophy, fibrosis, inflammation, and endothelial dysfunction, and dies between 7 and 8 weeks from severe heart failure (Damage et al., 1999; Mervaala et al., 2001; Wellner et al., 2005; Fischer et al., 2008; Finckenberg et al., 2012; Haase et al., 2014). Treatment with an sGC stimulator improved cardiac function, cardiac fibrosis, and inflammation, with minimal effects on cardiac hypertrophy (Wilck et al., 2018). sGC activators have also shown cardio-protective effects in another HFpEF model (Dahl salt-sensitive model: DSS) (Kolijn et al., 2020), where an sGC activator (cinaciguat) phosphorylates titin and improves passive stiffness. In human cardiomyocytes from HFpEF patients, cinaciguat phosphorylates titin and improves passive tension, associated with a reduction in proinflammatory cytokines and oxidative stress markers (Kolijn et al., 2020). sGC-bound cofactor heme (Fe2+) is oxidized to Fe3+ under oxidative conditions, leading to the inactive Apo form that no longer is responsive to NO. sGC stimulators stimulate only Fe2+-sGC, while sGC activators act on oxidated sGC(Fe3+-sGC or Apo-sGC) (Krishnan et al., 2018) to produce cGMP. In oxidated conditions such as HFpEF, sGC activator might have an advantage. Although preclinical studies have revealed cardio-protective and anti-remodeling effects from NO-sGC-cGMP activation in either type of heart failure (HFrEF or HFpEF), clinical studies...
| Study | Drugs | meanEF (%) | Number | Female (%) | NPs (pg/ml) | Outcomes | Notes |
|-------|-------|------------|--------|------------|-------------|----------|-------|
| McMurray et al. (2014), PARADIGM-HF | Sacubitril-Valsartan (LCZ696) | 29.6 | 4187 | 21.0 | BNP 255, NT-proBNP 1631 | A composite of death from CVD or hospitalization 21.8% vs 26.5% HR 0.80, 95% CI 0.73 to 0.87, p < 0.001 | |
| | enalapril | 29.4 | 4212 | 22.6 | BNP 251, NT-proBNP 1594 | | |
| Velazquez et. al. (2019) PIONEER-HF | Sacubitril-Valsartan | 24 | 440 | 25.7 | NT-proBNP 4821 | The time-averaged reduction in the NT-proBNP at weeks 4 and 8 to the baseline -46.7% vs -25.3%(ratio of change 0.76, 95% CI 0.69 to 0.85) | |
| | enalapril | 25 | 441 | 30.2 | NT-proBNP 4710 | | |
| Solomon et al. (2019) PARAGON-HF | Sacubitril-Valsartan | 57.6 | 2419 | 51.6 | NT-proBNP 904 | Cardiovascular death 8.5% vs 8.9% HR 0.95, 95% CI 0.79 to 1.16 | A composite outcome of hospitalization and cardiovascular death in female RR 0.73 95% CI 0.59 to 0.90 |
| | Valsartan | 57.5 | 2403 | 51.8 | 915 | Total Hospitalization 690 vs 797 HR 0.85, 95% CI 0.72 to 1.0 | |
| Pieske et al. (2021) PARALLAX | Sacubitril-Valsartan | 56.7 | 1286 | 50.2 | NT-proBNP 786 | The reduction in NTproBNP at week 12 The adjusted geometric mean ratio 0.84 (95% CI, 0.80- 0.88; p < 0.001) | No significant between-group difference in the Kansas City Cardiomyopathy Questionnaire clinical summary score 12.3 vs 11.8 (mean difference, 0.52; 95% CI, −0.93 to 1.97) No improvement in NYHA class 23.6% vs 24.0% of patients (adjusted odds ratio, 0.98; 95% CI, 0.81 to 1.18) 6-minute walking distance improved among women but decreased among men 6.59 vs −12.07 (p = 0.0024) Individualized comparator: enalapril at a target dose of 10, valsartan at a target dose of 160 mg, or placebo (no RAS inhibitor). |
| | Individualized comparator | 56.2 | 1286 | 51.2 | 760 | 6-minute walk difference at week 24. No significant between-group from baseline 9.7 m vs 12.2 m (adjusted mean difference, −2.5 m; 95% CI, −8.5 to 3.5; p = 0.42) | |
| Armstrong et al. (2020a) VICTORIA | Vericiguat | 29.3 | 2526 | 24.0 | NT-proBNP 2803 | The composite of death from any cause or hospitalization for heart failure 37.9% vs 40.9% HR 0.90, (95% CI 0.83 to 0.98, p = 0.02) | |
| Udelson et al. (2020) CAPACITY HFpEF | Placebo | 27.9 | 2524 | 23.9 | NT-proBNP 2821 | Changes in peak VO2: −0.26 vs −0.04 mL/kg/min 1286 (95% CI, −0.83 to 0.31 and −0.49 to 0.56) | |
| | Praliciguat | 61.9 | 91 | 38.5 | NT-proBNP 260 | | |
| Armstrong et al. (2020b) VITALITY-HFpEF | Placebo | 59.8 | 90 | 44.4 | 228.5 | The mean changes in the KCOQ PLS 5.5 points in the 15-mg/d vericiguat group 6.5 points in the 10-mg/d vericiguat group 6.9 points in the placebo group | The overall mortality rate was 4.1% (n = 32) 10 (3.8%) in the 15-mg vericiguat group 15 (5.7%) in the 10 mg vericiguat group 7 (2.7%) in the placebo group 8 cardiovascular deaths (3.0%) in the 15-mg vericiguat group 12 (4.6%) in the 10-mg vericiguat group 4 (1.5%) in the placebo group |
| | Vericiguat 15 mg | 56.8 | 264 | 53.0 | NT-proBNP 1364.5 | | |
| | Vericiguat 10mg | 55.8 | 263 | 47.1 | 1339.1 | differences between either vericiguat dosage and placebo were not statistically significant | |
| | Placebo | 56.3 | 262 | 46.2 | 1644.2 | | |
have yielded mixed results. Two meta-analyses of controlled clinical trials (928 patients in 14 studies (De Vecchis et al., 2017), 555 patients in 13 studies (De Vecchis et al., 2018)) demonstrate that PDE5 inhibitors improve clinical outcomes, exercise capacity, and pulmonary hemodynamics in patients with HFrEF, but not HFpEF. The negative results in HFpEF might be partially attributable to the female-specific response of PDE5i depending on estrogen levels, given the prevalence of HFpEF in older women: nearly half of the patients were older women (average age 67) in the negative RELAX trial. Epidemiological studies have demonstrated that women are likely to develop HFpEF. In clinical trials of HFpEF women account for around 50–60% of the trial cohorts (Forman and Gaziano, 2009; Savill, 2014), whereas they account for 20–25% of those of HFrEF (Pablo, 2017; Zannad et al., 2018; Pieske et al., 2019). In a recent multicenter, observational study, female sex was reported to be independently associated with the presence of diastolic dysfunction and worse clinical outcomes (Sotomi et al., 2021). Sex-hormone estrogen plays a pivotal role in cGMP-PKG signal coupled with NO via estrogen receptor (ERα)-mediated non-nuclear signaling. In diseased conditions like heart failure, eNOS activity is impaired and PKG undertakes oxidation and localizes in cytosol, inhibiting protective effects of PKG signaling independent of cGMP and enhancing cardiac remodeling via target proteins like TRPC6. PDE5 inhibitor, sildenafil, reveals protective effects only under the condition of sufficient oxidated PKG1α, while sGC stimulator improves cardiac remodeling independent of PKG redox status.

Despite promising preclinical results, however, a clinical study testing vericiguat in patients with HFpEF turned out negative (Vitality HFpEF). Although the reason for the negative results remains an open question, the redox status related to HFpEF might be speculated to be involved. NO–sGC–cGMP signaling can be compromised either by reducing the bioavailability of NO or by altering the redox state of sGC (Costell et al., 2012). Several groups reported that redox conditions altered cysteine residues (Cys) on sGC, affecting its catalytic or regulatory functions (Craven and DeRubertis, 1978a; Craven and DeRubertis, 1978b; Braughler, 1983). The redox status also alters the heme conditions within sGC. Heme iron in the reduced status (Fe²⁺) is necessary for NO binding, and sGC stimulator can stimulate only the reduced form of sGC, while the sGC activator can activate both reduced sGC and oxidized sGC (containing Fe³⁺) (Evgenov et al., 2006). In rat external iliac arteries without endothelium, peroxynitrite was reported to alter the redox state of sGC. Under the exposure of peroxynitrite, vascular relaxation induced by an sGC stimulator was impaired, whereas that by an sGC activator was enhanced. Additionally, this response correlated well with tissue levels of cGMP (Tawa et al., 2014). In Sprague Dawley rats fed with high salt/fat diet, an sGC activator, but not an...
sGC stimulator, attenuated the development of cardiac hypertrophy in a blood pressure-independent manner (Evgenov et al., 2006). Although there are no data about sGC redox status in patients with heart failure, inflammation and oxidative stress conditions in HFrEF might critically affect the efficacy of cGMP-modifying drugs (Tawa et al., 2014).

Thus, an sGC activator might serve as a potential novel treatment of HFrEF. So far, cinaciguat, an sGC activator, has been tested only in acute heart failure, with increased hypotensive events but no clear benefits, and sGC activators have not yet been explored in patients with chronic heart failure.

**NP-pGC Pathway (PDE9 and PDE5)**

Natriuretic peptides stimulate transmembrane receptor guanylate cyclase to produce cGMP. Atrial and B-type natriuretic peptides (ANP, BNP) bind to receptor particulate guanylyl cyclase A (pGC-A or NPRA), while C-type natriuretic peptide (CNP) binds to particulate guanylyl cyclase B (pGC-B or NPRB). pGC-A is localized at T-tubules and pGC-B is distributed throughout the sarcolemma. This spatial difference renders compartmentalized ANP/NPRA/cGMP signaling vs. CNP/NPRB/cGMP: the former have little impact on contractility and the latter have positive-lusitropic effects (Kuhn, 2016; Subramanian et al., 2018; Michel et al., 2020). cGMP from NP-pGC axis is degraded by PDE9 (Volpe et al., 2016; Goetze et al., 2020), which is expressed prominently in the brain and less in the heart (GraceKim et al., 2017). Similar to PDE5, myocardial PDE9 expression is low under physiological conditions but is upregulated under disease conditions such as HFrEF and aortic stenosis (Lee et al., 2015). PDE9 inhibition, either with a pharmacological or a genetic approach, suppressed cardiac hypertrophy in rodent pressure-overload (PO) model (Lee et al., 2015; Kokkonen-Simon et al., 2018; Richards et al., 2021).

Importantly, both PDE5i and PDE9i similarly improve diastolic distensibility and ameliorate cardiac remodeling, associated with better profiles of hypertrophic/fibrosis-related gene expression (Lee et al., 2015), (Bishu et al., 2011a); however, comprehensive analyses of RNA-sequence data of myocardium reveals significant differences between PDE5i and PDE9i (Kokkonen-Simon et al., 2018), particularly in miRNA profiles related to hypertrophy and fibrosis: marked down-regulation of pro-hypertrophic and pro-fibrotic miRs by PDE5i vs. virtually no effect by PDE9i.

As previously described, ARNI exhibited favorable outcome in female patients with HFrEF (Solomon et al., 2019; Pieske et al., 2021). There has been no explanation provided for this observation of female-only benefit. We would speculate that this might be possibly related to difference of plasma NPs levels. Female patients with HFrEF are reported to exhibit lower plasma NPs levels as follows. ARNI might compensate lower levels of NPs in female patients with HFrEF. In HFrEF patients, plasma BNP levels are reported to be lower than in HFrEF (Harada et al., 2017); interestingly, women with HFrEF had lower BNP levels than men [43.9 vs. 76.1 pmol/L, p = 0.0193 (Tasevska-Dinevska et al., 2011), 104 vs 133, p < 0.001 (Savarese and D’Amario, 2018)] while in HFrEF the levels of NPs were inconsistent. One group reported that the plasma levels of ANP and BNP were similar in both genders (ANP: 114.9 vs. 141.2 pg/ml, p = 0.2606, BNP: 252.0 vs. 381.9 pg/ml, p = 0.1577). Another group reported that the plasma levels of NT-proBNP were higher in female HFrEF (8481 vs. 7543 pg/ml, p < 0.001) (Kim et al., 2017) and there is another group reporting that plasma NT-proBNP levels were similar in both genders (2532 vs. 2677 pg/ml, p = 0.978) (Sobhani et al., 2018).

Another possible reason why ARNI is effective in female HFrEF might be related to CNP regulation. CNP exerts biological effects by binding to two types of natriuretic receptors; cGMP-coupled NPR-B and NPR-C (Chauhan et al., 2003; Villar et al., 2007). Endothelial deletion of CNP or global deletion of NPR-C revealed hypertensive phenotype only in female mice (Moyes et al., 2014), while the absence of eNOS and COX-1 in endothelial cells had no effect on mean blood pressure in female mice, but resulted in significantly high blood pressure in male animals (Scotland et al., 2005).

These suggest the pivotal contribution of CNP to female blood pressure maintenance. It is thus tempting to speculate that cardiac protection from ARNI therapy might depend more on the regulation of CNP in females than in males, although the contribution of cGMP might be unclear.

Although PDE5 hydrolyzes cGMP coupled with NO under normal conditions. PDE5 could become interactive with NPs-derived cGMP under stressed conditions (Zhang et al., 2012). Cardiomyocyte PDE5 is normally localized at Z-bands of sarcomeres, but becomes diffusely localized when exposed to pathological stress such as TAC or NOS inhibition (Nagayama et al., 2008; Zhang et al., 2012). In a dog hypertension model produced by bilateral renal wrapping, sildenafil treatment with concomitant BNP administration enhances plasma cGMP concentration, and recovers left ventricular diastolic capacitance in association with titin phosphorylation compared with sildenafil treatment alone (Bishu et al., 2011b). The beneficial synergistic effects of the combined PDE5 and NPs were also reported in pulmonary hypertension (PH). In a mouse model of hypoxia-induced PH, global deletion of NPRA blunts the beneficial effects of sildenafil on right ventricular systolic pressure (Zhao et al., 2003). Also, in hypoxia-induced PH rats, ANP and sildenafil show synergistic effects on decreasing right ventricular systolic pressure and on increasing plasma cGMP levels (Preston et al., 2004). Furthermore, a recent clinical trial of pulmonary arterial hypertension also demonstrated that the combined inhibition of nephrilysin and PDE5 increase both plasma NP and cGMP levels and decreased pulmonary vascular resistance without affecting systemic blood pressure (Hobbs et al., 2019), which makes contrast to the concomitant use of PDE5 inhibitor (sildenafil) with sGC stimulator (riociguat) having been reported to be associated with hypotension but without beneficial effects on hemodynamics or exercise capacity (Galiè et al., 2015). The combination of pGC-related pathway and PDE5 might be a potential therapeutic option also in heart failure.

**PKG Oxidation in Failing Heart**

cGMP activated PKG targets various molecules to regulate cellular function in cardiomyocytes (Takimoto, 2012),
including RGS2/4, TRPC6, proteasome systems, mitochondria, and sarcomere components. Two PKG genes, prkg1 and prkg2, encode PKG1 and PKG2, respectively, and PKG1 is the primary isotype in cardiomyocyte. PKG1 is activated classically by cGMP, but also by oxidation (Figure 2): When oxidized, a cysteine residue C43(C42 in mice) forms a disulfide bond to form a homodimer of PKG1 (Burgoyne et al., 2007). Oxidized PKG1 is increased in failing hearts, though it accounts for only a small portion of PKG1 in normal hearts (Paulus et al., 2013; Nakamura et al., 2015; Prsyazhnya et al., 2016). Oxidative PKG1 resides only at cytosol but not at the plasma membrane, while unoxidized PKG1 resides in both (Nakamura et al., 2015). Therefore, oxidized PKG1 is no longer able to exert beneficial effects by the mechanisms mediated by membrane-localized PKG1, including inhibition of TRPC6-Cn-NFAT hypertrophy signaling and TSC2-mTORC1 metabolic/autophagy signaling (Oeing et al., 2020). Interestingly, PKG1 oxidation is required for the anti-remodeling effects from PDE5i as cytosol-localized PDE5 needs cGMP-activation via its GAF domain, while sGC stimulation exerts anti-remodeling effects independent of redox status of PKG1 (Nakamura et al., 2018). PDE5 inhibitor could be effective only under the sufficient myocardial stress to oxidate PKG1a, whereas an sGC stimulator provides benefits independent of redox conditions.

CONCLUSION

cGMP/PKG signaling can be augmented by stimulation of either NO-GS/G pathway or NP-pGC pathway. Although activation of either provides anti-remodeling benefits, they do not necessarily share the same molecular mechanisms in common. Furthermore, benefits might be also affected by the PKG redox status. Although ample preclinical evidence shows the benefits of cGMP/PKG augmentation in HFrEF or HfPEF models, clinical studies thus far provide consistent efficacy of cGMP/PKG augmentation in patients with HFrEF and limited efficacy in patients with HfPEF. Further studies would be helpful to better understand the pathophysiology of HfPEF and the development of novel treatments.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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