Sildenafil Improves Exercise Hemodynamics and Oxygen Uptake in Patients With Systolic Heart Failure

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Background—Heart failure (HF) is frequently associated with dysregulation of nitric oxide–mediated pulmonary vascular tone. Sildenafil, a type 5 phosphodiesterase inhibitor, lowers pulmonary vascular resistance in pulmonary hypertension by augmenting intracellular levels of the nitric oxide second messenger, cyclic GMP. We tested the hypothesis that a single oral dose of sildenafil (50 mg) would improve exercise capacity and exercise hemodynamics in patients with chronic systolic HF through pulmonary vasodilation.

Methods and Results—Thirteen patients with New York Heart Association class III HF underwent assessment of right heart hemodynamics, gas exchange, and first-pass radionuclide ventriculography at rest and with cycle ergometry before and 60 minutes after administration of 50 mg of oral sildenafil. Sildenafil reduced resting pulmonary arterial pressure, systemic vascular resistance, and pulmonary vascular resistance, and increased resting and exercise cardiac index (p<0.05 for all) without altering mean arterial pressure, heart rate, or pulmonary capillary wedge pressure. Sildenafil reduced exercise pulmonary arterial pressure, pulmonary vascular resistance, and pulmonary vascular resistance/systemic vascular resistance ratio, which indicates a selective pulmonary vasodilator effect with exercise. Peak VO₂ increased (15±9%) and ventilatory response to CO₂ output (Ve/VCO₂ slope) decreased (16±5%) after sildenafil treatment. Improvements in right heart hemodynamics and exercise capacity were confined to patients with secondary pulmonary hypertension (rest pulmonary arterial pressure >25 mm Hg).

Conclusions—The present study shows that in patients with systolic HF, type 5 phosphodiesterase inhibition with sildenafil improves peak VO₂, reduces Ve/VCO₂ slope, and acts as a selective pulmonary vasodilator during rest and exercise in patients with HF and pulmonary hypertension. (Circulation. 2007;115:59-66.)

Key Words: cyclic GMP heart failure pulmonary hypertension sildenafil type 5 phosphodiesterase

Right ventricular (RV) performance is an important determinant of prognosis and exercise capacity in patients with severe left ventricular (LV) systolic dysfunction (LVSD). In chronic LVSD, dysregulation of vascular smooth muscle tone commonly leads to an increase in pulmonary vascular resistance (PVR). Therefore, elevated PVR in patients with heart failure (HF) has been targeted in an effort to improve overall cardiac performance.

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Administration of the selective pulmonary vasodilator, inhaled nitric oxide (NO), to patients with LVSD reduces PVR and increases cardiac index (CI) without alteration of systemic arterial pressure. Inhaled NO also increases exercise capacity and RV ejection fraction (RVEF) in HF patients with pulmonary hypertension (PH). However, inhaled NO increases pulmonary capillary wedge pressure (PCWP) in patients with LVSD and may precipitate pulmonary edema. Inhaled NO is also technically challenging to administer continuously to ambulatory patients. Cyclic GMP (cGMP), the second messenger of NO in vascular smooth muscle cells, represents an alternative target for pharmacologic augmentation through inhibition of phosphodiesterases (PDEs) responsible for its catabolism.

Sildenafil is a selective inhibitor of PDE5, the predominant PDE isoform responsible for hydrolysis of cGMP in the lungs. Sildenafil has been shown to be as effective a pulmonary vasodilator as inhaled NO in patients with primary PH and has recently been shown to improve exercise capacity, resting hemodynamics, and World Health Organization functional class in patients with idiopathic PH and PH associated with connective tissue disease or with repaired...
congenital systemic-to-pulmonary shunts.\textsuperscript{11} In patients with PH secondary to chronic HF, sildenafil lowers resting PVR and PCWP and increases CI without causing systemic hypotension.\textsuperscript{12}

Abnormal systemic vascular tone is also a hallmark of HF, which contributes to diminished skeletal muscle perfusion and heightened systemic vascular resistance (SVR). Sildenafil has been shown to improve endothelium-dependent, flow-mediated brachial artery dilation in patients with HF.\textsuperscript{13,14} Furthermore, sildenafil may improve nonuniformity in skeletal muscle unit perfusion that predisposes HF patients to early anaerobic metabolism during exercise.\textsuperscript{15} Hence, multiple mechanisms exist by which PDE5 inhibition may augment exercise capacity and ameliorate symptoms in patients with HF.

Sildenafil has previously been shown to increase peak VO\textsubscript{2} and increase the efficiency of ventilatory response to CO\textsubscript{2} output (V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} slope) in patients with predominantly New York Heart Association class II HF.\textsuperscript{16,17} However, no studies to date have investigated the effects of sildenafil on exercise hemodynamic measurements and peripheral oxygen extraction, variables which may provide insight into the mechanisms by which sildenafil improves exercise capacity in HF. We carried out simultaneous measurement of exercise capacity and hemodynamics in response to sildenafil to evaluate the short-term effects of this agent on RV and LV performance and pulmonary and systemic vascular tone. We tested the hypothesis that administration of the pulmonary vasodilator sildenafil can augment exercise capacity by improving RV function in patients with class III HF.

Methods
The study population included patients with LVSD (LVEF <0.35) and stable New York Heart Association class III HF for at least 3 months despite maximal medical therapy who were referred to the Massachusetts General Hospital Heart Failure Service. Patients with provoked ischemia, chronic obstructive pulmonary disease, or ongoing nitrate therapy were excluded. Data compiled for each patient included clinical history and physical examination, exercise test results, radionuclide ventriculography, and spirometry. The study protocol was approved by the Subcommittee of the Massachusetts General Hospital on Human Studies, and informed consent was obtained from all patients.

Cardiopulmonary Exercise Testing
Cardiopulmonary exercise testing (CPET) with upright cycle ergometry and respiratory gas exchange was performed with previously reported methods.\textsuperscript{1} In brief, exercise testing was carried out after an overnight fast with a 6.25 to 12.5 W/min incremental ramp protocol. Breath-to-breath respiratory gas exchange was continuously measured with a metabolic cart interfaced to the ergometer (Medical Graphics Corp., St. Paul, Minn). Minute ventilation (VE), oxygen uptake (VO\textsubscript{2}), CO\textsubscript{2} output (VCO\textsubscript{2}), and respiratory exchange ratio were calculated. Peak VO\textsubscript{2} was defined as the highest VO\textsubscript{2} measured during the last minute of symptom-limited exercise. The ventilatory anaerobic threshold (AT) was determined by the V-slope method.\textsuperscript{18} Ventilatory efficiency was assessed by calculation of the slope of the increase in ventilation with respect to CO\textsubscript{2} output (V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}}) with values measured between rest and AT.

First-Pass Radionuclide Ventriculography and Hemodynamic Measurements
Rest and exercise first-pass radionuclide ventriculography of both ventricles were performed at the time of cycle ergometry as previously described.\textsuperscript{1} In brief, a multicrystal camera (System 77; Baird Corp., Bedford, Mass) was used to detect technetium-labeled red blood cells in a region of interest placed over either the left or right ventricle. Volumetric measurements were taken as the average of values from 6 to 8 consecutive heartbeats and were indexed to body size by dividing by the calculated body surface area. The EF of each ventricle was calculated as (end-diastolic counts – end-systolic counts)/end-diastolic counts.

Right heart catheterization was performed by insertion of a 7F balloon-tipped triple-lumen pulmonary artery catheter via the right internal jugular vein before the second CPET. Right atrial, RV, pulmonary arterial, and pulmonary capillary wedge pressures were measured, and cardiac output was determined with the Fick oxygen technique. RV stroke work index (gm-m/m\textsuperscript{2}) was calculated as the stroke volume index (ml/m\textsuperscript{2}) × [mean PAP – RAP] mm Hg × 0.0136. A 22-gauge radial arterial catheter was placed for continuous measurement of mean arterial pressure, and lactic acid and blood gas assessments were performed at 1-minute intervals during CPET. SVR, PVR, and CI were calculated with standard formulas. PH was defined by resting PAP >25 mm Hg.

Measurement of Serum Lactate and Sildenafil Levels
Systemic arterial blood samples were deproteinized and enzymatically assayed for lactate concentration using an Analox Instruments LM3 analyzer (London, England). Serum sildenafil levels were measured by liquid chromatography-tandem mass spectrometry (Covance Laboratories, Indianapolis, Ind) as previously described.\textsuperscript{19}

Study Protocol
All patients underwent a baseline maximal CPET (CPET #1). Two days (±2 days) after CPET #1, patients underwent placement of a pulmonary artery catheter and arterial line, followed by repeat CPET with continuous hemodynamic monitoring (CPET #2: Figure 1). During CPET #2, patients were permitted to exercise only until they reached 90% of their VO\textsubscript{2} at which their AT occurred in CPET #1. This threshold was chosen to permit complete recovery and repeat exercise testing with the pulmonary artery catheter in place for a limited period of time, so as to minimize potential risks to patients.

Patients underwent a 120-minute rest period in between their submaximal exercise test (CPET #2) and their final maximal CPET (CPET #3). All patients received a single oral dose of sildenafil (50 mg) 60 minutes before the start of exercise in CPET #3. Blood
**TABLE 1. Baseline Characteristics of Study Subjects**

Characteristic | Value
--- | ---
No. | 13
Age, mean y ± SEM | 47 ± 9 (33 to 59)
Cause
Ischemic | 6
Nonischemic | 7
Gender, M/F | 11:2
Heart failure pharmacotherapy, n/N | Diuretic 13/13
ACE inhibitor or angiotensin receptor blocker 11/13
β-Adrenergic receptor antagonist 9/13
Spironolactone 6/13
Amiodarone 6/13
Weight, mean kg ± SEM | 87.3 ± 3.3 (70.0 to 102.2)
LVEF, mean ± SEM | 0.32 ± 0.02 (20 to 38)
RVEF, mean ± SEM | 0.33 ± 0.03 (16 to 50)
FVC, mean ± predicted SEM | 79 ± 5.9 (52 to 114)
FEV₁, mean ± predicted SEM | 74 ± 5.4 (51 to 116)
DLCO, mean ± predicted SEM | 79 ± 4.2 (56 to 110)

ACE indicates angiotensin-converting enzyme; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; and DLCO pulmonary diffusing capacity. Numbers in parentheses indicate the range of values.

**Statistical Analysis**

All measurements are presented as means ± SEM. Measurements of gas exchange variables were compared between CPETs #1 and #3 before and after the administration of sildenafil. Measurements of hemodynamic variables during CPET #2 before sildenafil administration were compared with hemodynamic measurements during the submaximal portion of CPET #3 at a matched workload. Paired Student t tests were used to test hypotheses that compared before and after sildenafil administration outcomes within subjects for continuous variables that were demonstrated to be normally distributed with the Wilk-Shapiro test. Unpaired Student t tests were used for between-group comparisons of normally distributed continuous variables. The relationship between changes in exercise variables after sildenafil treatment and hemodynamic measurements were assessed with a Pearson correlation coefficient. A probability value ≤ 0.05 was accepted as statistically significant.

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**

**Study Population**

Thirteen patients with New York Heart Association class III HF participated in the present study. Baseline patient characteristics, medications, ventriculographic measurements, and pulmonary function tests are shown in Table 1. All patients had undergone optimization of their HF pharmacotherapy in the 30 days before the study. None of the patients had evidence of a significant underlying pulmonary disease. Mean resting PAP and PCWP before sildenafil administration were elevated at 28 ± 4 mm Hg and 14 ± 4 mm Hg, respectively, and CI was depressed at 1.8 L/min per m². PVR was 290 ± 36 dyne·sec/cm² (Table 2) and 7 of the patients had resting PH.

As assessed in CPET #1, exercise capacity was depressed as indicated by peak V̇O₂ of 1015 ± 84 mL/min and a peak workload of 83 ± 7 W.

**Effects of Sildenafil on Hemodynamic Measurements**

Lactate levels immediately before CPET #2 and #3 were similar (1.8 ± 0.2 versus 1.7 ± 0.2 mmol/L), which suggests that metabolic recovery occurred before CPET #3. The mean sildenafil level immediately before the start of CPET #3 was 237 ± 23 ng/mL, which is similar to levels reported in pharmacokinetic studies in normal individuals. Sildenafil was well tolerated by all patients; specifically there was no symptomatic hypotension, facial flushing, or vision changes.

**TABLE 2. Hemodynamic Values at Rest and During Exercise Before and After Sildenafil Administration**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPET #2 Rest</th>
<th>CPET #2 Sildenafil</th>
<th>t × (df)</th>
<th>P</th>
<th>CPET #3 Rest</th>
<th>CPET #3 Sildenafil</th>
<th>%Δ</th>
<th>t × (df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>76 ± 3</td>
<td>73 ± 3</td>
<td>3 ± 3</td>
<td>−1.32</td>
<td>0.21</td>
<td>80 ± 3</td>
<td>78 ± 3</td>
<td>0 ± 3</td>
<td>0.55</td>
</tr>
<tr>
<td>Heart rate, beats × min⁻¹</td>
<td>76 ± 4</td>
<td>77 ± 5</td>
<td>1 ± 2</td>
<td>−0.27</td>
<td>0.66</td>
<td>91 ± 6</td>
<td>91 ± 6</td>
<td>0 ± 3</td>
<td>0.03</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>4 ± 1</td>
<td>5 ± 1</td>
<td>27 ± 22</td>
<td>0.59</td>
<td>0.56</td>
<td>9 ± 2</td>
<td>7 ± 1</td>
<td>−13 ± 7</td>
<td>−1.73</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>28 ± 4</td>
<td>22 ± 2</td>
<td>10 ± 3</td>
<td>−2.25</td>
<td>0.03</td>
<td>36 ± 5</td>
<td>31 ± 4</td>
<td>−10 ± 3</td>
<td>−2.55</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>14 ± 4</td>
<td>12 ± 2</td>
<td>6 ± 5</td>
<td>−0.80</td>
<td>0.19</td>
<td>19 ± 3</td>
<td>18 ± 3</td>
<td>−6 ± 5</td>
<td>−1.13</td>
</tr>
<tr>
<td>PVR, dyne · s · cm²</td>
<td>290 ± 36</td>
<td>215 ± 25</td>
<td>27 ± 7</td>
<td>−2.98</td>
<td>0.007</td>
<td>280 ± 62</td>
<td>192 ± 30</td>
<td>−21 ± 5</td>
<td>4.24</td>
</tr>
<tr>
<td>SVR, dyne · s · cm²</td>
<td>1700 ± 133</td>
<td>1374 ± 176</td>
<td>19 ± 4</td>
<td>−4.70</td>
<td>0.0005</td>
<td>1102 ± 91</td>
<td>990 ± 78</td>
<td>−8 ± 5</td>
<td>−1.42</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>0.17 ± 0.27</td>
<td>0.16 ± 0.2</td>
<td>4 ± 6</td>
<td>−0.96</td>
<td>0.35</td>
<td>0.24 ± 0.06</td>
<td>0.19 ± 0.05</td>
<td>−11 ± 8</td>
<td>−2.16</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>1.8 ± 0.1</td>
<td>2.1 ± 0.2</td>
<td>20 ± 6</td>
<td>3.70</td>
<td>0.003</td>
<td>2.7 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>12 ± 4</td>
<td>2.85</td>
</tr>
<tr>
<td>RV stroke work index</td>
<td>7.7 ± 1.6</td>
<td>6.7 ± 1.1</td>
<td>1 ± 1</td>
<td>−1.21</td>
<td>0.26</td>
<td>8.2 ± 1.0</td>
<td>8.3 ± 1.2</td>
<td>2 ± 6</td>
<td>0.23</td>
</tr>
<tr>
<td>C(a−v)O₂, ml O₂/dL blood</td>
<td>8.3 ± 0.4</td>
<td>7.6 ± 0.3</td>
<td>17 ± 3</td>
<td>−2.48</td>
<td>0.028</td>
<td>11.9 ± 0.6</td>
<td>11.1 ± 1.2</td>
<td>−4 ± 2</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Values are mean ± SEM unless otherwise indicated. %Δ indicates mean ± SEM percent change after sildenafil administration; MAP, mean arterial pressure; and C(a−v)O₂, difference in oxygen content between arterial and venous blood.
The administration of sildenafil 60 minutes before CPET #3 reduced resting mean PAP (14±5%), PVR (21±7%), and SVR (19±4%), and increased CI (20±2%) (all P<0.05) but did not alter resting heart rate, mean arterial pressure, PCWP, RAP, RV stroke work index, C(a-v)O₂, or PVR/SVR ratio (Table 2).

Exercise hemodynamic variables were measured at 90% AT before and after sildenafil administration (CPET #2 and CPET #3, respectively). Similar lactic acid levels were observed at submaximal exercise before and after sildenafil (2.3±0.2 versus 2.4±0.2 mmol/L).

Sildenafil decreased mean exercise PAP and PVR (11±3% and 21±5%, respectively, both P<0.05) and increased CI (12±4%, P<0.05) (Table 2). Sildenafil did not change exercise SVR or RV stroke work index, and PVR/SVR with exercise fell by 11±8% (P=0.05). The magnitude of reduction in exercise PVR/SVR after sildenafil administration correlated directly with resting PAP (r=0.73, P<0.01). Sildenafil did not significantly change mean arterial pressure, HR, or PCWP with exercise.

Sildenafil was associated with a significant increase in RVEF both at rest (0.34±0.03 to 0.4±0.03, P=0.001) and with exercise (0.34±0.03 to 0.44±0.04, P<0.001), whereas LVEF was unchanged.

**Effects of Sildenafil on Parameters of Exercise Capacity**

Measurements of exercise capacity were compared between CPET #1 and CPET #3 (after sildenafil administration). Peak VO₂ increased from 1.01±0.08 L/min to 1.10±0.05 L/min, and V̇E/V̇CO₂ slope decreased from 39±3 to 34±2 (both P<0.05) after sildenafil treatment. Augmentation of peak VO₂ with sildenafil correlated with mean resting PAP before sildenafil administration (r=0.75, P<0.01). Sildenafil administration was associated with a modest reduction in oxygen extraction C(a-v)O₂ at 90% AT (Table 2) but no change in peak workload (83±7 versus 88±6 W [P=0.17]).

**Effects of Sildenafil on Patients With and Without Pulmonary Hypertension**

As sildenafil appeared to show a pulmonary vasodilator effect proportionate to the degree of baseline PH, patients were separated into 2 groups. Patients with PH (Group +PH, n=7) had a mean resting PAP of 37±6 mm Hg, and those without PH (Group -PH, n=6) had a mean resting PAP of 17±1 mm Hg. The 2 groups did not differ in age, sex, cause of HF, or sildenafil levels (data not shown).

Sildenafil administration in Group +PH reduced mean resting PAP (27±7%), PVR (34±6%), and SVR (22±4%, all P<0.05) without altering PCWP (19±6 mm Hg) or cardiac output (Figure 2). Sildenafil had no effect on hemodynamic parameters in Group -PH patients at rest.

In Group +PH, sildenafil decreased mean exercise PAP and PVR (15±5% and 40±6%, respectively, P<0.05) (Figure 2) without altering PCWP (25±4 mm Hg). SVR tended to decrease but not significantly (8±6%, P=0.08). Sildenafil increased exercise CI (14±6%) and decreased PVR/SVR ratio (26±6%) in Group +PH (both P<0.05, Figure 2 and 3, respectively). The reduction in PVR and PVR/SVR ratio was greater in the Group +PH than in the Group -PH, in which no changes in any of the exercise hemodynamic parameters were observed.

Between-group (+PH versus -PH) comparisons of hemodynamic changes associated with sildenafil administration demonstrated that exercise PVR and PVR/SVR ratio were reduced to a greater extent in +PH compared with -PH patients, whereas other hemodynamic variables did not differ significantly at rest or with exercise (Figure 2).

Resting RVEF increased from 0.34±0.04 to 0.42±0.04 (P<0.01), and exercise RVEF increased from 0.35±0.03 to 0.5±0.05 (P<0.001) after sildenafil treatment in Group +PH (Figure 4). No differences in RVEF were observed in Group -PH patients after treatment with sildenafil. A modest increase in resting LVEF was observed in the +PH group but
Group -PH (Table 2). A corresponding decrease in C(a-v)O₂ with exercise was observed in Group +PH but not in Group -PH. Peak workload increased from 78±6 to 88±7 W, and V̇E/V̇CO₂ slope decreased from 43±45 to 36±3 in Group +PH (both $P<0.05$) after sildenafil administration, whereas sildenafil did not alter either of these parameters in Group -PH. Sildenafil had no significant effect on the proportion of physiological dead space to tidal volume at peak exercise or the partial pressure of end tidal CO₂ (Pₜₚ₇₈CO₂) at AT in either group (Table 3).

**Discussion**

In this study, we evaluated the hypothesis that administration of a single oral dose of the PDE5 inhibitor sildenafil (50 mg) would improve, through pulmonary vasodilation, exercise capacity and exercise hemodynamics in patients with chronic systolic HF. We found that sildenafil, at plasma levels similar to those reported in pharmacokinetic studies in normal individuals at 60 minutes, improves exercise capacity, reduces PAP, PVR, and PVR/SVR ratio and augments CI during exercise, increases RVEF both at rest and with exercise, and improves ventilatory efficiency (V̇E/V̇CO₂ slope).

Sildenafil did not alter HR, PCWP, or mean arterial pressure and did not cause hypotension in any patients. Post hoc stratification of patients by presence or absence of PH demonstrates that improvements in hemodynamics and exercise capacity were predominantly seen in patients with secondary PH.

**Effects on Hemodynamics**

Our group has previously reported that sildenafil produces pulmonary and systemic vasodilation, decreases LV filling pressure, and increases CI without causing systemic hypotension in resting patients with PH secondary to HF. In this study, we extended these findings by demonstrating that sildenafil acts predominantly as a pulmonary vasodilator during exercise. In patients with HF and PH, sildenafil reduces PAP and PVR, which leads to an improved RV performance (higher RVEF) and increased CI.

PDE5 is the principle enzyme responsible for cGMP catabolism in the lungs and has been shown in animal models to be upregulated in pulmonary vascular smooth muscle cells under conditions associated with PH. We observed that the relative selectivity of sildenafil for the pulmonary vasculature during exercise correlated with resting PAP in the present study. Hence, our observation that sildenafil is a relatively selective pulmonary vasodilator in HF may be attributable to a higher relative abundance of PDE5 in the pulmonary vasculature compared with the systemic vasculature in the presence of PH. In the NO-deficient state of HF with secondary PH, putative regional differences in PDE5 activity may only become apparent with a stimulus that increases NO availability, such as exercise-mediated increase in blood flow.

Our observation that sildenafil lowers PAP and PVR at rest is consistent with that of Guazzi et al; however, unlike Guazzi and colleagues, in this study we observed that sildenafil increased CI at rest. Our patient population differed from that studied by Guazzi et al in that mean baseline CI was...
lower in our patients, and PVR was >2 times greater. Hence, the beneficial effects on RV afterload reduction may have been more apparent in our patient population at rest. Moreover, in patients with PH without LV systolic HF studied by Michelakis and colleagues, sildenafil increased CI by 17% at rest. Finally, a 12-week study of sildenafil administration in patients with PH showed a dose-dependent increase in resting CI. Thus, patients with HF who develop the phenotype of secondary PH may derive clinical benefit from treatment with sildenafil in a manner that is proportionate to the severity of PH.

**Effects of Sildenafil on Exercise Performance**

The improvement in maximal exercise capacity observed after sildenafil treatment may be attributable to several mechanisms. First, sildenafil may have improved CI through a NO-cGMP–mediated reduction in PAP and PVR, a hypothesis which is supported by the improvement in RVEF observed with sildenafil. The correlation between the change in peak VO2 with sildenafil treatment and baseline PAP also suggests that reduction in RV afterload may have mediated the improvement in exercise capacity. Consistent with this finding, our group previously demonstrated that inhaled NO augments exercise capacity in the subset of HF patients with impaired RVEF but not in HF patients with preserved RVEF.

Sildenafil has also been shown to improve flow-mediated vasodilation in HF and therefore may augment skeletal muscle perfusion. We did not directly measure flow-mediated vasodilation in this study, but we did observe an augmentation in CI after sildenafil administration that likely resulted in increased skeletal muscle perfusion. Patients with HF have intrinsic skeletal muscle changes, including atrophy, and reduced oxidative enzyme capacity that predispose them to impaired oxygen extraction. However, the peak exercise C(a-v)O2 of 14.3±0.6 mL/dL in our study population with a mean hemoglobin of 14.2±0.5 g/dL indicates normal maximal oxygen extraction, and we observed no improvement in oxygen extraction at rest or with exercise after sildenafil administration. At rest, C(a-v)O2 was inversely correlated with resting cardiac output (r=-0.7, P<0.05). This relationship persisted with exercise (r=-0.83, P<0.005), which indicates a preserved compensatory ability to extract oxygen to a greater extent when cardiac output is limited during exercise. If abnormal extraction was the limiting factor to exercise capacity, this tight inverse relationship would not be expected. Hence, sildenafil likely improved peak VO2 by augmenting the contribution of cardiac output to VO2, via pulmonary vasodilation–mediated improvement in RV performance.

An exaggerated ventilatory response (VE) to CO2 output (VCO2) occurs in HF patients and inversely correlates with prognosis. Possible explanations for this inefficient ventilation include either an augmentation of the central drive to ventilation or abnormal ventilation/perfusion (V/Q) matching. It is unlikely that sildenafil improved V/Q matching, as we did not observe a decrease in dead space ventilation during exercise after its administration. On the other hand, the reduction in PAP with exercise observed after sildenafil administration may have led to a decrease in J receptor activation in the pulmonary interstitium, and thus a decrease in the central ventilatory drive. Furthermore, sildenafil has been reported to improve perfusion of hypoxemic skeletal muscle in HF patients. This effect may have lead to attenuation of an exaggerated chemoreflex-mediated ventilatory drive during exercise, and an improvement in ventilatory efficiency.

Several vasodilators have been shown to reduce PVR and SVR and thereby improve cardiac performance in HF. However, only inhaled NO has been shown to be a selective pulmonary vasodilator in HF, and it can lead to an increase in PCWP in HF patients. Sildenafil is a relatively selective pulmonary vasodilator with exercise that does not increase PCWP, likely because of concomitant reduction in LV afterload. In a previous study from our laboratory, sildenafil was observed to decrease resting LV end-systolic pressure by 11%. Therefore, compared with inhaled NO, the hemodynamic effects of sildenafil make it a potential candidate for the treatment of HF patients with elevated PVR. Further investigation of the long-term clinical effects of sildenafil are indicated to determine whether the observed hemodynamic benefits of this agent translate to improved HF outcomes.

**Limitations**

This study should be considered as a preliminary pilot investigation because of its small sample size and lack of adjustment for multiple comparisons. Our findings in this

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**TABLE 3. CPET Data Before and After Sildenafil Administration Stratified by the Presence or Absence of Pulmonary Hypertension (Mean PAP>25 mm Hg at Rest)**

<table>
<thead>
<tr>
<th></th>
<th>CPET #1 PH group</th>
<th>CPET #1 PH group</th>
<th>CPET #1 PH group</th>
<th>CPET #3 PH group</th>
<th>CPET #3 PH group</th>
<th>t × (df</th>
<th>P</th>
<th>CPET #1 PH group</th>
<th>CPET #1 PH group</th>
<th>CPET #3 PH group</th>
<th>CPET #3 PH group</th>
<th>t × (df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time, sec</td>
<td>329±29</td>
<td>360±29</td>
<td>10±3</td>
<td>–3.29</td>
<td>0.02</td>
<td>372±39</td>
<td>358±53</td>
<td>–5±5</td>
<td>0.67</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO2, mL/min</td>
<td>0.95±0.11</td>
<td>1.10±0.06</td>
<td>26±16</td>
<td>–2.22</td>
<td>0.03</td>
<td>1.10±0.12</td>
<td>1.11±0.93</td>
<td>3±3</td>
<td>0.36</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>78±6</td>
<td>89±7</td>
<td>13±5</td>
<td>–2.78</td>
<td>0.03</td>
<td>88±14</td>
<td>88±11</td>
<td>5±8</td>
<td>0.03</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.18±0.05</td>
<td>1.14±0.07</td>
<td>–4±3</td>
<td>–1.35</td>
<td>0.20</td>
<td>1.18±0.05</td>
<td>1.11±0.04</td>
<td>6±2</td>
<td>2.47</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve/VO2 slope</td>
<td>43±5</td>
<td>36±3</td>
<td>–22±9</td>
<td>–2.50</td>
<td>0.05</td>
<td>35±3</td>
<td>32±3</td>
<td>8±3</td>
<td>2.44</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(aO2)kAAT</td>
<td>32±2</td>
<td>34±2</td>
<td>7±6</td>
<td>1.12</td>
<td>0.37</td>
<td>35±2</td>
<td>34±1</td>
<td>–3±3</td>
<td>–1.06</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO2/VT</td>
<td>0.25±0.03</td>
<td>0.26±0.03</td>
<td>10±8</td>
<td>1.16</td>
<td>0.49</td>
<td>0.20±0.01</td>
<td>0.21±0.02</td>
<td>3±12</td>
<td>0.21</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

%Δ indicates mean±SEM percent change after sildenafil administration; P(aO2)kAAT, partial pressure of end tidal CO2 at the anaerobic threshold; RER, respiratory exchange ratio; VD, dead space ventilation; and VT, tidal volume.
pilot study have prompted a larger confirmatory study that is currently underway.

The patients in the present study underwent 2 exercise tests on the same day to limit risk of repeated pulmonary arterial catheter insertion on separate days. The study was not placebo-controlled; hence, we are unable to determine whether antecedent exercise influenced hemodynamic or gas exchange parameters and therefore confounded interpretation of sildenafil treatment. However, in similar studies of HF patients given placebo, even repeating maximum CPET on the same day resulted in no differences in peak workload achieved, peak VO₂, or other gas exchange parameters. 17 In addition, at the start of the CPET #3 on day 2 (±2 days) of our protocol, lactate levels had returned to baseline, which suggested metabolic recovery from initial exercise. Furthermore, in similar patients undergoing CPET with hemodynamic monitoring, we observed that the hemodynamic parameters return to baseline values within 10 minutes of cessation of exercise (data not shown). In our study, 120 minutes elapsed between exercise studies; therefore it is unlikely that hemodynamic changes in CPET #3 were attributable to initial exercise.

Conclusions

The data presented in this study indicate that the oral PDE5 inhibitor sildenafil can be safely administered to patients with chronic severe HF in whom it reduces RV afterload and increases CI both at rest and with exercise. In addition, administration of a single dose of sildenafil increases RVEF and peak VO₂ and improves ventilatory efficiency, all of which have been shown to predict prognosis in HF. The observed benefits in exercise capacity and hemodynamic parameters were apparent only in patients with HF and secondary PH. If proven safe and effective for longer periods of administration, PDE5 inhibition may be useful in the treatment of HF, particularly of HF with secondary PH.

Acknowledgments

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Disclosures

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References

In chronic systolic heart failure (HF), dysregulation of vascular smooth muscle tone commonly leads to an increase in pulmonary vascular resistance. Sildenafil, a type 5 phosphodiesterase inhibitor, lowers pulmonary vascular resistance in pulmonary arterial hypertension by augmentation of intracellular levels of the nitric oxide second messenger, cyclic GMP. In the present study, a single oral dose of sildenafil (50 mg) was safely administered to 13 patients with chronic severe HF undergoing right heart catheterization and exercise testing. Sildenafil reduced pulmonary vascular resistance and increased cardiac index both at rest and with exercise. In addition, administration of sildenafil increased exercise capacity and improved ventilatory efficiency, both of which have been shown to predict prognosis in HF. The observed benefits in exercise capacity and hemodynamic parameters were apparent only in patients with HF and secondary pulmonary hypertension. If proven safe and effective for longer periods of administration, type 5 phosphodiesterase inhibition may be useful in the treatment of HF, particularly of HF with secondary pulmonary hypertension.
Sildenafil Improves Exercise Hemodynamics and Oxygen Uptake in Patients With Systolic Heart Failure
Gregory D. Lewis, Justine Lachmann, Janice Camuso, John J. Lepore, Jordan Shin, Maryann E. Martinovic, David M. Systrom, Kenneth D. Bloch and Marc J. Semigran

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