ORIGINAL RESEARCH

Cardiorenal Effects of Long-Term Phosphodiesterase V Inhibition in Pre–Heart Failure

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BACKGROUND: Phosphodiesterase V (PDEV) is upregulated in heart failure, leading to increased degradation of cGMP and impaired natriuresis. PDEV inhibition improves the renal response to B-type natriuretic peptide in animal models. We tested the hypothesis that long-term PDEV inhibition would improve renal function and cardiorenal response after short-term volume load in subjects with pre–heart failure.

METHODS AND RESULTS: A total of 20 subjects with pre–heart failure (defined as an ejection fraction ≤45% without previous diagnosis of heart failure) and renal impairment were randomized in a 2:1 manner to tadalafil or placebo. Baseline echocardiography and renal clearance study were performed, followed by a short-term saline load and repeated echocardiography and renal clearance study. Subjects then received either tadalafil at a goal dose of 20 mg daily or placebo, and the study day was repeated after 12 weeks. Long-term tadalafil did not improve glomerular filtration rate (median increase of 2.0 mL/min in the tadalafil group versus 13.5 mL/min in the placebo group; \( P = 0.54 \)). There was no difference in urinary sodium or cGMP excretion with PDEV inhibition following short-term saline loading.

CONCLUSIONS: Glomerular filtration rate and urinary sodium/cGMP excretion were not significantly different after 12 weeks of tadalafil compared with placebo. These results do not support the use of PDEV inhibition to improve renal response in patients with pre–heart failure.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01970176.

Key Words: cGMP ■ heart failure ■ phosphodiesterase type 5 inhibition ■ renal function

Individuals with asymptomatic left ventricular systolic dysfunction, also referred to as pre–heart failure (PHF) or stage B heart failure, have a higher risk of progression to clinical heart failure and death than those with normal left ventricular systolic function.1 Although several factors may explain this observation, it is becoming increasingly apparent that dysfunctional cardiorenal response to sodium and fluid load is present.2 Interventions aimed to restore normal cardiorenal response to sodium and fluid load may be beneficial in improving outcomes in individuals with PHF.

cGMP is the second messenger of the natriuretic peptide and NO systems and is metabolized by phosphodiesterase V (PDEV). PDEV is known to be upregulated in heart failure, which results in a greater degradation of cGMP and impaired natriuresis.3 PDEV inhibition had cardioprotective effects in response to pressure overload in a mouse model.4 Currently, PDEV inhibitors are only approved for the treatment of erectile dysfunction and pulmonary hypertension.

We have previously shown that individuals with PHF have impaired renal cGMP activation without a change...
in natriuresis after short-term volume expansion. This impaired renal response was rescued by administration of subcutaneous B-type natriuretic peptide (BNP). Recently, we reported improved cardiac function but worsened renal function in response to short-term volume expansion in subjects with PHF receiving 1 dose of the PDEV inhibitor tadalafil and subcutaneous BNP. However, the cardiorenal effects of long-term PDEV inhibition in individuals with PHF are not known.

The present study tested the hypothesis that long-term PDEV inhibition with 12 weeks of tadalafil will improve renal function, measured by glomerular filtration rate (GFR), in patients with PHF. In addition, after a short-term volume load, we hypothesized that subjects receiving tadalafil would have improved urinary sodium and cGMP excretion compared with those receiving placebo. We also measured cardiac function with echocardiography to assess the effects of long-term PDEV inhibition.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

This study was a randomized, double-blind, placebo-controlled trial to assess the cardiorenal effects of long-term PDEV inhibition in subjects with PHF and renal impairment. The study was approved by Mayo Clinic’s Institutional Review Board, and all participants provided written informed consent.

Study Population

The study population included subjects with PHF (defined as a left ventricular ejection fraction [LVEF] ≤45% without clinical signs/symptoms and previous diagnosis of heart failure), New York Heart Association class I, and renal impairment with a calculated creatinine clearance of ≤90 mL/min. In addition, subjects were required to have a 6-minute walk distance of ≥450 m, unless limited by orthopedic conditions. Key exclusion criteria included the presence of hypotension (systolic blood pressure <90 mm Hg), current/anticipated need for nitrate therapy, use of α-blocker medications, severe renal dysfunction (creatinine clearance <30 mL/min), use of loop diuretics, current use of PDEV inhibitor for pulmonary hypertension, and significant valvular heart disease. A full list of inclusion and exclusion criteria can be found in Table S1.

Nonstandard Abbreviations and Acronyms

| Acronym | Definition                        |
|---------|----------------------------------|
| HFrEF   | heart failure with reduced ejection fraction |
| PDEV    | phosphodiesterase V              |
| PHF     | pre–heart failure                |

CLINICAL PERSPECTIVE

What Is New?

- This randomized, placebo-controlled study evaluated the cardiorenal effects of long-term phosphodiesterase V inhibition in patients with preclinical heart failure.
- Long-term phosphodiesterase V inhibition with 12 weeks of tadalafil does not improve the renal function, as measured by glomerular filtration rate, or increase natriuresis in subjects with pre–heart failure.

What Are the Clinical Implications?

- Treatment with phosphodiesterase V inhibition does not improve the cardiorenal response in patients with pre–heart failure.
Subjects were then randomized in a 2:1 manner to receive tadalafil, 5 mg, or matching placebo. We chose to randomize in a 2:1 manner because of feasibility with enrolling a small group of subjects in this proof-of-concept pilot physiological study. Specifically, we hypothesized that there would be large differences in end points between the treatment group and placebo but smaller differences within subjects. Because the within treatment group differences are relevant and to assess tolerability of treatment, we enrolled twice the number of subjects to provide better power for the within-subject comparisons in the treatment group. The Mayo Clinic Department of Biomedical Statistics and Informatics provided the randomization schedule, and the Mayo Clinic Pharmacy dispensed study drug in blinded manner. Subjects were given the study drug in the Clinical Research Unit, and blood pressure and heart rate were monitored at regular intervals for 4 hours. If, after 2 hours, the systolic blood pressure was >95 mm Hg, then an additional 5 mg of tadalafil or placebo was administered. Subjects were dismissed from the Clinical Research Unit on either 5 or 10 mg of tadalafil (depending on blood pressure) or matching placebo.

Blood draws for electrolytes were performed at 1 and 6 weeks after the first study visit. Subjects were instructed to monitor their blood pressure daily for the duration of the study. If the systolic blood pressure was >100 mm Hg after 2 weeks, tadalafil was increased in 5-mg increments to a target dose of 20 mg daily or highest dose tolerated. After the 12-week study period, subjects returned to the Clinical Research Unit for their second study visit, during which renal clearance assessment, echocardiography, and short-term saline load were performed in a similar manner as the first study visit.

Study Outcomes

The primary end point of this study is the change in GFR, and secondary end points included change in urinary sodium excretion and urinary cGMP excretion in response to short-term saline loading after 12 weeks of study drug. We also assessed changes in echocardiographic features from baseline after 12 weeks, specifically changes in LVEF, diastolic function, right ventricular function, and estimated right ventricular systolic pressure.

Renal Clearance Procedure and Neurohormonal Analysis

A priming dose of iothalamate and para-aminohippurate, calculated according to body size, was infused to measure GFR and effective renal plasma flow, respectively. This was followed by a constant rate intravenous sustaining dose, which was calculated according to estimated kidney function. After the equilibration period of 45 minutes, urine and blood samples were collected as described in the study procedures. Plasma and urine concentrations of iothalamate and para-aminohippurate were measured by the Mayo Core Renal Laboratory. GFR and renal plasma flow were calculated using the following equation (U=urine concentration; P=plasma concentration; V=urine flow [mL/min]):

$$\text{GFR (mL/min)} \text{ or RPF (mL/min)} = \frac{U_{\text{iothalamate or PAH}} \times V}{P_{\text{iothalamate or PAH}}}$$

Plasma and urine cGMP were measured by radio-immunoassay, as previously described. Plasma BNP was measured by fluorescence immunoassay (Biosite Diagnostics), as previously described.
**Sample Size and Statistical Analysis**

Results at each time point were summarized, and differences between time points were also calculated and summarized. Summarization for continuous data included median and quartiles, whereas categorical data were summarized with counts and percentages. Group comparisons of measures at each time point as well and changes between time points were based on Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables. For comparisons of changes within group, signed rank tests were used. SAS version 9.4 was used for analyses. P<0.05 was considered to be statistically significant for the primary end point. Secondary end points were tested without correction for multiple comparisons and were considered exploratory.

On the basis of our previous studies in asymptomatic systolic dysfunction, we were able to construct the magnitude of difference that could be detected for GFR and urinary sodium and cGMP excretion after volume expansion before study initiation. With a total of 20 subjects, we estimated 80% power for detecting a difference of 17 mL/min in GFR between the tadalafil and placebo groups, a difference believed to be clinically meaningful. In addition, 20 subjects were estimated to provide 80% power for detecting a difference of 140 mEq/min and 280 pmol/min between groups for urinary sodium and urinary cGMP excretion, respectively. We estimated the SD for GFR to be 12 mL/min and the SDs for urinary sodium excretion and urinary cGMP excretion to be 100 and 200 mEq/min, respectively.

**RESULTS**

**Study Population**

A total of 20 subjects were randomized in a 2:1 manner to receive tadalafil (n=14) or placebo (n=6). Baseline characteristics of the subjects are shown in Table 1 and were similar between groups. The median age in the tadalafil group was 71 years compared with 64 years in the placebo group, and the overall cohort was predominantly men (65%). The median LVEF in both groups was ≈37%. Baseline laboratory measures of kidney and humoral function were similar between groups. The median LVEF in both groups was 52.0 ± 12.0% compared with 57.2 ± 10.9% in the placebo group; P=0.04. Similarly, secondary end points of renal plasma flow and urine flow were not different between the 2 groups at 12 weeks. Long-term PDEV inhibition with tadalafil did not affect other secondary end points, including sodium excretion (median increase of 20.1 mEq/min in the tadalafil group versus a decrease of 37.5 mEq/min in the placebo group; P=0.41). Also, the change in cGMP excretion from baseline to week 12 was similar between groups.

The change in aldosterone levels was not different between groups (median decrease of 0.5 ng/dL in the tadalafil group versus an increase of 2.5 ng/dL in the placebo group; P=0.11). Long-term PDEV inhibition did not affect levels of atrial natriuretic peptide and BNP at 12 weeks (Table 2).

**Cardiorenal Response to Volume Expansion at Visit 1**

Volume expansion with normal saline (0.9% at 0.25 mL/kg per minute for 1 hour) was performed at visit 1 before randomization to treatment groups. Similar to prior data, there was no significant increase in GFR, renal plasma flow, urine flow, urinary sodium or cGMP excretion, and plasma cGMP in subjects with PHF in response to volume expansion (Table S2). Similarly, there was no change in ejection fraction, cardiac index, ratio of the transmitral early diastolic peak velocity (E) to the early diastolic tissue Doppler velocity of the mitral annulus (e’) (E/e’), and right ventricular systolic pressure with volume expansion. The lack of activation of plasma and renal cGMP in response to volume expansion suggests impaired baseline cGMP response in these subjects.

**Renal and Humoral Effects of 12 Weeks of Long-Term PDEV Inhibition**

Treatment with 12 weeks of tadalafil did not lead to a significant change in the primary end point of GFR when compared with placebo (median increase of 2.0 mL/min in the tadalafil group versus 13.5 mL/min in the placebo group; P=0.54; Table 2). Similarly, secondary end points of renal plasma flow and urine flow were not different between the 2 groups at 12 weeks. Long-term PDEV inhibition with tadalafil did not affect other secondary end points, including sodium excretion (median increase of 20.1 mEq/min in the tadalafil group versus a decrease of 37.5 mEq/min in the placebo group; P=0.41). Also, the change in cGMP excretion from baseline to week 12 was similar between groups.

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**Echocardiographic Parameters After 12 Weeks of Long-Term PDEV Inhibition**

Secondary end points, including echocardiographic parameters at baseline and after 12 weeks of tadalafil, are shown in Table 2. Long-term PDEV inhibition with tadalafil did not result in a change in cardiac index measured by echocardiography. No differences in LVEF were observed between groups. Although diastolic function parameters did not differ between groups, there was a decrease in left atrial volume index with tadalafil (median left atrial volume index decrease of 2.5 mL/m² with tadalafil versus an increase of 5 mL/m² with placebo; P=0.04).

**Cardiorenal Response to Volume Expansion After 12 Weeks of Long-Term PDEV**

Volume expansion with saline was performed to assess whether long-term PDEV inhibition would potentiate the natriuretic and cardiorenal response in subjects with PHF. The median change (interquartile range) in GFR from
Table 1. Baseline Characteristics

| Parameter                  | Tadalafil (n=14) | Placebo (n=6) | P value |
|----------------------------|------------------|---------------|---------|
| Age, y                     | 71 (58–73)       | 64 (54–73)    | 0.74    |
| Sex (women), n (%)         | 6 (43)           | 1 (17)        | 0.26    |
| BMI, kg/m²                 | 27.4 (26.5–31.7) | 34.4 (28.1–38.6) | 0.34    |
| Hypertension, n (%)        | 7 (50)           | 3 (50)        | 1.00    |
| Diabetes, n (%)            | 3 (21)           | 2 (33)        | 0.57    |
| Coronary artery disease, n (%) | 6 (43)     | 3 (50)        | 0.77    |
| ACE inhibitor/ARB, n (%)   | 11 (79)          | 5 (83)        | 0.81    |
| β Blocker, n (%)           | 13 (93)          | 6 (100)       | 0.50    |
| Thiazide diuretic, n (%)   | 2 (14)           | 0 (0)         | 0.53    |
| Heart rate, BPM            | 123 (106–128)    | 119 (95–146)  | 0.90    |
| Systolic BP, mm Hg         | 68 (57–77)       | 64 (59–67)    | 0.34    |
| Diastolic BP, mm Hg        | 123 (106–128)    | 119 (95–146)  | 0.90    |
| 6-Minute walk distance, m  | 448 (427–465)    | 444 (381–573) | 0.99    |
| GFR, mL/min*               | 74 (47–98)       | 75 (68–91)    | 0.97    |
| RPF, mL/min                | 269 (161–414)    | 337 (272–410) | 0.54    |
| Urine flow, mL/min         | 5.4 (3.0–8.1)    | 5.5 (3.8–6.9) | 0.87    |
| Sodium excretion, mEq/min  | 138.4 (110.0–227.4) | 150.5 (118.8–253.0) | 0.87 |
| Urinary cGMP generation, pmol/min | 607.6 (299.8–722.1) | 513.2 (416.3–749.8) | 0.80 |
| Ejection fraction, %       | 37.5 (29.0–44.0) | 37.0 (35.0–43.0) | 1.00 |
| Cardiac index, mL/min per m² | 2.4 (2.4–2.6) | 2.2 (2.0–2.7) | 0.46 |
| LAVI, mL/m²                | 39.5 (31.0–45.0) | 47.5 (27.0–50.0) | 0.28 |
| E/e'                       | 13.9 (10.0–24.0) | 23.5 (14.0–33.0) | 0.12 |
| RVSP, mm Hg (n=19)*        | 29.0 (27.0–32.0) | 33.0 (32.0–34.0) | 0.05 |
| ANP, pg/mL                 | 82.0 (12.5–161.0) | 73.6 (53.7–102.0) | 0.71 |
| BNP, pg/mL (n=19)          | 92.0 (83.0–145.0) | 88.0 (66.0–158.0) | 0.69 |
| Aldosterone, ng/dL (n=17)  | 5.2 (3.2–8.4)    | 7.1 (4.2–9.3)  | 0.34    |
| Plasma cGMP, pmol/mL       | 3.3 (1.0–4.3)    | 2.2 (1.7–2.6)  | 0.68    |

Data are presented as median (interquartile range) and number (percentage) for categorical variables. ACE indicates angiotensin-converting enzyme; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BPM, beats per minute; E/e', ratio of the transmirtal early diastolic peak velocity (E) to the early diastolic tissue Doppler velocity of the mitral annulus (e'); GFR, glomerular filtration rate; LAVI, left atrial volume index; RPF, renal plasma flow; and RVSP, right ventricular systolic pressure.

*Measured GFR with iothalamate clearance at visit 1.

†We were able to estimate RVSP in 5 of 6 placebo subjects and all 14 subjects in the tadalafil group.

baseline to after volume expansion was not significantly different between groups [4.5 [−18.5 to 11.0] mL/min in subjects receiving tadalafil versus −6.25 [−30.0 to −1.5] mL/min with placebo; P=0.25; Figure 2). Similarly, there was no difference in renal plasma flow or urine flow between groups with short-term saline load. The change in urinary sodium excretion and cGMP excretion from baseline to after volume expansion between the tadalafil and placebo groups was also not different (P=0.80 and P=0.32, respectively; Figure 2).

Cardiac index, measured by echocardiography, increased from baseline to after volume expansion at 12 weeks in those receiving tadalafil, but not in those receiving placebo (increase in cardiac index of 0.29 mL/min per m² with tadalafil versus decrease of 0.04 mL/min per m² with placebo; P=0.05; Table 3). The change in right ventricular systolic pressure and ejection fraction from baseline to after volume expansion at 12 weeks was not different between groups. E/e’, a surrogate measure of left ventricular filling pressure, was similar between groups after volume expansion at 12 weeks.

Adverse Events

Adverse events are noted in Table 4, and dose reduction of tadalafil occurred in 8 subjects. The presence of any adverse event occurred in 7 subjects (50%) receiving tadalafil and 1 subject (17%) receiving placebo. The most common adverse event was diarrhea, which occurred in 3 subjects who received tadalafil. There were no cases of symptomatic hypotension in either group.

DISCUSSION

This proof-of-concept, randomized, placebo-controlled physiological study assessed the effects of long-term PDEV inhibition with tadalafil in subjects with PHF. We found that 12 weeks of tadalafil did not improve renal function or increase sodium/cGMP excretion compared with placebo. Left atrial volume index, a surrogate for left ventricular filling pressure, was lower and cardiac index improved after volume expansion in those treated with tadalafil. Taken together, our findings suggest that long-term PDEV inhibition with tadalafil does not affect cardiorenal function in subjects with PHF, although there may be an improvement in cardiac hemodynamics with long-term tadalafil.

Patients with PHF are classified as having stage B heart failure and are at high risk for developing symptomatic heart failure. Current guidelines recommended the use of angiotensin-converting enzyme inhibitors in patients with stage B heart failure who have a low LVEF. This recommendation is based on the SOLVD (Studies of Left Ventricular Dysfunction) Prevention Trial, in which >4000 patients with asymptomatic reduced LVEF were randomized to enalapril versus placebo. These investigators found a reduced incidence of symptomatic heart failure and heart failure hospitalizations in patients randomized to...
enalapril. Aside from angiotensin-converting enzyme inhibitors, therapies aimed at preventing progression from asymptomatic heart failure to symptomatic heart failure are lacking.

One of the hallmarks of congestive heart failure is the impaired renal response to sodium load. The mechanism of impaired renal function in heart failure is poorly understood. We have previously investigated the role of phosphodiesterase V (PDEV) inhibition in Stage B heart failure and found that it significantly improves renal function.

### Table 2. Change in Cardiorenal and Echocardiographic Parameters at Baseline and After 12 Weeks of Long-Term PDEV Inhibition

| Parameter                        | Tadalafil (n=14) | Placebo (n=6) | P value |
|----------------------------------|-----------------|---------------|---------|
| GFR, mL/min                      | 2.0 (−11.0 to 18.0) | 13.5 (−12.0 to 25.0) | 0.54    |
| RPF, mL/min                      | 5.0 (−51.0 to 54.0) | 17.0 (−64.0 to 81.0) | 0.95    |
| Urine flow, mL/min               | 0.1 (−1.6 to 1.1) | −1.0 (−1.3 to 3.0) | 0.80    |
| Sodium excretion, mEq/min        | 20.1 (−45.7 to 85.9) | −37.5 (−83.0 to 59.1) | 0.41    |
| Urinary cGMP generation, pmol/min| 76.0 (−21.4 to 274.5) | 28.5 (−111.0 to 199.5) | 0.56    |
| Aldosterone, ng/dL (n=17)        | −0.5 (−4.0 to 0.4) | 2.5 (1.0 to 3.5) | 0.11    |
| ANP, pg/mL                       | 10.8 (0 to 54.1) | 4.9 (−16.4 to 32.3) | 0.34    |
| BNP, pg/mL (n=19)                | 1.0 (−57.0 to 15.0) | 4.5 (−19.0 to 30.0) | 0.69    |
| Ejection fraction, %             | 0.5 (−2.0 to 2.0) | −3.0 (−5.0 to −2.0) | 0.12    |
| Cardiac index, mL/min per m²     | −0.1 (−0.1 to 0.1) | 0.3 (−0.1 to 0.3) | 0.16    |
| LAVI, mL/m²                      | −2.5 (−8.0 to 2.0) | 5.0 (3.0 to 5.0) | 0.04    |
| E/e'                             | 2.3 (−3.0 to 3.0) | −3.0 (−3.0 to 4.7) | 0.66    |
| RVSP, mm Hg (n=19)               | 0 (−2.0 to 1.0) | −1.0 (−4.5 to 8.5) | 0.78    |
| SBP, mm Hg                       | −9.0 (−16.0 to −6.0) | −5.0 (−5.0 to 14.0) | 0.06    |
| DBP, mm Hg                       | 0 (−6.0 to 5.0) | −1.0 (−6.0 to 5.0) | 0.99    |

Data are presented as median (interquartile range). P value compares change from visit 1 to visit 2 between tadalafil and placebo. ANP indicates atrial natriuretic peptide; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; E/e', ratio of the transmitral early diastolic peak velocity (E) to the early diastolic tissue Doppler velocity of the mitral annulus (e'); GFR, glomerular filtration rate; LAVI, left atrial volume index; PDEV, phosphodiesterase V; RPF, renal plasma flow; RVSP, right ventricular systolic pressure; and SBP, systolic blood pressure.

### Figure 2. Renal parameters before and after short-term saline load at 12 weeks.

Effect of long-term phosphodiesterase V inhibition on the primary end point of glomerular filtration rate (GFR) (A) and secondary end points of urinary sodium excretion (B), cGMP excretion (C), urine flow (D), and renal plasma flow (RPF) (E) at baseline and during volume expansion (VE). Data are presented as Tukey box plots, which show the median, interquartile range, and “whiskers” for each variable, which are 1.5 times the interquartile range. No significant difference in the renal parameters was found, both between groups and within groups.
shown that disruption of the cGMP and NO system can contribute to cardiorenal dysfunction in a canine model of acute heart failure.11 Interestingly, in patients with PHF, renal cGMP activation was impaired and no change in natriuresis was observed after short-term volume expansion compared with normal subjects, who had an increase in urinary cGMP and sodium excretion after volume expansion.2 In that study, the impaired renal response in patients with PHF was rescued by administration of subcutaneous BNP before volume expansion. Thus, potentiation of the cGMP system in patients with asymptomatic systolic dysfunction could be a potential therapeutic strategy to prevent progression to symptomatic heart failure.

PDEV is an enzyme responsible for the degradation of cGMP and is abundant in the kidney vasculature. Natriuresis and GFR are modulated in part by renal cGMP. More important, PDEV is known to be upregulated in heart failure. A small study in a canine model of heart failure showed that PDEV inhibition potentiated the renal response to BNP, specifically improving GFR and renal cGMP generation.3 There was also an improvement in cardiac output after 10 days of PDEV inhibition. Recently, our group published the results of a study evaluating the effects of short-term PDEV inhibition with and without subcutaneous BNP on the cardiorenal response to volume expansion in subjects with PHF.5 We found no improvement and actually worsening of GFR, renal plasma flow, and glomerular filtration rate in subjects treated with short-term PDEV inhibition and subcutaneous BNP. Left atrial volume index and cardiac function, measured by ejection fraction, improved after volume expansion in subjects receiving PDEV inhibition and subcutaneous BNP compared with PDEV inhibition alone. These findings are concordant with the findings of our current study of long-term PDEV inhibition.

Several studies have evaluated PDEV inhibition in heart failure with reduced ejection fraction (HFrEF). In patients with HFrEF and secondary pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg), sildenafil improved peak oxygen consumption (VO2) and 6-minute walk distance with reduced pulmonary vascular resistance.12 Another study randomized patients with HFrEF (ejection fraction <40%) to sildenafil or placebo and found that sildenafil improved peak VO2 and quality of life.13 In addition, sildenafil improved echocardiographic parameters, such as E/e’, left ventricular mass index, and left atrial volume index. An ongoing study (NCT 01616381) is currently assessing the effects of sildenafil on symptoms and 6-minute walk distance in patients with HFrEF.

Interest in targeting the cGMP system for treatment of heart failure has significantly increased after the results of the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial were published.14 In that trial, patients with symptomatic HFrEF were randomized to the soluble guanylate cyclase stimulator vericiguat or placebo. Patients randomized to vericiguat had a lower rate of the composite end point of cardiovascular death or hospitalization for heart failure compared with placebo. Adverse events related to renal function were not different between groups. Forthcoming analyses from this study will likely enhance our understanding of the renal response to vericiguat in this patient population.

### Table 3. Change in Cardiorenal and Echocardiographic Parameters at 12 Weeks Before and After Volume Expansion

| Parameter                   | Tadalafil (n=14)   | Placebo (n=6) | P value |
|-----------------------------|--------------------|---------------|---------|
| ANP, pg/mL                  | 9.3 (−3.0 to 32.6) | 14.2 (−26.9 to 56.0) | 0.74    |
| BNP, pg/mL (n=19)           | 0.5 (−6.0 to 5.5)  | 4.0 (2.0 to 6.0)  | 0.43    |
| cGMP, pmol/mL               | 0.5 (−0.2 to 1.0)  | 0.4 (0.1 to 0.9)  | 0.87    |
| Ejection fraction, %        | 2.0 (−1.0 to 3.0)  | 2.0 (2.0 to 3.0)  | 0.68    |
| Cardiac index, mL/min per m²| 0.3 (0.2 to 0.5)   | 0 (−0.2 to 0.1)   | 0.05    |
| RVSP, mm Hg (n=19)          | 2.0 (0 to 5.0)     | 2.5 (0 to 5.5)    | 0.94    |
| E/e’                        | 0 (−1.0 to 3.0)    | −1.7 (−6.0 to 0)  | 0.27    |

Data are presented as median (interquartile range). P value compares change from baseline to after volume expansion between tadalafil and placebo. ANP indicates atrial natriuretic peptide; BNP, B-type natriuretic peptide; E/e’, ratio of the transmitral early diastolic peak velocity (E) to the early diastolic tissue Doppler velocity of the mitral annulus (e’); and RVSP, right ventricular systolic pressure.

### Table 4. Adverse Events

| Parameter                        | Tadalafil (n=14) | Placebo (n=6) | Results are shown as number (percentage). All P values comparing groups are >0.05 |
|----------------------------------|-----------------|---------------|----------------------------------------------------------------------------------|
| Any adverse event                | 7 (50)          | 1 (17)        |                                                                                  |
| Symptomatic hypotension          | 0 (0)           | 0 (0)         |                                                                                  |
| Diarrhea                         | 3 (21)          | 0 (0)         |                                                                                  |
| Indigestion                      | 2 (14)          | 0 (0)         |                                                                                  |
| Urinary tract infection          | 1 (7)           | 1 (17)        |                                                                                  |
| Headache                         | 1 (7)           | 0 (0)         |                                                                                  |
| Muscle cramps                    | 1 (7)           | 0 (0)         |                                                                                  |

Interest in targeting the cGMP system for treatment of heart failure has significantly increased after the results of the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial were published.14 In that trial, patients with symptomatic HFrEF were randomized to the soluble guanylate cyclase stimulator vericiguat or placebo. Patients randomized to vericiguat had a lower rate of the composite end point of cardiovascular death or hospitalization for heart failure compared with placebo. Adverse events related to renal function were not different between groups. Forthcoming analyses from this study will likely enhance our understanding of the renal response to vericiguat in this patient population.
The present study was the first-in-human study of the effects of long-term PDEV inhibition in patients with PHF. Long-term PDEV inhibition with tadalafil did not improve GFR or urinary sodium/cGMP excretion. A potential explanation for the findings could be that tadalafil lowered blood pressure, which decreased the renal perfusion pressure. The decrease in renal perfusion pressure may have adversely affected renal parameters and could explain the lack of benefit of renal response with PDEV inhibition.

This study has limitations. This was a small, proof-of-concept pilot study, and as such, we may have missed small changes in end points attributable to variability of the measured parameters. In addition, we did not correct for multiple end points, and therefore, the significance of secondary end points, such as left atrial volume index and cardiac index, should be viewed with caution. Also, more female subjects were randomized in the tadalafil group compared with the placebo group, and randomization was not stratified by sex. However, we are not aware of any data suggesting differential cardiorenal response to PDEV inhibition based on sex.

In this first-in-human study of the effect of long-term PDEV inhibition in subjects with PHF, we found renal function, as measured by GFR and urinary sodium/cGMP excretion, was not significantly different after 12 weeks of tadalafil. These results do not support the use of long-term PDEV inhibition to improve renal function in patients with PHF.

ARTICLE INFORMATION
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Disclosures
Drs Burnett and Chen have patented designer natriuretic peptides. The remaining authors have no disclosures to report.

Supplementary Material
Tables S1–S2

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SUPPLEMENTAL MATERIAL
**Table S1. Full list of inclusion/exclusion criteria.**

| Inclusion Criteria                                                                 | Exclusion Criteria                                                                                       |
|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| • Age ≥ 21 years                                                                   | • Hypotension (SBP < 90 mm Hg or DBP < 50 mm Hg)                                                       |
| • Preclinical systolic dysfunction (defined as a left ventricular ejection fraction ≤ 45% without clinical signs/symptoms and previous diagnosis of heart failure) | • Current or anticipated need for nitrate therapy                                                       |
| • New York Heart Association Class I                                               | • Symptoms/signs of heart failure or history of heart failure                                           |
| • Minimal 6-minute walk distance of > 450 meters, unless limited by orthopedic reasons | • Use of alpha antagonists or Cytochrome P450 3A4 inhibitors (ie ketoconazole, itraconazole, cimetidine, etc) and inability to stop medications for duration of study |
| • Estimated GFR of ≤ 90 ml/min and > 30 ml/min as assessed by MDRD formula        | • Diagnosis of retinitis pigmentosa, or history of nonischemic optic neuropathy, untreated proliferative retinopathy, or unexplained visual disturbance |
|                                                                                  | • Use of PDEV inhibitor for pulmonary hypertension or use of PDEV inhibitor for erectile dysfunction and unwilling |


to stop medication for the duration of the study

- Significant valvular heart disease (grade III/IV), hypertrophic or restrictive cardiomyopathy, or primary pulmonary hypertension
- Severe congenital heart disease
- Unstable arrhythmias
- Recent percutaneous coronary intervention or coronary artery bypass grafting (within 60 days)
- Recent stroke (within 3 months)
- Severe liver disease (AST or ALT > 3x normal or bilirubin > 2x normal)
- Serum sodium < 125 mEq/dL or > 150 mEq/dL
- Serum potassium < 3.2 mEq/dL or > 5.9 mEq/dL
- Hemoglobin < 9 g/dL
- Received any investigational drug within 1 month of consent
- Females who are pregnant or breastfeeding
- Patient unlikely to comply with study protocol, as determined by investigators.

DBP indicates diastolic blood pressure; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PDEV, phosphodiesterase V; SBP, systolic blood pressure.
Table S2. Change in cardiorenal and echocardiographic parameters from baseline in response to volume expansion at Visit 1 in subjects with preclinical systolic dysfunction.

| Parameter                        | Tadalafil       | Placebo         | p-value |
|----------------------------------|-----------------|-----------------|---------|
| **GFR, mL/min**                  | 1.3 (-7.5, 13.5)| -3.5 (-19.0, 4.5)| 0.51    |
| **RPF, mL/min**                  | -11.8 (-101.0, 24.0)| -40.5 (-78.5, 12.5)| 0.71    |
| **Urine flow, mL/min**           | 1.8 (0.8, 3.0)  | 0.8 (-0.4, 2.6) | 0.32    |
| **Sodium excretion, mEq/min**    | 40.2 (5.8, 139.3)| 5.8 (-6.0, 71.0) | 0.25    |
| **Urinary cGMP generation, mEq/min** | -4.6 (-53.2, 50.9) | -111.7 (-291.8, 24.4) | 0.19    |
| **Plasma cGMP, pmol/mL**         | 0.6 (0, 1.0)    | 0.3 (-0.1, 0.5) | 0.22    |
| **Ejection fraction, %**         | 1.5 (0, 5.0)    | 0.5 (-2.0, 8.0) | 0.54    |
| **Cardiac Index, mL/min/m2**     | 0.1 (-0.2, 0.2) | 0.4 (0.1, 0.5)  | 0.09    |
| **E/e’**                         | 1.0 (-2.5, 4.0) | -2.0 (-2.0, 0)  | 0.12    |
| **RVSP, mm Hg**                  | 2.5 (1.0, 4.0)  | 2.0 (0, 2.0)    | 0.57    |
Data are presented as median (interquartile range). ANP indicates atrial natriuretic peptide; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; RPF, renal plasma flow; LAVI, left atrial volume index; RVSP, right ventricular systolic pressure.