# Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction : A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study

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# Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

## A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study

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***Background***—The prevalence of heart failure with preserved ejection fraction is increasing. The prognosis worsens with pulmonary hypertension and right ventricular (RV) failure development. We targeted pulmonary hypertension and RV burden with the phosphodiesterase-5 inhibitor sildenafil.

***Methods and Results***—Forty-four patients with heart failure with preserved ejection fraction (heart failure signs and symptoms, diastolic dysfunction, ejection fraction ≥50%, and pulmonary artery systolic pressure >40 mm Hg) were randomly assigned to placebo or sildenafil (50 mg thrice per day). At 6 months, there was no improvement with placebo, but sildenafil mediated significant improvements in mean pulmonary artery pressure (−42.0±13.0%) and RV function, as suggested by leftward shift of the RV Frank-Starling relationship, increased tricuspid annular systolic excursion (+69.0±19.0%) and ejection rate (+17.0±8.3%), and reduced right atrial pressure (−54.0±7.2%). These effects may have resulted from changes within the lung (reduced lung water content and improved alveolar-capillary gas conductance, +15.8±4.5%), the pulmonary vasculature (arteriolar resistance, −71.0±8.2%), and left-sided cardiac function (wedge pulmonary pressure, −15.7±3.1%; cardiac index, +6.0±0.9%; deceleration time, −13.0±1.9%; isovolumic relaxation time, −14.0±1.7%; septal mitral annulus velocity, −76.4±9.2%). Results were similar at 12 months.

***Conclusions***—The multifaceted response to phosphodiesterase-5 inhibition in heart failure with preserved ejection fraction includes improvement in pulmonary pressure and vasomotility, RV function and dimension, left ventricular relaxation and distensibility (structural changes and/or ventricular interdependence), and lung interstitial water metabolism (wedge pulmonary pressure decrease improving hydrostatic balance and right atrial pressure reduction facilitating lung lymphatic drainage). These results enhance our understanding of heart failure with preserved ejection fraction and offer new directions for therapy.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01156636.

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**Key Words:** diastolic heart failure ■ heart failure ■ pulmonary hypertension

Heart failure (HF) with preserved ejection fraction (EF) (HFpEF) is a public health problem and a major topic in clinical cardiology. Its prevalence is, indeed, increasing, and the outcome is similar to HF with left ventricular (LV) systolic dysfunction.[1,2] Pulmonary hypertension (PH) in HFpEF is highly prevalent and often severe, and, as in LV systolic dysfunction,[3] is a predictor of morbidity and mortality.[4] Because of the thin wall and distensibility, the right ventricle (RV) is more vulnerable by an excessive afterload than by preload. The pulmonary circulation is a central determinant of RV afterload, and an increase in RV ejection impedance can easily result in RV failure, tricuspid regurgitation, and central venous pressure (CVP) rise.

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Development of RV failure is viewed unanimously as a predictor of poor prognosis,[3,4] but the underlying mechanisms have not been investigated extensively. Interestingly, recent studies have emphasized the importance of the rise in CVP, mainly in regard to its backward deleterious influence on renal function.[5,6]

Because of the prevalence and clinical significance of left-sided PH, attenuation of the pulmonary vascular tone and of the RV hemodynamic burden is an important target of HF therapy. Attempts with endothelin receptor antagonists[7] or

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prostacyclin analogues[8] were basically unsuccessful. Experimental models and human studies have shown that, in HF, nitric oxide (NO)–dependent pulmonary vasodilatation is impaired[9] and primarily contributes to pulmonary endothelial dysfunction.[9,10] Accordingly, therapeutic strategies with agents that increase the NO pathway, such as nitrates[11] or phosphodiesterase-5 (PDE5) inhibitors, have been tested.[12–14] PDE5 inhibitors offer the double advantage of selectively dilating the pulmonary vessels without producing tachyphylaxis.[15]

In this 1-year study, the primary end point was to probe whether pulmonary hemodynamics and RV performance in HFpEF with PH may be targets of PDE5 inhibition with sildenafil. Related to this, we also took the opportunity to expand the pathophysiological perspectives with regard to CVP elevation and its prognostic correlates on the basis of the concept that the superior vena cava is the place of convergence for the pulmonary lymphatic ducts to drain via thoracic ducts, and the lymphatic pump is a basic safety factor against pulmonary edema. CVP elevation, by raising the outflow pressure and thereby reducing the flow of lymph, might contribute to lung interstitial overflow[16] that further increases impedance to RV ejection, cardiac extramural pressure, and CVP.[5]

## Methods

### Study Population

Because hypertensive heart disease in elderly patients is a common precursor to HFpEF,[17] the study population was recruited among patients with high blood pressure referred to the Hypertension Clinic at San Paolo Hospital in Milan, Italy, and at Virginia Commonwealth University, Richmond, because of recent onset of dyspnea and limitation in physical activity. These symptoms were not reported in the past despite long-standing pressure elevation that necessitated antihypertensive medications. Ninety-four consecutive patients were identified between January 15, 2006, and December 18, 2008.[18] Dosages of renin-angiotensin system $\beta$-receptor blockers (primarily metoprolol and atenolol) and $Ca^{2+}$ channel blockers (Table 1) had been stable in these patients for at least 6 months. Diuretics (primarily chlorthalidone 25 mg/d or furosemide 50 to 75 mg/d, which in 4 cases were combined with spironolactone 25 to 50 mg/d), were started over the last 1 or 2 months in the majority of patients because of dyspnea and ankle swelling. Heart failure was independently adjudicated by 3 cardiologists on the basis of presence of ≥2 major criteria (nocturnal dyspnea, distention of the jugular veins, moist rales over the lung bases, protodiastolic sound) or the presence of 1 major criterion together with 3 minor criteria (liver enlargement, edema in the feet or ankles not resolving after a night's rest, accentuation of $P_2$, tricuspid systolic murmur, fatigue, signs of interstitial edema at chest roentgenogram). Inclusion criteria were as follows: LVEF ≥50%, sinus rhythm, and no hospitalization in the 6 months preceding recruitment.

Patients receiving nitrates, with a history of pulmonary disease or in whom alternative causes of PH were likely, or with angina pectoris, acute coronary syndrome, atrial flutter/fibrillation with more than a trace of mitral or aortic regurgitation or stenosis, anemia, pericardial disease, renal failure (creatinine >2 mg/dL), cardiac amyloidosis, genetically determined cardiomyopathy, or systemic diseases precluding participation were not considered. An additional a priori inclusion requirement was a pulmonary artery (PA) systolic pressure ≥40 mm Hg at a preliminary ultrasound estimation.[5] Seventy-five recruited patients (71%) fulfilled these criteria, 31 of whom (27%) did not consent to participate. The remaining 44 provided their written consent to the study after detailed explanation of purposes, procedures to be undertaken, and possible risks and benefits and made up the final population of subjects with HFpEF with PH.

**Table 1. Baseline Demographic and Clinical Characteristics and Cardiovascular Parameters in the Placebo and Sildenafil Groups**

| | Placebo | Sildenafil |
|---|---|---|
| n | 22 | 22 |
| Age, y (range) | 73 (53–79) | 72 (62–81) |
| Men | 18 | 17 |
| Body surface area, $m^2$ | 1.93±0.28 | 1.95±0.26 |
| Body mass index, kg/ $m^2$ | 30.2±8.9 | 31.8±11.3 |
| Hypertension | 22 | 22 |
| Hypertension+diabetes mellitus | 3 | 4 |
| LV ejection fraction, % | 60±6 | 60±4 |
| Heart rate, bpm | 69±10 | 71±8 |
| Systolic blood pressure, mm Hg | 147±17 | 153±15 |
| Diastolic blood pressure, mm Hg | 84±11 | 87±13 |
| Cardiac index, $L \cdot min \cdot m^2$ | 2.33±0.64 | 2.39±0.59 |
| Stroke volume index, $mL \cdot m^2$ | 33±3 | 35±4 |
| Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 2694±688 | 2717±724 |
| LV mass index, $g/m^2$ | 168.2±10.5 | 166.4±12.1 |
| Concentric remodeling | 6 | 7 |
| Concentric hypertrophy | 10 | 8 |
| Eccentric hypertrophy | 6 | 7 |
| E, m/s | 0.88±0.21 | 0.91±0.26 |
| A, m/s | 0.89±0.23 | 0.93±0.19 |
| E/A ratio | 0.93±0.42 | 0.95±0.36 |
| Deceleration time, ms | 243±45 | 254±53 |
| Isovolumic relaxation time, ms | 88±21 | 85±18 |
| E′ septal, m/s | 0.048±0.024 | 0.051±0.030 |
| E/E′ ratio | 17.04±6.18 | 16.97±7.84 |
| TE′−E, ms | 24±5 | 26±6 |
| Drug therapy | | |
| Diuretics (%) | 18 (82) | 16 (72) |
| ACEI/ARB (%) | 21 (95) | 21 (95) |
| Digoxin (%) | 2 (9) | 3 (13) |
| $\beta$-Blockers (%) | 17 (77) | 19 (86) |
| $Ca^{2+}$ channel blockers (%) | 4 (18) | 6 (27) |

LV indicates left ventricular; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; E, peak early mitral inflow velocity; A, peak late mitral inflow velocity; E′, early mitral annulus diastolic velocity; and TE′−E, time interval between E′ onset and E-wave velocity.

### Study Protocol

This was a double-blind, randomized, placebo-controlled, 1-year study. Patients were randomly assigned in a 1:1 ratio according to computer-generated random numbers to receive placebo (22 patients) or the PDE5 inhibitor sildenafil 50 mg thrice daily (22 patients). The current drug treatment prescribed by the referring physician was kept unchanged throughout the trial in all but 3 patients in the placebo group. For evaluations at baseline and at 6 and 12 months, patients underwent medical review, routine laboratory work, chest x-ray, hemodynamic and ultrasound measurements, pulmonary function tests, and quality-of-life assessment. They at-

tended the Hypertension Clinic monthly for physical examination, symptom and ECG recording, compliance assessment (pill count method), and active drug or placebo supply (by a nurse who was unaware of the study aims and design) for the duration of the trial. The protocol was approved by the institutional review boards.

## Hemodynamic Measurements

Circulatory measurements were performed in the morning with the patient in a fasting state, in the supine position, without premedication. A 7F thermodilution balloon-tipped catheter was inserted percutaneously, under local anesthesia, into an antecubital vein and floated under fluoroscopy to the right atrium (RA), then advanced to the RV, the PA, and the wedge position. Pressure transducers were balanced against atmospheric pressure, and the zero reference level for recordings was 5 cm below the sternal angle. Mean pressures were obtained by electronic damping. Heart rate and cardiac output (determined by thermodilution) were also recorded. The criteria for a satisfactory wedge pulmonary pressure (WPP) were as follows: change from the typical PA waveform to the typical WPP waveform on inflation of the balloon catheter; the WPP was taken at end-expiration during 5 ordinary quiet breaths and was characterized by distinct "a" and "v" waveforms, with the "v" wave occurring after the T wave of the ECG; blood withdrawn from the catheter had an oxygen saturation within the systemic arterial range. Measurement of the RV ejection time was obtained by recording, at a speed of 100 mm/s, of the pulmonary pressure tracing (from the beginning upstroke to the trough of the incisura); the interval was calculated from the mean of measurements on 5 consecutive beats. The RV mean rate of systolic ejection was determined by dividing the stroke volume by the RV ejection time. Pulmonary arteriolar resistance (PAR) (in Wood units) and total peripheral resistance index (TPR) (in dyne $\cdot$ s $\cdot$ cm$^{-5}$) were calculated as the ratio of mean PA pressure minus mean WPP to cardiac output and of mean systemic arterial pressure minus mean RA pressure to cardiac index, respectively. Pulmonary effective arterial elastance (change in pressure for a change in volume), a measure of the net arterial load faced by the RV during systole, was approximated invasively by the ratio of pulmonary end-systolic pressure to stroke volume.[19]

Measurements were performed in the steady state at least 30 minutes after the endovascular procedure was completed, when heart rate and pressures had definitely stabilized. Determinations were performed twice, at 15-minute intervals, during which the catheter was withdrawn in a central venous position; the average of the 2 measurements was taken as the representative value of each subject. Determinations of arterial $O_2$ and $CO_2$ tension and pH were performed on arterial blood samples obtained during quiet, regular respiration.

## Pulmonary Function Evaluations

Forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and lung diffusion capacity for carbon monoxide (DLCO) were assessed by the Sensormedics Vmax Pulmonary Function Test System (Yorba Linda, CA) according to the American Thoracic Society performance criteria.[20] To adjust for height, age, and sex, we used prediction equations for $FEV_1$ and FVC.[21] DLCO was determined twice with washout intervals of at least 4 minutes (the results were averaged) with a standard single-breath technique. The diffusion capacity of the alveolar-capillary membrane ($D_M$) and the capillary blood volume available for gas exchange were determined by the classic method described by Roughton and Forster.[22] The reproducibility of the method in our laboratory has been reported previously.[23] The single-breath alveolar volume was derived by methane dilution. The proportion of total pulmonary diffusive resistance ($DLCO/D_M$) was calculated. In each subject, pleural pressure was estimated with a rubber 2-mL volume esophageal balloon introduced through the nose into the esophagus, placed at a distance of 45 cm from the balloon tip to the nares and connected to a pressure transducer through a polyethylene tube. Pleural and vascular pressures were recorded simultaneously on the same recording system. A chest roentgenogram scoring method was used to determine extravascular lung water.[24]

## Doppler Echocardiography

Ultrasound evaluations (IE33, Philips ultrasound machine) were performed by 2 registered cardiac sonographers according to a standardized protocol and read by an echocardiologist who was unaware of the study design.

Each patient underwent standard M-mode, 2-dimensional, and color Doppler imaging, continuous pulsed Doppler examination, and tissue Doppler imaging, which sought to estimate RV and LV dimensions, wall thickness, LVEF, and pulmonary artery systolic pressure and to assess LV diastolic function by measuring mitral inflow velocities (E, A), septal annulus relaxation velocity (E′), and the time interval difference between E′ and E (TE′−E).[25] Additional parameters included LV mass indexed by body surface area,[26] relative wall thickness, mean velocity of circumferential fiber shortening, and tricuspid annular plane systolic excursion.[27] All parameters were the average of measurements in triplicate.

## Quality of Life

Breathlessness, fatigue, and emotional function of daily living were assessed with a 16-question congestive HF questionnaire with answers scored from 1 (worst) to 7 (best)[28] (see the online-only Data Supplement).

## Statistical Analysis

Change in mean pulmonary artery pressure was used to estimate the sample size needed to achieve adequate statistical power for the current investigation. We assumed a 20% decrease of mean pulmonary artery pressure ($\approx$7 mm Hg) after treatment in the experimental group and a SD of change of 5.5 mm Hg.[12] Thus, at an $\alpha$ of 0.05 and a power of 0.90, a sample size of 18 patients per group was calculated for the current investigation. Additionally, we factored a 20% safety margin for patients lost to follow-up and therefore targeted a recruitment of 22 patients per group. Their characteristics at baseline were compared with an unpaired *t* test or Fisher exact test.

Repeated-measures ANOVA was used to determine whether a significant ($P<0.05$) difference in the change across time occurred between the 2 groups. For variables for which a significant time×group interaction was observed, ANOVA was used to assess a within-group time effect, and the Student 2-sample *t* test was used to assess a group effect with Bonferroni adjustment.

The relationships between changes in RV systolic function and pulmonary arterial elastance and between those in alveolar capillary membrane conductance and pulmonary and right heart hemodynamics were assessed with the Pearson coefficient of correlation. Values are mean±SD. Statistical analyses were performed with the use of Stata 7.0 software package (Stata, College Station, TX).

# Results

As shown in Table 1, demographic and hemodynamic variables and current drug treatment in patients randomized to placebo were comparable to those in patients randomized to sildenafil.

Both groups fulfilled the suggested criteria for the diagnosis of HFpEF[29]: symptoms and signs of HF, LVEF ≥50%, and evidence of LV diastolic dysfunction. In either population, the LV mass and relative wall thickness indices were increased,[30] systemic vascular resistance index was high, and cardiac index was low. No patient in the sildenafil group was lost to follow-up; in the placebo group, 2 patients were withdrawn at months 7 and 9 because at repeated Holter monitoring they showed persistent atrial fibrillation. Three patients receiving placebo required potentiation of diuretics during the trial because of paroxysmal nocturnal dyspnea, increase of jugular venous distention, and basilar rales.

**Table 2. Right Heart and Pulmonary Hemodynamics and Quality of Life at Baseline and After 6- and 12-Month Administration of Placebo or Sildenafil**

| | Placebo | | | Sildenafil | | |
|---|---|---|---|---|---|---|
| Variables | Baseline | 6 mo | 12 mo | Baseline | 6 mo | 12 mo |
| Mean right atrial pressure, mm Hg | 23.1±5.5 | 22.0±5.2 | 24.1±4.3 | 23.0±4.6 | 10.6±3.6*† | 9.3±3.4*† |
| Pulmonary artery systolic pressure, mm Hg | 52.1±5.1 | 53.0±5.8 | 55.6±5.5 | 54.5±6.3 | 30.4±3.6*† | 28.0±3.7*† |
| Pulmonary artery diastolic pressure, mm Hg | 29.7±6.2 | 30.4±5.4 | 32.8±5.1 | 31.6±5.0 | 18.6±4.5*† | 16.7±3.5*† |
| Mean pulmonary artery pressure, mm Hg | 36.8±5.1 | 37.8±4.9 | 39.6±4.7 | 39.0±5.0 | 22.3±3.7*† | 20.8±3.3*† |
| Mean wedge pulmonary pressure, mm Hg | 21.9±2.0 | 22.4±1.8 | 22.2±1.6 | 22.0±2.5 | 18.7±2.3*† | 17.8±1.9*† |
| Transpulmonary gradient, mm Hg | 14.5±2.3 | 15.5±1.9 | 17.9±1.7 | 16.2±1.6 | 3.8±2.1*† | 3.3±1.8*† |
| Pulmonary arteriolar resistance, Wood units | 3.27±0.9 | 3.42±1.02 | 3.96±1.03* | 3.88±1.38 | 1.18±0.50*† | 1.00±0.56*† |
| Pulmonary arterial elastance, mm Hg/mL | 0.69±0.08 | 0.73±0.09 | 0.80±0.02 | 0.75±0.1 | 0.39±0.05*† | 0.36±0.07*† |
| RV end-diastolic pressure, mm Hg | 20.1±5.4 | 20.9±4.5 | 21.3±4.0 | 20.0±4.4 | 12.8±3.4*† | 11.2±3.3*† |
| RV mean systolic ejection rate, mL/s | 242±20.6 | 231±24.2 | 221±25.9 | 236±30.0 | 276±25.1*† | 275±29.7*† |
| TAPSE, mm | 11.2±2.5 | 10.6±2.3 | 11.5±1.8 | 11.3±2.2 | 19.2±2.3*† | 19.7±1.9*† |
| RV maximal short-axis dimension, cm | 5.5±0.8 | 5.7±0.7 | 5.7±0.6 | 5.6±0.7 | 5.0±0.5*† | 4.9±0.6*† |
| Quality of life | | | | | | |
| Breathlessness | 16.6±6.0 | 15.2±3.1 | 16.1±4.5 | 16.0±5.4 | 22.2±6.5*† | 23.4±7.6*† |
| Fatigue | 20.3±4.3 | 21.2±4.7 | 19.8±5.3 | 19.2±4.5 | 27.5±5.6*† | 28.9±5.4*† |
| Emotional function | 25.4±5.4 | 22.3±5.1 | 22.7±5.9 | 23.9±6.1 | 29.2±4.7*† | 30.2±4.8*† |

RV indicates right ventricular; TAPSE, tricuspid annular plane systolic excursion.
*$P<0.01$ vs baseline; †$P<0.01$ vs corresponding placebo value.

## Pulmonary and Right Heart Hemodynamics

At baseline, systolic, diastolic, and mean PA pressures were raised similarly in the 2 cohorts, and, in agreement with preliminary echo-Doppler estimation, endovascular systolic PA pressure exceeded 40 mm Hg in each case. Mean WPP was increased in either population (Table 2).

As shown in Table 2, in patients receiving sildenafil, at 6 months we recorded a substantial decrease from baseline of systolic, diastolic, and mean PA pressures; changes at 6 and 12 months in mean PA pressure averaged −16.7±3.1 and −18.2±2.4 mm Hg, respectively, and were significantly different from those in the placebo arm (+1.0±0.7 and +2.8±1.1 mm Hg); with sildenafil, PAR decreased by 69.0±18.0%, and the mean WPP was lowered by 15.7±3.1%. No significant changes in all of these variables occurred with placebo at the same periods. Individual and mean (±SD) values for PAR at baseline and after 6 and 12 months of placebo or sildenafil are reported in Figure 1.

In both groups, baseline mean RA pressure and RV end-diastolic pressure were raised, and the RV systolic function, as evaluated by tricuspid annular plane systolic excursion (<15 mm in each case), was depressed.[26] Sildenafil significantly lowered RA pressure (by 54.0±7.2% at 6 months and by 59.0±7.8% at 12 months), RV end-diastolic pressure (by 48.0±9.0% and 55.0±10.0%), and maximal short-axis dimension (by 10.0±3.0% and 12±2.0%). Figure 2 reports a plot of individual values of RV end-diastolic pressure against stroke volume in the placebo and sildenafil groups at baseline and at 6 months. The relationship was definitely shifted leftward after sildenafil treatment. At the same time interval, in the active treatment arm and not in the placebo arm, there was also a significant increase in tricuspid

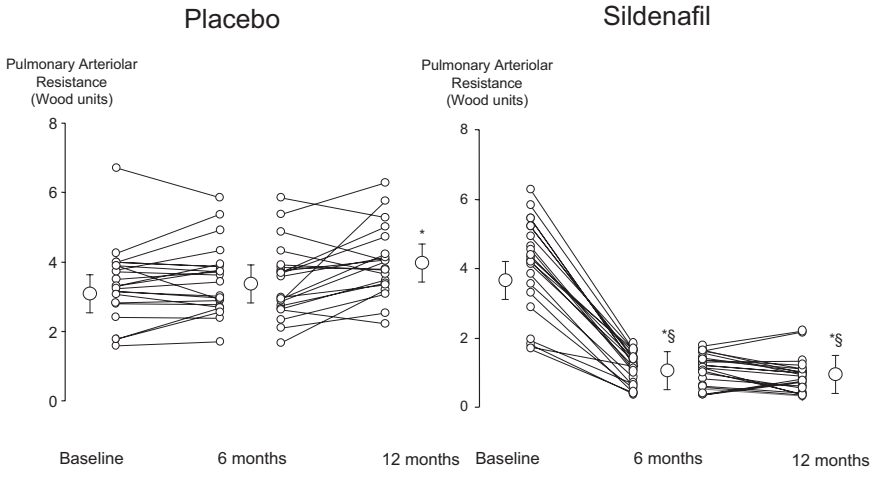


**Figure 1.** Individual and mean (±SD) values for pulmonary arteriolar resistance at baseline and after 6 and 12 months of placebo or sildenafil. *$P<0.01$ vs baseline; §$P<0.01$ vs corresponding placebo value.

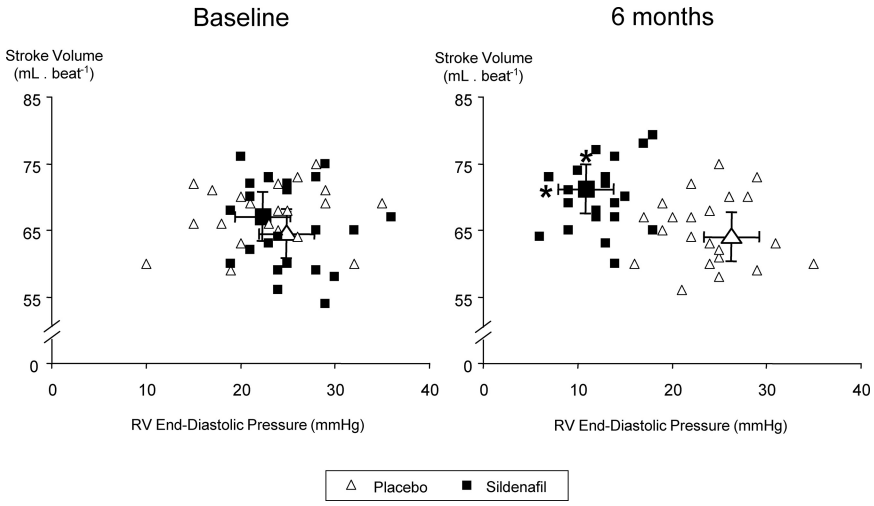


**Figure 2.** Right ventricular (RV) end-diastolic pressure–stroke volume relationship at baseline and after 6 months of placebo or sildenafil. Individual and mean (±SD) values are shown. *$P<0.01$ vs placebo.

annular plane systolic excursion (+69.0±19.0% and +68±18.0%) and in RV mean rate of systolic ejection (+17.0±8.3% and +16.0±8.0%). Figure 3 shows that these changes were inversely related to those in RV afterload (pulmonary arterial elastance) at both 6 and 12 months in the active treatment group and not in the placebo group.

## Systemic and Left Heart Hemodynamics

No significant change in the variables reported in Table 3 occurred across time in patients receiving placebo. On the contrary, patients receiving active treatment showed, at both 6 and 12 months, increase of cardiac index, calculated TPR (mainly because of the substantial reduction in mean RA pressure), E/A ratio, E′, and LV internal dimension; and decrease of interventricular septum, posterior wall and relative wall thickness, LV mass index (at 12 months), E/E′, TE′−E, deceleration time, and isovolumic relaxation time. Blood pressure, LVEF, and mean velocity of circumferential fiber shortening did not significantly vary from baseline values.

## Pulmonary Function

At baseline, variables reported in Table 4 were similar in both populations. $FEV_1$, FVC, and DLCO in these patients were lower than normal predicted values. $O_2$ and $CO_2$ tension and pH of the arterial blood and pleural pressure were within normal limits. In the sildenafil group, at both 6 and 12 months, there was a significant increase of $FEV_1$, FVC,

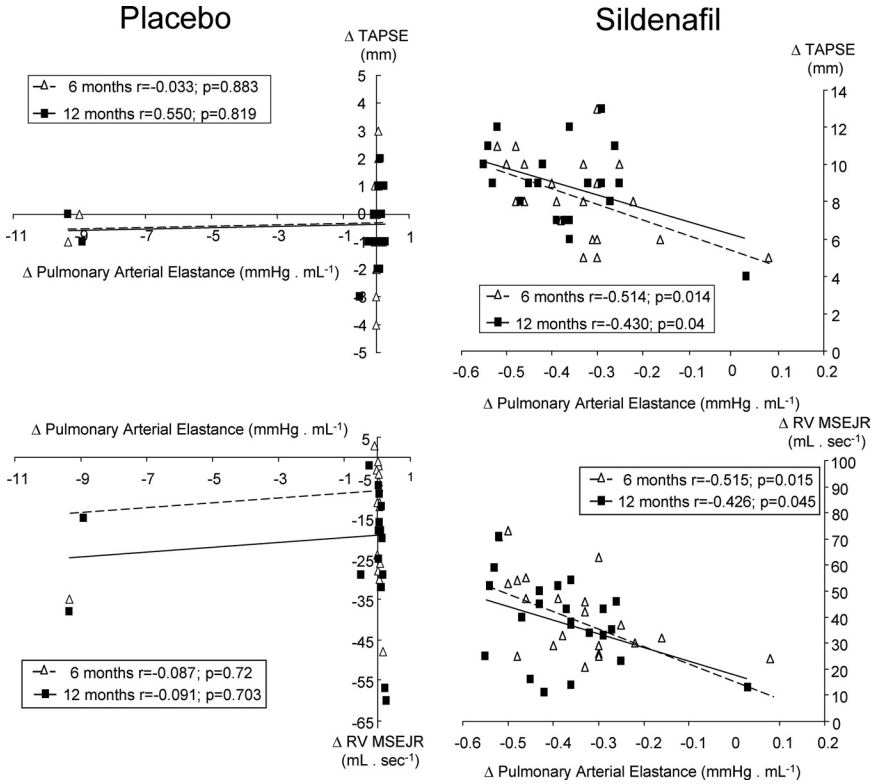


**Figure 3.** Relationship of changes from baseline in pulmonary arterial elastance with changes in tricuspid annular plane systolic excursion (TAPSE) and right ventricular (RV) mean systolic ejection rate (MSEJR) at 6 and 12 months of placebo or sildenafil.

**Table 3. Left Ventricular and Systemic Hemodynamics and Left Ventricular Dimensions at Baseline and After 6- and 12-Month Administration of Placebo or Sildenafil**

| | Placebo | | | Sildenafil | | |
|---|---|---|---|---|---|---|
| | Baseline | 6 mo | 12 mo | Baseline | 6 mo | 12 mo |
| Systolic arterial pressure, mm Hg, | 147±17 | 149±16 | 150±14 | 150±15 | 152±13 | 154±12 |
| Diastolic arterial pressure, mm Hg | 84±11 | 84±10 | 86±15 | 87±13 | 89±12 | 90±12 |
| Mean arterial pressure, mm Hg | 105±12 | 106±11 | 107±10 | 109±11 | 110±13 | 111±9 |
| Mean wedge pulmonary pressure, mm Hg | 21.9±2.0 | 22.4±1.8 | 22.2±1.6 | 22.0±2.5 | 18.7±2.3†‡ | 17.8±1.9†‡ |
| Cardiac index, $L \cdot min \cdot m^2$ | 2.33±0.64 | 2.28±0.60 | 2.32±0.56 | 2.39±0.59 | 2.49±0.62‡ | 2.51±0.51†‡ |
| Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 2694±688 | 2809±625 | 2859±710 | 2717±721 | 3157±690†‡ | 3114±698†‡ |
| LV ejection fraction, % | 60±6 | 56±8 | 58±7 | 60±4 | 59±5 | 63±3‡ |
| Velocity of circumferential fiber shortening, circumferences/s | 0.79±0.1 | 0.77±0.08 | 0.78±0.09 | 0.81±0.1 | 0.78±0.09 | 0.79±0.08 |
| LV relative wall thickness, index | 0.48±0.06 | 0.50±0.04 | 0.50±0.05 | 0.49±0.07 | 0.45±0.06†‡ | 0.41±0.05†‡ |
| LV internal dimension, cm | 5.0±0.3 | 5.0±0.2 | 5.1±0.2 | 5.0±0.3 | 5.3±0.2†‡ | 5.5±0.2†‡ |
| Interventricular septum thickness, cm | 1.35±0.08 | 1.37±0.09 | 1.39±0.1 | 1.34±0.1 | 1.28±0.08†‡ | 1.22±0.07†‡ |
| LV posterior wall thickness, cm | 1.27±0.09 | 1.27±0.12 | 1.29±0.11 | 1.26±0.10 | 1.21±0.08‡ | 1.15±0.08†‡ |
| LV mass index, $g/m^2$ | 168.2±10.5 | 165.1±11.6 | 174.8±10.4 | 166.4±12.1 | 167.2±9.9 | 163.9±11.2‡ |
| Deceleration time, ms | 243±47 | 248±32 | 249±41 | 254±53 | 219±37†‡ | 218±34†‡ |
| Isovolumic relaxation time, ms | 92±21 | 94±20 | 94±23 | 97±18 | 83±18†‡ | 80±20†‡ |
| E, m/s | 0.88±0.21 | 0.85±0.22 | 0.85±0.24 | 0.91±0.26 | 0.97±0.29†‡ | 0.99±0.25†‡ |
| A, m/s | 0.89±0.23 | 0.98±0.20† | 1.10±0.13† | 0.93±0.19 | 0.88±0.15†‡ | 0.80±0.10†‡ |
| E/A ratio | 0.93±0.42 | 0.89±0.36 | 0.78±0.32† | 0.95±0.36 | 1.09±0.31†‡ | 1.13±0.34†‡ |
| E′ septal, m/s* | 0.048±0.022 | 0.046±0.026 | 0.044±0.030 | 0.051±0.029 | 0.090±0.023†‡ | 0.099±0.029†‡ |
| E/E′ ratio* | 18.33±6.71 | 18.40±5.85 | 19.31±6.12 | 17.80±7.52 | 10.65±3.67†‡ | 10.64±3.73†‡ |
| TE′−E, ms* | 24±5 | 22±8 | 23±5 | 26±6 | 7±4†‡ | 3±7†‡ |

LV indicates left ventricular; E, peak early mitral inflow velocity; A, peak late mitral inflow velocity; E′, early mitral annulus diastolic velocity; and TE′−E, time interval between E′ onset and E-wave velocity.

*Average data for 20 patients in the placebo group and 19 in the sildenafil group.

†$P<0.01$ vs baseline; ‡$P<0.01$ vs corresponding placebo value.

DLCO, $D_M$, capillary blood volume available for gas exchange, and $D_M$/alveolar volume, a decrease in lung extravascular water score, and no significant changes in arterial $O_2$ and $CO_2$ tension and pH. Pleural pressure showed a trend toward reduction. These parameters were not affected by placebo (Table 4). In both groups at baseline, the alveolar capillary membrane conductance ($D_M$) inversely correlated with RA pressure (placebo: $r=-0.54$, $P=0.01$; sildenafil: $r=-0.59$, $P=0.03$) and with WPP (placebo: $r=-0.62$, $P=0.02$; sildenafil: $r=-0.53$, $P=0.04$). After sildenafil, $D_M$ improvement significantly correlated with changes in RA pressure (Figure 4). $D_M$ changes with placebo were minimal and were unrelated to both WPP and RA pressure (Figure 4).

## Quality of Life

Table 2 shows that breathlessness, fatigue, and emotional function did not change across time with placebo and improved significantly with sildenafil.

# Discussion

A basic feature of HFpEF is that a disease originating as LV diastolic dysfunction at a certain point of its natural history converts to right heart disease, which becomes predominant in the pathophysiological scenario and determines the outcome. The primary link between the 2 sides of the heart seems to be the development of pulmonary vasoconstriction and hypertension and RV overload. Whether elevation of the PAR in this syndrome can be prevented with pharmacological interventions remains undefined. The current antihypertensive regimen in these patients, including angiotensin converting enzyme inhibitors/angiotensin receptor blockers, $\beta$-blockers, and $Ca^{2+}$ channel blockers in a few cases, did not seem to be effective in this respect. In particular, $\beta$-blockers have been reported to be ineffective for mortality and rehospitalization risks for patients with HFpEF.[31]

Sildenafil treatment was associated with sustained reduction in calculated PAR and possibly in pulmonary vascular calibers. However, before pulmonary vasomotility can be invoked, it is axiomatic that passive mechanisms for decreasing vascular caliber be fully taken into account. Increase in transmural pressure (arising from an increase in either PA or left atrial pressure), changes in intrathoracic pressure, decrease in pericapillary edema, and increase in pulmonary blood flow are the main passive mechanisms. In our study, the first of these possibilities can easily be ruled out because pressures were not raised but reduced. Intrathoracic pressure tended to become lower. Pericapillary edema was probably

**Table 4. Pulmonary Function Data, Arterial Carbon Dioxide and Oxygen Tension and pH, and Pleural Pressure and Extravascular Lung Water Score at Baseline and After 6 and 12 Months in Patients Receiving Placebo or Sildenafil**

| | Placebo | | | Sildenafil | | |
|---|---|---|---|---|---|---|
| Variables | Baseline | 6 mo | 12 mo | Baseline | 6 mo | 12 mo |
| Forced expiratory volume in 1 s, % predicted | 72±4 | 70±3 | 69±4 | 69±5 | 80±4*† | 79±5*† |
| Forced vital capacity, % predicted | 69±5 | 71±6 | 68±6 | 67±4 | 79±5*† | 81±3*† |
| $P_{CO_2}$, mm Hg | 36.1±2.0 | 35.6±1.8 | 36.3±1.9 | 35.2±1.7 | 36.1±1.4 | 35.8±2.1 |
| $P_{O_2}$, mm Hg | 93.4±1.5 | 95.5±1.2 | 93.9±1.0 | 94.2±1.3 | 94.8±1.4 | 95.6±1.5 |
| pH | 7.435±0.003 | 7.432±0.002 | 7.433±0.004 | 7.429±0.001 | 7.431±0.003 | 7.436±0.002 |
| Pleural pressure, mm Hg | | | | | | |
| Inspiratory | −5.3±0.91 | −5.1±0.84 | −5.2±0.78 | −5.2±0.85 | −5.6±0.78 | −5.7±0.82 |
| Expiratory | −2.0±0.73 | −2.1±0.77 | −1.9±0.74 | −2.1±0.71 | −2.8±0.75 | −2.7±0.79 |
| Extravascular lung water score | 13.5±3 | 14.1±4 | 13.8±3 | 14.2±4 | 9.3±3*† | 9.1±2*† |
| $D_{LCO}$, mL · min$^{-1}$ · mm Hg$^{-1}$ | 22.1±4.1 | 21.8±3.7 | 22.4±4.5 | 21.1±4.0 | 24.5±13.8*† | 24.1±3.9*† |
| $D_{LCO}$, % predicted | 75.2±5.9 | 76.6±6.8 | 74.8±7.7 | 74.3±7.6 | 81.0±6.5*† | 80.6±7.1*† |
| $D_M$, mL · min$^{-1}$ · mm Hg$^{-1}$ | 31.9±4.7 | 32.4±5.1 | 31.3±4.9 | 32.7±4.3 | 37.9±4.9*† | 37.6±5.1*† |
| Vc, mL | 95.2±13.5 | 93.7±12.3 | 91.4±11.6 | 92.5±10.6 | 94.7±11.3*† | 94.9±12.4*† |
| $D_{LCO}/D_M$, % | 68.3±6.9 | 67.7±7.1 | 68.1±6.3 | 67.5±6.7 | 65.9±6.3 | 66.0±6.8 |
| $D_M$/VA, mL · min$^{-1}$ · mm Hg$^{-1}$ · L$^{-1}$ | 5.7±1.3 | 5.6±1.4 | 5.7±1.2 | 5.9±1.2 | 6.8±1.3*† | 6.8±1.5*† |

$D_{LCO}$ indicates lung diffusing capacity for carbon monoxide; $D_M$, alveolar-capillary membrane diffusion capacity; Vc, blood capillary volume; and VA, alveolar volume.
*$P<0.01$ vs baseline; †$P<0.01$ vs corresponding placebo value.

attenuated, and its role is discussed below. Pulmonary blood flow, indeed, was increased; however, were it the exclusive mediator of the PAR reduction, PA pressure would not be expected to decrease.

Once developed, can pulmonary vasoconstriction and hypertension be reversed? If they can, do clinical course and prognosis improve? The present study provides a positive answer to the first of these basic questions, documenting that inhibition of cGMP degradation with the PDE5 inhibitor sildenafil in HFpEF promotes a sustained pulmonary active vasodilatation with reduction of PA pressure and improvement in right heart hemodynamics. These changes differed quite significantly from those in the placebo arm, in which PAR increase over the course of the study with an unchanged WPP may suggest that there is actual remodeling going on rather than simply vasoconstriction.

Regardless of EF, elevation in LV filling pressure leads to passive pulmonary venous congestion and postcapillary PH.[10] A reactive increase in pulmonary arterial tone or intrinsic arterial remodeling can result in an increased transpulmonary pressure gradient superimposed on the pulmonary venous pressure. This occurs in patients with mitral stenosis[10] and in HF with reduced EF.[32] Observations from a population-based report by Lam et al[4] revealed that in hypertensive patients with HFpEF, the passive contribution of venous PH may not by itself account for the increased PA pressure, and the authors postulated an additional precapillary component of PA hypertension mediated by functional or organic arteriolar disorders. Our results were obtained invasively and showed that after adjustment for WPP, PAR, which reflects PA hypertension added to venous hypertension, was elevated in all patients.

This study also provides a more precise quantification of the transpulmonary gradients in HFpEF than that obtained with noninvasive methods. Values of pulmonary vascular pressure and resistance in this category of patients are definitely lower than in those with PA hypertension,[33] and the vasodilating and pressure-lowering efficacy of similar doses of sildenafil is substantially greater, suggesting that the background for caliber reduction of the pulmonary vessels may be quite different.

In regard to the mediators of precapillary PH, in previous studies in patients with high blood pressure without HF, PA pressure was found to be higher than the highest in normotensive controls,[34] and pulmonary vessels were found to be supersensitive to catecholamines[35] and hyperresponsive to alveolar hypoxia.[36] In these patients, the $Ca^{2+}$ channel blocker nifedipine was able to modulate the baseline PAR[37] and to blunt the hyperreactivity to hypoxia,[36] suggesting that an alteration in $Ca^{2+}$ handling may be involved in the excessive pulmonary vessel contractility.[37] Although elevated circulating catecholamines and hypoxia are 2 biochemical profiles of HF, it is interesting to note that, in the present study, even in patients whose current antihypertensive therapy included $Ca^{2+}$ channel blockers, PDE5 inhibition produced a significant pulmonary vasorelaxation effect. This suggests that inhibition of cGMP breakdown is probably a mechanism of vasodilatation different from and additional to that mediated through $Ca^{2+}$ channels. Notably, in HF patients with high PAR, the transpulmonary cGMP release has been found to be lower than in patients with low PAR, and sildenafil has been effective whatever the responsiveness to the pulmonary vasodilation test with prostaglandin $E_1$.[38] The described peculiarities of pulmonary vasomotility in hypertension may explain the highly selective effects of sildenafil

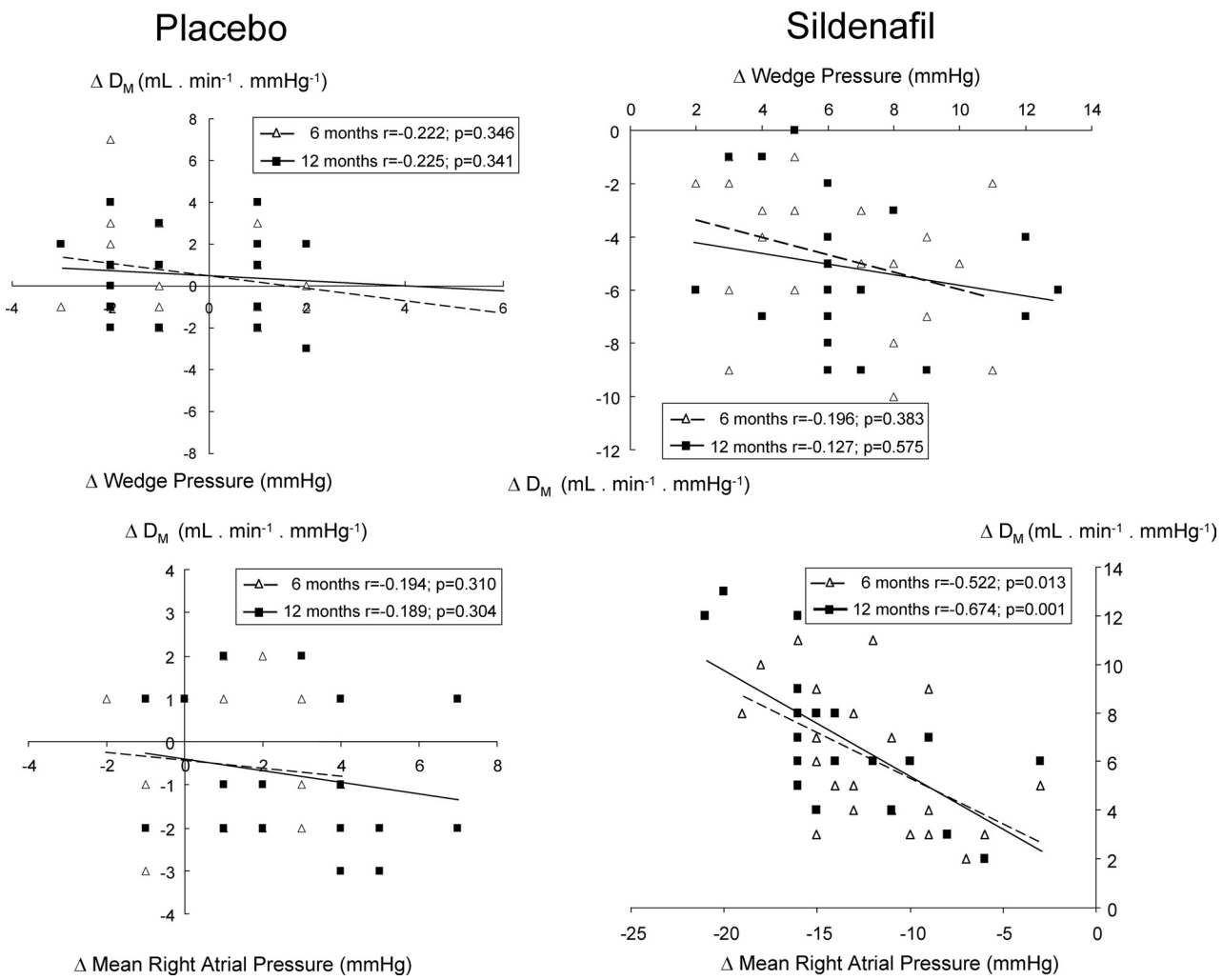


**Figure 4.** Relationship between changes from baseline in mean right atrial and wedge pulmonary pressures and changes in alveolar-capillary membrane conductance ($D_M$) at 6 and 12 months of placebo or sildenafil.

on the pulmonary vessels of these patients. Altogether our findings, despite the fact that they do not provide proof, are consonant with the interpretation of impaired NO activity as a mediator of precapillary PH in HFpEF.[9] Hypothetically, the residual elevation of PA pressure after sildenafil may reflect the residual proportion of resistance attributable to vascular remodeling[14] that, even in the long run, is not fully influenced by PDE5 inhibition. Accordingly, pulmonary hemodynamic variables at 6 and 12 months were similar.

In the active treatment arm, systolic RV function was improved, as shown by a leftward shift of the Frank-Starling relationship and by an increase in tricuspid annular plane systolic excursion and mean rate of systolic ejection. The inverse correlation between changes in pulmonary effective arterial elastance and changes of each of these 2 variables suggests a cause-and-effect relationship between the unloading effect of sildenafil and the improvement in RV systolic function. It cannot be ruled out that an enhanced contractility is involved in this effect because, in RV hypertrophy, PDE5, which is expressed in the fetal RV, is selectively reexpressed, and inhibition of this enzyme enhances RV contractility.[39] Improvement of RV function was accompanied by an impressive fall in CVP (RA pressure).

In regard to the left heart, therapy led to improvements in LV structure as reflected in decreased wall thickness and mass, in systolic function as reflected by a slight increase in cardiac index (despite reduced filling pressures and increased TPR), and in diastolic function as reflected by increase in E/A ratio and E′ velocity and by a decrease in E/E′ and TE′−E.[25]

Potential changes in contractility were probed by measuring LVEF and mean velocity of circumferential fiber shortening, 2 popular indices of contractile function. They did not change significantly, but drawbacks that should be taken into account are that both are afterload dependent and that impedance to LV ejection (TPR) was raised in our patients. The unusual finding of increased TPR with PDE5 inhibition may be explained reasonably by 2 facts: This was specifically a population of patients with high blood pressure who were taking antihypertensive medications and who also had clinical presentation consistent with HFpEF; the substantial reduction in RA pressure with treatment had a major role in raising calculated TPR.

Animal and human studies[40] have documented that PDE5 inhibition has remarkable cardiac antihypertrophic and antifibrotic effects that can benefit cardiomyocyte relaxation and increase LV distensibility. These properties may explain our observations on LV structure and diastolic function, even though it is unclear whether an effect is a direct consequence of the other or whether both derive from a pharmacological or biological activity on similar pathways. An intriguing and possibly complementary explanation of changes in LV diastolic function may be the interaction between the 2 ventricles through direct transseptal pressure transmission and/or alteration in pericardial pressure. Changes in intrapericardial pressure generally match those in the RA. RA pressure elevation therefore reduces LV transmural (or distending) pressure so that, for transmural pressure to be preserved, intracavitary pressure must rise. Transmural pressure regulates the degree of LV filling, whereas an increase in intracavitary pressure triggers venous PH and fluid transudation into the pulmonary interstitium. Thus, RV and RA distension in our patients may have adversely altered LV relaxation and compliance properties, and sildenafil could have modulated them by reducing right heart pressures and volumes.

The magnitude of improvement of E′, E/E′, and TE′−E is somewhat surprising, particularly in the absence of major reduction in WPP. Although these findings cannot be fully explained and require confirmation in further studies, they suggest an influence of treatment on delayed relaxation, which is thought to represent one of the central abnormalities in HFpEF patients. This is remarkable in its own right and also because, at variance with a number of antihypertensive agents when used in patients with high blood pressure and diastolic dysfunction,[41] the dissociation of benefits from changes in LV pressure load reflects a specific activity of PDE5 inhibition.

Another important aspect related to diastole is whether postcapillary hypertension triggers precapillary vasoconstriction and then whether improvement in LV diastolic properties, by decreasing the LV filling pressure and the postcapillary vasoconstrictor stimulus, also contributes to the transpulmonary gradient modulation by PDE5 inhibition in this category of patients.

As mentioned above, the lymphatic lung drainage converges into the superior vena cava, and the lymphatic pump is fundamental in the physiology of lung fluid exchange. Because CVP elevation hinders this safety mechanism, 2 questions may follow: Was the lymphatic drainage impeded in our patients? Did CVP fall restore this mechanism? The role of the lymphatic pump becomes crucial in case of imbalance of the hydrostatic equilibrium, such as occurs with LV diastolic dysfunction and pulmonary venous pressure elevation. Definite answers are lacking, but some considerations may be appropriate.

In our patients, baseline DLCO was lower than normally predicted, primarily because of reduced conductance of the alveolar-capillary membrane ($D_M$). A reason may be that an excess of fluid in the interstitial lung space lengthened the diffusion path between alveoli and capillaries. At baseline, $D_M$ inversely correlated with WPP (hydrostatic imbalance) and RA pressure (lymphatic pump failure). After PDE5 inhibition, associated with reduction of PAR and RA pressure, there was a decrease of the extravascular lung water index and an increase of DLCO (primarily mediated by improvement in $D_M$), $FEV_1$, and FVC, as well as a trend toward a decrease of the pleural pressure. All of these variations are consistent with reduction of the lung fluid content.[42] Both an improvement in hydrostatic balance due to reduction in WPP and a restored lymphatic pump due to lowered CVP could have affected the amount of lung interstitial water. Changes in RA pressure significantly correlated with those in $D_M$, suggesting a role for RV dysfunction in producing lung interstitial edema in this syndrome. Reabsorption of excessive fluid from the loose interstitial space could reduce the interstitial fluid pressure that compresses and affects the caliber of extra-alveolar vessels, namely, venules and arterioles,[43] and further increases RV ejection impedance.

On these bases, it may be inferred that cGMP enhancement with the PDE5 inhibitor sildenafil interrupts a positive feedback loop that involves PAR, RV hemodynamic burden, CVP, lung lymphatic pump, and interstitial fluid and pulmonary vessel compliance. These changes, together with improvement in left-sided filling pressures, provide the mechanistic background for PA pressure modulation and RV function improvement.

Some study limitations should be acknowledged. Because of the small sample size, precision for estimation of the magnitude of effects is fairly low. In addition, the number of statistical tests may inflate type I error. The unprecedented magnitude of changes in E′ and E/E′ will require careful study and confirmation. The postulated vicious circle triggered by elevated CVP as a background for progression of the HFpEF syndrome and for the negative prognosis associated with right heart involvement should be regarded, at present, only as a stimulating working hypothesis. The ability of PDE5 inhibition to prevent right heart dysfunction, as well as to improve outcome when the RV is already failing, is not proven. Although the multiple etiologies of HFpEF[17,29] share LV diastolic dysfunction as a common background, this complex syndrome probably requires that our understanding is refined and focused on the pathophysiology and treatment of each single etiology. We therefore suggest that the results of this study apply to HFpEF patients with a high blood pressure etiology.

In conclusion, this study provides evidence that PH can be a therapeutic target in HFpEF and that PDE5 inhibition is an effective means to achieve this goal. The resulting sustained improvement in right heart function has encouraging prognostic implications and may stimulate further pathophysiological and therapeutic perspectives.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

Heart failure with left ventricular diastolic dysfunction and preserved ejection fraction is a considerable public health concern. Its prevalence is increasing rapidly, and the outcome is similar to that of systolic heart failure. Because of development of pulmonary vasoconstriction and hypertension, heart failure with preserved ejection fraction may turn into right ventricular failure, an event highly predictive of poor outcome. Thus, prevention and treatment of the unfavorable backward hemodynamic and vascular effects are relevant clinical challenges. In heart failure, nitric oxide–dependent pulmonary vasodilatation is impaired. Because phoshodiesterase-5 is highly expressed in the lungs and its inhibition potentiates nitric oxide signaling by increasing cGMP concentration, we tested whether sildenafil could benefit patients with heart failure with preserved ejection fraction. In this 1-year, placebo-controlled, randomized study, we found that at 6 and 12 months, sildenafil, and not placebo, improved life quality; reduced pulmonary artery, wedge, and right atrial pressures and right ventricular end-diastolic pressure and dimension; shifted leftward the right ventricular Frank-Starling relationship; increased cardiac output and contractile function in parallel with decrease of pulmonary artery elastance; and improved alveolar-capillary membrane gas conductance, whose changes inversely correlated with those in mean right atrial pressure. Thus, in heart failure with preserved ejection fraction, sildenafil modulates pulmonary vasoconstriction, improves right ventricular function, and reduces right ventricular dimensions. As a consequence, chronic phoshodiesterase-5 inhibition may facilitate left ventricular filling through ventricular interdependence. Alveolar-capillary membrane gas conductance improvement likely reflects lung interstitial water reabsorption, and its relationship with right atrial pressure suggests that pulmonary lymphatic drainage, a safety mechanism against interstitial edema, is at least partially restored by right atrial pressure reduction. Results may lead to promising prognostic insights.

**SUPPLEMENTAL MATERIAL**

## Additional Information Regarding QOL

The QOL questionnaire utilized in this trial is currently used in chronic heart failure studies to assess the participants' feeling as to limitations imposed by the disease. It assesses the areas of somatic, depressive and active functions of daily life and, as such, is a quality of life indicator. The questionnaire consists of 10 questions regarding breathlessness, fatigue, emotional function, with answers scored from 1 (worst) to 7 (best). It was advantageous in that the patients were able to complete the questionnaire alone. A cardiologist and / or a psychologist also interviewed participants who indicated significant score changes from baseline at any point during the study, mainly concerning dyspnea and exercise tolerance.