Sildenafil Improves Exercise Capacity and Quality of Life in Patients With Systolic Heart Failure and Secondary Pulmonary Hypertension

Gregory D. Lewis, MD; Ravi Shah, MD; Khurram Shahzad, MD; Janice M. Camuso, RN; Paul P. Pappagianopoulos, MEd; Judy Hung, MD; Ahmed Tawakol, MD; Robert E. Gerszten, MD; David M. Systrom, MD; Kenneth D. Bloch, MD; Marc J. Semigran, MD

Background—Patients with systolic heart failure (HF) who develop secondary pulmonary hypertension (PH) have reduced exercise capacity and increased mortality compared with HF patients without PH. We tested the hypothesis that sildenafil, an effective therapy for pulmonary arterial hypertension, would lower pulmonary vascular resistance and improve exercise capacity in patients with HF complicated by PH.

Methods and Results—Thirty-four patients with symptomatic HF and PH were randomized to 12 weeks of treatment with sildenafil (25 to 75 mg orally 3 times daily) or placebo. Patients underwent cardiopulmonary exercise testing before and after treatment. The change in peak \( \Delta V_{\dot{O}_2} \) from baseline, the primary end point, was greater in the sildenafil group (1.8 ± 0.7 mL·kg\(^{-1}\)·min\(^{-1}\)) than in the placebo group (−0.27 mL·kg\(^{-1}\)·min\(^{-1}\); \( P = 0.02 \)). Sildenafil reduced pulmonary vascular resistance and increased cardiac output with exercise (\( P < 0.05 \) versus placebo for both) without altering pulmonary capillary wedge or mean arterial pressure, heart rate, or systemic vascular resistance. The ability of sildenafil treatment to augment peak \( V_{\dot{O}_2} \) correlated directly with baseline resting pulmonary vascular resistance (\( r = 0.74, P = 0.002 \)) and indirectly with baseline resting right ventricular ejection fraction (\( r = −0.64, P = 0.01 \)). Sildenafil treatment also was associated with improvement in 6-minute walk distance (29 m versus placebo; \( P = 0.047 \)) and Minnesota Living With Heart Failure score (−14 versus placebo; \( P = 0.01 \)). Subjects in the sildenafil group experienced fewer hospitalizations for HF and a higher incidence of headache than those in the placebo group without incurring excess serious adverse events.

Conclusions—Phosphodiesterase 5 inhibition with sildenafil improves exercise capacity and quality of life in patients with systolic HF with secondary PH. (Circulation. 2007;116:1555-1562.)

Key Words: exercise ■ heart failure ■ hypertension, pulmonary
effects of PDE5 inhibition on cardiopulmonary exercise capacity, RV and LV performance, and pulmonary and systemic vascular tone. We tested the hypothesis that chronic administration of sildenafil can augment exercise capacity by reducing PVR in patients with HF and secondary PH.

Methods

Study Design
This placebo-controlled, double-blind, parallel-group, single-center study (ClinicalTrials.gov number NCT00309790) evaluated the efficacy and safety of treatment with sildenafil for 12 weeks in patients with systolic HF receiving standard HF therapy. The Massachusetts General Hospital Pharmacy was responsible for the blinding and randomization procedures. The investigators adjudicated all primary and secondary end points and reviewed data on safety before unblinding of the study. No confidentiality agreement existed between the authors and Pfizer (Sandwich, United Kingdom), which provided the study medication.

Inclusion and Exclusion Criteria
The present study, conducted in accordance with the ethical guidelines of the Declaration of Helsinki II, was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital. Written informed consent was obtained from all patients. We screened patients referred to the Massachusetts General Hospital Heart Failure Center who were ≥18 years of age, had LVSD (LV ejection fraction [EF] <0.4), and had New York Heart Association class II to IV chronic HF despite standard HF therapies. Patients were required to have secondary PH as defined by a mean pulmonary arterial pressure >25 mm Hg. Patients who enrolled in a previous study of the short-term effects of 1-time administration of sildenafil on exercise capacity were eligible to enroll in this study. Patients with a noncardiac limitation to exercise, provocable ischemia, hemodynamic instability, or ongoing nitrate therapy were excluded. Additional exclusion criteria included concentric LV hypertrophy, critical aortic stenosis, or long-term use of medications that inhibit cytochrome P450 3A4.

Study Protocol
At study entry, the subjects’ clinical history was reviewed, and physical examination, echocardiography, and measurements of concentrations of hemoglobin, plasma N-terminal brain natriuretic peptide, aldosterone, and catecholamines were performed. Patients then underwent cardiopulmonary exercise testing with simultaneous hemodynamic monitoring and first-pass radionuclide ventriculography. These studies were repeated on completion of the 12-week study. Quality of life, assessed by the Minnesota Living With Heart Failure Questionnaire (a 21-question self-administered instrument in which scores can range from 0 to 5 for each question and higher scores indicate a poorer quality of life) and 6-minute walk distance were determined at baseline and after 6 and 12 weeks.

The initial dose of the study medication was 25 mg sildenafil or placebo administered 3 times daily. Study medication was uptitrated every 2 weeks to 75 mg 3 times daily as tolerated. After completion of the study protocol, all patients were offered sildenafil treatment with clinical surveillance by the investigators.

Study Procedures
Right heart catheterization was performed by insertion of a 7F balloon-tipped triple-lumen catheter placed in the pulmonary artery via the internal jugular vein before cardiopulmonary exercise testing. A 22-gauge catheter was placed in the radial artery for continuous measurement of mean arterial pressure. Blood gas assessments were performed at 1-minute intervals during the cardiopulmonary exercise testing. Breath-to-breath respiratory gas exchange was measured at rest and during exercise with a metabolic cart interfaced to the ergometer (Medical Graphics Corp, St Paul, Minn). Oxygen uptake (VO₂), carbon dioxide output (VCO₂), and respiratory exchange ratio were calculated. Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were measured in the upright position while patients were seated on the bicycle. Cardiac output at rest and during exercise was determined with the Fick oxygen technique, including the measured VO₂. Systemic vascular resistance (SVR) and PVR were calculated using standard formulas.

Cardiopulmonary exercise testing with upright cycle ergometry and respiratory gas exchange was performed using previously reported methods. Peak VO₂ was defined as the highest oxygen uptake, averaged over 5 consecutive breaths, during the last minute of symptom-limited exercise. Rest and exercise first-pass radionuclide ventriculography of both ventricles was performed at the time of cycle ergometry as previously described. In brief, a multiscrystal camera (System 77, Baird Corp, Bedford, Mass) was used to detect technetium-99m-labeled red blood cells in a region of interest overlaying each ventricle. The EF of each ventricle was calculated as the average of end-diastolic counts minus end-systolic counts divided by end-diastolic counts from 6 to 8 consecutive heartbeats. The LV end-diastolic volume was calculated from the region of interest with the use of a single-plane area length method. Plasma N-terminal brain natriuretic peptide levels were determined by enzyme immunoassay (Alpeco Diagnostics, Salem, NH), and aldosterone, catecholamines, and blood hemoglobin were measured in the Massachusetts General Hospital Clinical Chemistry Laboratory.

Statistical Analysis
The Wilk-Shapiro test was used to assess the normality of distribution of the data. All continuous, normally distributed measurements are presented as the mean±SEM. For clinical characteristics, comparisons between groups for continuous variables were performed with unpaired 2-sample t tests or the Wilcoxon signed-rank test, as appropriate. Association between categorical variables was assessed with the χ² or Fisher exact test. Paired Student t or the Wilcoxon signed-rank test was used to test hypotheses that compared outcomes within subjects at baseline and at 12 weeks for continuous variables as appropriate. One-way ANOVA was used to assess the effect of treatment on differences in the change in continuous variables measured at baseline and at 12 weeks of study drug treatment. Two-way ANOVA, followed by Dunnett’s multiple-comparison test, was used to assess the significance of differences in the 6-minute walk distance and quality-of-life scores within treatment groups at enrollment and after 6 and 12 weeks of therapy. The relationship between changes in exercise variables with sildenafil treatment and hemodynamic measurements were assessed with the Pearson or Spearman correlation coefficient as appropriate.

A single interim analysis was conducted by the Data Safety and Monitoring Committee after enrollment of 24 patients to assess safety and futility using an O’Brien-Fleming procedure with values of P<0.001 for early cessation for efficacy and P>0.3 for futility based on analysis of the primary end point, peak oxygen uptake (VO₂). A value of P<0.049 was considered significant for this primary end point. Values of P<0.05 were accepted as statistically significant for other comparisons.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Thirty-four subjects with LVSD, New York Heart Association class II to IV HF, and secondary PH were randomly assigned to receive placebo (n=17) or sildenafil (n=17) 3 times daily for 12 weeks. Four subjects had previously completed a study of single-dose administration of sildenafil and were recruited on the basis of availability, willingness to participate, and fulfillment of entry criteria. These participants had previously demonstrated only a 2±4% increase in peak VO₂ after one-time administration of sildenafil.
Subjects in the active treatment group were receiving 49±6 mg of sildenafil 3 times daily on completion of 12 weeks of study. All subjects received at least 1 dose of study medication. No deaths occurred during the study, and 2 patients in each group withdrew from the trial. With the exception of forced vital capacity, no statistically significant differences existed between the 2 treatment groups (Table 1). Six patients in the placebo group and 4 patients in the sildenafil group required up titration of loop diuretics during the trial, whereas 1 patient in the placebo group and 3 patients in the sildenafil group underwent downtitration of loop diuretics (P=0.32 for comparison between treatment groups). Titration of neurohormonal antagonists did not differ between the 2 treatment groups.

Exercise Capacity
All patients surpassed their anaerobic thresholds and achieved respiratory exchange ratios in excess of 1.0 (data not shown), consistent with maximum effort during exercise. The primary outcome variable, V\(\text{O}_2\) at peak exercise, increased from 12.2±0.7 to 13.9±1.0 mL·kg\(^{-1}\)·min\(^{-1}\) in the sildenafil group (P=0.02) and did not change in the placebo group (Figure 1A). The change in peak V\(\text{O}_2\) from baseline among patients treated with sildenafil (1.8±0.7 mL·kg\(^{-1}\)·min\(^{-1}\)) was greater than the change in the placebo group (−0.27 mL·kg\(^{-1}\)·min\(^{-1}\); P=0.02). Analysis of the individual components of V\(\text{O}_2\), namely cardiac output and oxygen extraction [C(a-v)\(\text{O}_2\)], indicated that cardiac output increased with sildenafil treatment (Figure 1B), whereas C(a-v)\(\text{O}_2\) was unchanged (Table 2). Augmentation in peak V\(\text{O}_2\) with sildenafil treatment correlated directly with baseline resting PVR (r=0.64, P=0.01) but not with baseline peak V\(\text{O}_2\) (r=0.04, P=0.87). Stratification of patients receiving sildenafil by median RVEF (0.34) demonstrated a trend toward a greater improvement in peak V\(\text{O}_2\) at 12 weeks in those patients below the median RVEF (3.0±1.2 versus 0.7±0.5 mL·kg\(^{-1}\)·min\(^{-1}\); P=0.06).

Treatment with sildenafil for 12 weeks also improved the distance walked in 6 minutes (62 m versus baseline; P=0.004; Figure 3A). The placebo-corrected treatment effect of sildenafil at week 12 was 29 m (P=0.047).

### TABLE 1. Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sildenafil (n=17)</th>
<th>Placebo (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±4</td>
<td>62±3</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>Black, %</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Primary cause of HF, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>53</td>
<td>47</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>III</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±4</td>
<td>78±4</td>
</tr>
<tr>
<td>HF pharmacotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>77</td>
<td>89</td>
</tr>
<tr>
<td>β-Adrenergic receptor antagonist</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>76</td>
<td>29</td>
</tr>
<tr>
<td>Digoxin</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy, %</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Implantable cardiac defibrillator, %</td>
<td>83</td>
<td>88</td>
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<tr>
<td>RVEF</td>
<td>0.33±0.03</td>
<td>0.35±0.02</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.19±0.02</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>315±26</td>
<td>305±31</td>
</tr>
<tr>
<td>N-terminal brain natriuretic peptide, pg/ml</td>
<td>2042±236</td>
<td>1960±244</td>
</tr>
<tr>
<td>Distance walked in 6 min, m</td>
<td>379±25</td>
<td>352±21</td>
</tr>
<tr>
<td>Peak V(\text{O}_2), mL·kg(^{-1})·min(^{-1})</td>
<td>12.2±0.7</td>
<td>10.2±0.8</td>
</tr>
<tr>
<td>Minnesota Living With Heart Failure score</td>
<td>52±6</td>
<td>50±6</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>68±6*</td>
<td>79±4</td>
</tr>
<tr>
<td>FEV(_1), % predicted</td>
<td>67±3</td>
<td>63±6</td>
</tr>
<tr>
<td>DL(_{CO}), % predicted</td>
<td>67±6</td>
<td>59±5</td>
</tr>
</tbody>
</table>

Values are mean±SEM when appropriate. NYHA indicates New York Heart Association; ACE, angiotensin-converting enzyme; FVC, forced vital capacity; FEV\(_1\), forced expiratory volume in the first second; and DL\(_{CO}\), pulmonary diffusing capacity.

\*P<0.05 vs the placebo group.

![Figure 1](http://circ.ahajournals.org/Downloaded from http://circ.ahajournals.org/)
TABLE 2. Hemodynamic Values Measured in the Upright Position at Rest and During Exercise Before and After 12 Weeks of Treatment With Sildenafil or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±2</td>
<td>73±4</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>84±4</td>
<td>82±3</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>8±2</td>
<td>7±1</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>33±3</td>
<td>31±3</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>19±2</td>
<td>19±2</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>50±3</td>
<td>48±5</td>
</tr>
<tr>
<td>PVR, dyne-s/cm²</td>
<td>360±80</td>
<td>340±90</td>
</tr>
<tr>
<td>SVR, dyne-s/cm³</td>
<td>1930±250</td>
<td>2020±220</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>0.18±0.02</td>
<td>0.17±0.02</td>
</tr>
<tr>
<td>CI−VO₂, mL O₂/dL</td>
<td>8.88±0.57</td>
<td>9.23±0.57</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP indicates mean arterial pressure; PAP, pulmonary arterial pressure; and PCWP, pulmonary capillary wedge pressure. Probability values are for the comparison of baseline to week 12 measurements within groups.

*P<0.05 for comparison of the change with sildenafil treatment vs the change with placebo.

P=0.01) compared with baseline values (Table 2), indicating a selective pulmonary vasodilator effect. Sildenafil did not significantly change resting heart rate, mean arterial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, or cardiac index. At peak exercise, sildenafil treatment also reduced PVR (-23±6%; P=0.008 versus baseline) and PVR/SVR (-15±7%; P=0.015) and increased peak exercise cardiac output (38±10%; P=0.004 versus baseline; Figure 1B) and stroke volume (12±4%; P=0.03 versus baseline; Table 2). These changes in the sildenafil-treated patients were significant compared with those treated with placebo (P<0.05). Other hemodynamic measurements in sildenafil-treated patients did not differ from those obtained in patients receiving placebo (Table 2).

Patients treated with sildenafil demonstrated improvement in radionuclide RVEF both at rest (0.33±0.03 to 0.38±0.03; P=0.03) and at peak exercise (0.33±3 to 0.37±0.02; P=0.04); however, patients treated with placebo had no change in RVEF at rest or with exercise (P<0.05 versus...
Sildenafil therapy had no effect on LVEF or LV end-diastolic volume at rest or during exercise.

**Quality of Life and Biomarkers**

The mean Minnesota Living With Heart Failure score decreased (reflecting improvement) by 13±5 and 16±5 at weeks 6 and 12, respectively, among patients receiving sildenafil (P=0.007; Figure 3B) and did not change in patients receiving placebo. New York Heart Association class improved in 53% of patients receiving sildenafil compared with 7% of patients receiving placebo and worsened in 13% of patients receiving sildenafil versus 27% of patients receiving placebo (P=0.045 versus placebo). In patients treated with sildenafil, a trend was present toward a reduction in N-terminal BNP levels at 12 weeks compared with baseline (−575±365 pg/mL; P=0.11), and no change was observed in patients receiving placebo (15±474 pg/mL). Plasma creatinine, aldosterone, and norepinephrine did not differ between baseline and 12 weeks in either the sildenafil or placebo group.

**Safety**

Two patients in the sildenafil group did not complete the 12-week trial. One patient withdrew because of elective implantation of a cardiac resynchronization device at the discretion of her primary cardiologist; the second subject experienced ventricular tachycardia with syncope. In the placebo group, 1 patient withdrew as a result of pruritus, and another withdrew because of worsening HF that required circulatory support. Adverse events did not differ between the sildenafil and placebo groups (3 versus 7; P=0.28). No patients treated with sildenafil (41%) than in those receiving placebo (12%; P=0.047). The incidence of recurrent headaches did not differ between the sildenafil and placebo groups (3 versus 1 patient, respectively; P=0.28). No patients treated with sildenafil during the trial period or in the open-label phase reported loss of visual acuity. Fewer hospitalizations for HF occurred in patients treated with sildenafil than in patients receiving placebo (2 versus 7; P=0.046).

**Long-Term Treatment and Follow-Up**

Twenty-nine of the 30 patients who completed the 12-week trial elected to begin open-label sildenafil treatment. Of the 15 patients initially assigned to the sildenafil group, 12 have been taking sildenafil for >6 months; the other 3 recently completed the 12-week trial. In the cohort of patients treated with sildenafil for >6 months, a persistent improvement in 6-minute walk distance occurred (96±8 m; P=0.007 versus baseline), indicating a sustained improvement in exercise capacity with sildenafil therapy. In the open-label monitoring phase of this study, subjects were exposed to sildenafil for an additional 390 patient-months as of April 1, 2007. During this period, no sudden deaths occurred, and 1 individual experienced 1 appropriate implantable cardioverter-defibrillator discharge.

**Discussion**

In this randomized, double-blind, placebo-controlled study, we found that treatment with the PDE5 inhibitor sildenafil for 12 weeks improved exercise capacity as measured by peak VO2 and 6-minute walk distance, improved quality of life, and acted as a selective pulmonary vasodilator at rest and during exercise. Sildenafil was well tolerated and resulted in fewer HF hospital admissions compared with placebo treatment.

Exercise capacity as measured by peak VO2 or 6-minute walk distance is a well-established independent predictor of prognosis in patients with advanced systolic HF. The observed improvement in both peak VO2 and 6-minute walk distance in this 12-week trial extends results from a previous study showing that one-time administration of sildenafil to patients with HF improved peak VO2 and acted as a selective pulmonary vasodilator during exercise.

The improvement in exercise capacity (peak VO2) observed with sildenafil treatment in this study was attributable to augmentation of cardiac output because peripheral oxygen extraction was unchanged. Several mechanisms may account for this improvement in cardiac output. Sildenafil improved RV systolic function, as reflected by an increase in RVEF measured with radionuclide ventriculography. This augmentation in RV function was likely attributable to afterload reduction because sildenafil reduced PVR. Further support for this mechanism comes from the observation that those patients with a higher PVR had the greatest improvement in exercise capacity with sildenafil treatment. These findings are consistent with our previous observations that short-term administration of the selective pulmonary vasodilator inhaled nitric oxide augmented exercise capacity in HF patients with...
impaired RVEF but not those patients with preserved RVEF.22

It is probable that improved RV function during exercise led to augmentation of cardiac output by increasing LV filling. However, we did not observe a change in LV end-diastolic volume during sildenafil treatment, likely because radionuclide ventriculography during exercise lacks sufficient sensitivity to detect the small change in LV end-diastolic volume expected with the observed increase in stroke volume (6 mL; Table 2).

Two other mechanisms could account for augmentation of cardiac output with sildenafil therapy. It is possible that LV afterload reduction contributed to the improvement in cardiac output with exercise because we observed a trend toward a decrease in SVR in patients treated with sildenafil. Alternatively, it is conceivable that sildenafil increased ventricular contractility. Nagendran et al23 have suggested that PDE5 inhibition can increase RV contractility in the setting of RV hypertrophy. However, previous studies in animal models and in humans with HF have indicated that PDE5 inhibition does not alter myocardial contractility.24,25

The present study is the first to suggest that prolonged administration of a selective pulmonary vasodilator improves functional capacity in patients with HF. The improvement in quality of life in patients treated with sildenafil likely reflects enhanced exercise capacity, although other mechanisms related to direct central nervous effects of PDE5 inhibition26,27 are possible.

Clinical Implications

HF patients with RV dysfunction have a >2-fold increase in mortality compared with patients with preserved RV function and similar LVEF.1,6,9,28,29 Nevertheless, no currently available therapies specifically target RV performance in patients with HF. Previous trials of agents with pulmonary vasodilatory properties have not been effective for the treatment of LVSD. Bosentan, a nonsel ective endothelin receptor antagonist, caused fluid retention and failed to improve HF symptoms,30 potentially reflecting a negative inotropic effect of endothelin receptor blockade.31 Administration of eoprostenol, a prostacyclin analogue, to HF patients was associated with increased mortality, particularly in patients with coronary artery disease.32 Sildenafil, on the other hand, improves coronary flow reserve33 in patients with coronary artery disease and improves RV function.

Recent HF pharmacotherapy trials have failed to demonstrate an incremental benefit in outcomes compared with the combination of angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone receptor blockers.30,32,34 One notable exception is the combination of isosorbide dinitrate, a nitric oxide donor compound, and hydralazine in self-described black individuals with HF.35 Sildenafil and isosorbide dinitrate share a common signaling pathway involving the intracellular second messenger cGMP, suggesting that sildenafil may provide additional benefit to currently approved pharmacotherapies for HF. Sildenafil has several potential advantages over isosorbide dinitrate for the treatment of HF. Tachyphylaxis is commonly observed with chronic nitrate therapy and has not been seen in initial trials of PDE5 inhibitors.11 Moreover, in patients with secondary PH, sildenafil is a selective pulmonary vasodilator,12 unlike nitrates.36

The high prevalence of secondary PH in HF1–3 suggests that strategies to reduce pulmonary vascular tone may have applicability to the management of HF. Special subpopulations of HF patients that may derive particular benefit from PDE5 inhibition include patients awaiting cardiac transplantation with prohibitive elevations in PVR, LV assist device recipients with RV dysfunction, and patients who fail to respond to cardiac resynchronization therapy in the setting of secondary PH and RV dysfunction.57

Study Limitations

This study should be considered a pilot trial because of the small sample size. This small size may have resulted in the tendency for the placebo group to be older with a lower baseline peak VO2, although these differences were not statistically significant. We did not adjust for multiple exploratory analyses investigating the mechanism by which sildenafil improves exercise capacity. However, these mechanistic analyses revealed highly concordant changes among related indicators of RV performance (cardiac output, RVEF, PVR), supporting the validity of our conclusions that sildenafil improves RV function. We restricted enrollment to patients with secondary PH; however, the prevalence of PH in patients with chronic symptomatic LVSD1–3 suggests that this therapy may have broad applicability. Sildenafil was well tolerated by patients in this trial, but long-term studies with a greater number of patients are necessary to confirm the safety profile of this agent and its long-term effects on cardiovascular performance in patients with HF. Potential effects of PDE5 inhibition in patients with HF that require further investigation include vasodilation, which could result in excessive preload reduction and associated reduction in cardiac output; reduced heart rate augmentation with exercise54; and increased intrapulmonary right-to-left shunt flow, which has been observed in animal models55 and could adversely affect ventilation/perfusion matching in patients with advanced chronic lung disease.

Conclusions

Long-term treatment with oral PDE5 inhibition is a novel, well-tolerated approach to achieve selective pulmonary vasodilation in patients with HF and PH. In this study, sildenafil improved peak VO2, 6-minute walk distance, RVEF, and Minnesota Living With Heart Failure score, all of which predict prognosis in patients with HF. PDE5 inhibition may represent an important adjunctive therapy for patients with HF complicated by secondary PH if the beneficial effects observed in our study are confirmed in larger clinical trials.

Acknowledgments

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Disclosures
Dr Semigran has a sponsored research agreement with Pfizer Inc. and serves on the scientific advisory board for INO Therapeutics LLC. Dr Bloch also serves on the Scientific Advisory Board for INO Therapeutics LLC. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Patients with systolic heart failure (HF) who develop secondary pulmonary hypertension (PH) have reduced exercise capacity and increased mortality compared with HF patients without PH. Sildenafil, a type 5 phosphodiesterase inhibitor, lowers pulmonary vascular resistance in pulmonary arterial hypertension. In the present study, 34 patients underwent randomization to 12 weeks of treatment with sildenafil (25 to 75 mg orally 3 times daily) or placebo. Sildenafil treatment was associated with a reduction in pulmonary vascular resistance and improvement in exercise capacity as measured by peak oxygen consumption and distance walked in 6 minutes. In addition, subjects in the sildenafil group experienced fewer hospitalizations for HF and improved quality of life compared with those in the placebo group. If proven safe and effective in larger clinical trials, type 5 phosphodiesterase inhibition may be a useful treatment of HF complicated by secondary PH. Moreover, the high prevalence of secondary PH in HF suggests that such an approach may have broad applicability.
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