Long-Term Use of Sildenafil in the Therapeutic Management of Heart Failure

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Milan, Italy; and Richmond, Virginia

Objectives
This study sought to test the functional exercise capacity and endothelial function in a cohort of chronic heart failure (CHF) patients treated with chronic type 5 phosphodiesterase (PDE5) inhibitor.

Background
In CHF, endothelial dysfunction is involved in muscle underperfusion, ergoreflex oversignaling, and exercise ventilation inefficiency. Inhibition of PDE5 by improving endothelial dysfunction might be beneficial.

Methods
Stable CHF patients were randomly assigned to placebo (23 patients) or sildenafil at the dose of 50 mg twice per day (23 patients) in addition to their current drug treatment for 6 months, with assessments (at 3 and 6 months) of endothelial function by brachial artery flow-mediated dilatation (FMD), cardiopulmonary exercise testing, and ergoreflex response.

Results
In the sildenafil group only, at 3 and 6 months we observed reduction of systolic pulmonary artery pressure (from 33.7 to 25.2 mm Hg and 23.9 mm Hg), ergoreflex effect on ventilation (from 6.9 to 2.3 l·min⁻¹ and 1.9 l·min⁻¹), ventilation to CO₂ production slope (V̇E/V̇CO₂ from 35.5 to 32.1 and 29.8), and breathlessness (score) (from 23.6 to 16.6 and 17.2), and an increase of FMD (from 8.5% to 13.4% and 14.2%), peak V̇O₂ (from 14.8 to 18.5 ml·min⁻¹·kg⁻¹ and 18.7 ml·min⁻¹·kg⁻¹), and ratio of V̇O₂ to work rate changes (from 7.7 to 9.3 and 10.1). All changes were significant at p<0.01. In the sildenafil group, a significant correlation was found at 3 and 6 months between changes in FMD and those in ergoreflex. Changes in ergoreflex correlated with those in peak V̇O₂ and V̇E/V̇CO₂ slope. No adverse effects were noted except for flushing in 3 patients.

Conclusions
In CHF, improvement in exercise ventilation and aerobic efficiency with sildenafil is sustained and is significantly related with an endothelium-mediated attenuation of exercising muscle oversignaling. Chronic sildenafil seems to be a remedy based on CHF pathophysiology and devoid of remarkable adverse effects. (J Am Coll Cardiol 2007;50:2136–44) © 2007 by the American College of Cardiology Foundation

In chronic heart failure (CHF), much attention has lately been focused on the skeletal muscle as an elicitor of autonomic outflow, a mediator of fatigue, and a source of excessive ventilatory stimulus (1,2), which is subjectively interpreted as breathlessness sensation. Abnormal skeletal muscle signaling (3) due to stimulation by muscle metabolic byproducts (ergoreflex) is becoming a prominent concept in our quest to understand and treat this disease, and interventions effective in reducing the peripheral stimulus have been repeatedly advocated (2–5).

It is conceivable that muscle reflex contribution to ventilation can be reduced by improving endothelial function and up-regulating muscle perfusion because: 1) during exercise an endothelium-mediated vasodilation modulates neurogenic vasoconstriction and up-regulates muscle perfusion (6–8); 2) agonist-induced and shear-stress nitric oxide-mediated vasodilation are decreased in skeletal muscle circulation of patients with CHF compared with age-matched normal subjects (9–11); and 3) there is a link between endothelial function and ergoreflex activity (12,13).

Sildenafil is a specific inhibitor of type 5 phosphodiesterase (PDE5) that increases nitric oxide availability and nitric oxide-mediated vasodilation in CHF patients (9). Interest has therefore been focused on the potential of sildenafil to be beneficial in CHF (14). In acute studies, sildenafil
increased myocardial contractility (15), blunted adrenergic stimulation (16), reduced left ventricular afterload (15), and improved lung diffusion capacity (17), pulmonary hemodynamics at rest (17) and on exertion (18), and exercise ventilation efficiency and aerobic performance (17,18).

We investigated whether: 1) an endothelium-mediated modulation of muscle oversignaling is a mechanism whereby sildenafil can reduce exercise hyperventilation and heighten exercise capacity (19); and 2) the compound maintains this ability during chronic use without adverse effects, and if so, whether there is a rational basis for larger, long-term therapeutic trials with PDE5 inhibition in CHF.

**Methods**

**Study and control patients.** The trial included 46 male patients, whose age was younger than 65 years to minimize the influence of age on endothelial function (20), and who were referred to the outpatient Cardiopulmonary Unit at San Paolo Hospital, Milan, and to the Department of Physical Therapy at Virginia Commonwealth University for evaluation of CHF. They were in stable clinical condition compatible with New York Heart Association functional class II to III. The CHF was caused by ischemic or idiopathic cardiomyopathy. Eligibility criteria were consent to participate in the study after receiving detailed information about procedures, possible clinical benefits, and risks; negative exercise stress test prior to study initiation; forced expiratory volume in 1 s/forced vital capacity ratio >70%; left ventricular ejection fraction ≤45%, determined by echocardiography. Patients were not recruited if they were not able to complete a maximal exercise test or if they had systolic blood pressure >140 and <110 mm Hg, diabetes mellitus, therapy with nitrate preparations, history of sildenafil intolerance, significant lung or valvular diseases, neuromuscular disorders, atrial fibrillation (12), claudication, or peripheral vascular disease. Participants were not involved in any physical training program and were not receiving agents that could affect endothelial function (statins, antioxidant vitamins, xanthine oxidase inhibitors) or ergoreflex (aspirin) (21). They had never smoked or were ex-smokers of at least 8 months (22), with a pack-year index of smoking of <10. Their carboxyhemoglobin was <2%. All were symptomatic during exercise and limited by breathlessness and muscle fatigue. Current drug treatment of heart failure was stable and was that prescribed by the referring physician, including diuretics, ACE inhibitors, digoxin, beta-blockers, angiotensin

**Table 1 Clinical Characteristics of the Study Participants**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group</th>
<th>Sildenafil Group</th>
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<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>63 ± 4</td>
<td>62 ± 3</td>
</tr>
<tr>
<td>Gender, male/female</td>
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<td>23/0</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>26 ± 1</td>
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<tr>
<td>Etiology, IHD/DCM</td>
<td>10/13</td>
<td>11/12</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td>21.4 ± 4.3</td>
<td>23.6 ± 5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22.1 ± 6.4</td>
<td>19.6 ± 5.0</td>
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<tr>
<td>Emotional function</td>
<td>30.8 ± 7.1</td>
<td>32.6 ± 8.4</td>
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<tr>
<td>Blood tests</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5 ± 0.3</td>
<td>5.7 ± 0.5</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.3</td>
</tr>
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</table>

**Drug Therapy**

<table>
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<th>Drug Therapy</th>
<th>Average Daily Dose (mg)</th>
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<td>Furosemide</td>
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<td>Aldactone</td>
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<td>ACE inhibitors</td>
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<td>Enalapril</td>
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<td>Ramipril</td>
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<td>Losartan</td>
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<td>Angiotensin-1 receptor blockers</td>
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<tr>
<td>Metoprolol</td>
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</tr>
<tr>
<td>Carvedilol</td>
<td>16</td>
</tr>
</tbody>
</table>

**Abbreviations and Acronyms**

CHF = chronic heart failure
CPET = cardiopulmonary exercise testing
FMD = flow-mediated dilation
PDE5 = type 5 phosphodiesterase
VD/VT = dead space/tidal volume ratio
VCO2 = carbon dioxide production
VE = ventilation
VO2 = oxygen uptake
WR = work rate

ACE = angiotensin-converting enzyme; DCM = dilated cardiomyopathy; IHD = ischemic heart disease.
receptor blockers, or aldactone (Table 1). All subjects gave their written consent to the study, and none was excluded after study inclusion. The trial was approved by the local ethics committees and conformed to the Declaration of Helsinki. These patients’ data have not appeared in any previous publication from our groups.

Cardiopulmonary exercise testing (CPET). Patients performed a standard, progressively increasing (personalized ramp protocol) work rate (WR) CPET to maximum tolerance on a cycle ergometer in the upright position. Gas exchange measurements (Cardiopulmonary Metabolic Cart, Sensormedics Vmax Spectra, Yorba Linda, California) were obtained at rest (2 min) and during 2 min of unloaded leg cycling at 60 rpm, followed by a progressively increasing WR exercise. Heart rate, electrocardiogram (ECG), and cuff blood pressure were measured and recorded. Minute ventilation (V\text{E}), oxygen uptake (\text{VO}_2), carbon dioxide output (\text{VCO}_2), dead space/tidal volume ratio (V\text{D}/\text{V}\text{T}) and other exercise variables were computer-calculated breath-by-breath, interpolated second-by-second, and averaged at 10-s intervals. The V-slope analysis method was used to measure the anaerobic threshold (AT). Patients were encouraged to exercise to exhaustion (\text{VCO}_2/\text{VO}_2 >1.1) and stopped exercise as a result of breathlessness and/or fatigue. The slope of the relationship between V\text{E} and V\text{CO}_2 (V\text{E}/V\text{CO}_2) was calculated, by simple regression of data collected throughout exercise, as an established index of ventilatory efficiency (23). We also assessed the \text{VO}_2 at AT and the rate at which \text{VO}_2 increased per WR (\Delta\text{VO}_2/\Delta\text{WR}) as an indicator of aerobic efficiency (24). Peak \text{VO}_2 was computed as the average \text{VO}_2 values measured in the last 30 s of exercise.

Vascular studies. Brachial artery flow-mediated vasodilation (FMD) was investigated as previously reported (13). In brief, images were obtained by the same investigator throughout the study with a high-resolution ultrasound 11-MHz linear-array transducer (Philips Medical Systems, DA, Best, the Netherlands). After obtaining the clearest artery view, the transducer was held in position by a stereotactic clamp. Vasodilation was measured as the maximal change in brachial artery diameter during hyperemia after release of a cuff inflated (50 mm Hg greater than systolic pressure for 5 min) on the forearm. Diameter was measured in millimeters, coincident with the R waves on the ECG for 6 cardiac cycles, and the 6 measurements were averaged. The vasodilator response from repeated studies was evaluated by a technician who was blinded to the patient treatment and time sequence; images were stored on a video format and were then analyzed with image analysis software.

Flow velocity was measured by pulsed Doppler with range gate (1.5 mm) in the artery center. The cuff was inflated for 5 min and then rapidly deflated. A 90-s scan was taken immediately after deflation. Blood flow was calculated by multiplying the velocity time integral of the Doppler signal by the cross-sectional area of the vessel and the heart rate. Reactive hyperemia was calculated as absolute maximal change in flow during reactive hyperemia compared with baseline. The FMD was calculated as percent (reactive hyperemia — baseline/baseline × 100) maximal increase in diameter reached in 90 s after cuff release compared with baseline.

Ergoreflex assessment. The ergoreflex was evaluated using the method described by Scott et al. (25). A maximal voluntary handgrip test was measured as the greatest of the peak forces produced by 3 brief maximal handgrip contractions preliminarily performed before the test. Ergoreceptor stimulation consisted of a 2-min V\text{E} recording during rest, followed by a handgrip session that was performed twice in random order, according to the following protocol: 1) a 5-min session of rhythmic handgrip achieved by squeezing the balloon of a sphygmomanometer (30 squeezes/min) at 50% of the predetermined capacity, followed by a 3-min control recovery; and 2) the same protocol was followed soon after interruption of exercise by 3 min of blood stasis on the exercise arm by inflating an upper arm biceps tourniquet to 30 mm Hg greater than systolic blood pressure at the beginning of recovery. The difference of the changes in V\text{E} between the mean resting values and the average of the second and third minute recovery with and without post-handgrip circulatory occlusion represented the ergoreflex component of the ventilatory response to exercise.

Quality of life (QOL). Quality of life was assessed using a CHF questionnaire (26) that has a total of 16 questions: 5 to assess breathlessness, 4 to assess fatigue, and 7 to assess emotional function of daily living. The answers may be scored from 1 (worst function) to 7 (best function), with a maximum score of 112 (best QOL) and a minimum score of 16 (worst QOL).

Study protocol. The 46 enrolled patients were randomized to receive placebo or oral sildenafil 50 mg 3 times per day (27) in addition to their baseline pharmacological treatment. The trial duration was 6 months, and the study design is shown in Figure 1. Patients were admitted to the hospital and were maintained on their current therapy prescribed by the referring physician. After routine laboratory work, cardiac and pulmonary function evaluation, and ECG Holter monitoring, they performed a preliminary familiarization with the procedures for evaluation of brachial FMD and of the ergoreflex and with a graded CPET to determine peak \text{VO}_2. On the next day, in each patient these tests were repeated, left ventricular ejection fraction and pulmonary artery systolic pressure (by recording tricuspid jet velocity) were measured, and results were taken as the reference ones. On the next morning the response to sildenafil was assessed in all participants to verify whether the agent was similarly effective in patients randomized to placebo as in candidates to the active preparation treatment. Patients’ morning doses of their usual medications were withheld. After an overnight fast, in a quiet room, after 15 min rest, 50 mg sildenafil was administered orally. Two hours later, to coincide with the expected peak in the hemodynamic response (28), ejection fraction, pulmonary systolic pressure, brachial artery FMD,
ergoreflex, and CPET were reevaluated in that order. Then, patients were discharged and a 6-month double-blind trial of sildenafil (23 patients) versus placebo (23 patients) was begun with pulmonary systolic pressure, FMD, ergoreflex activation and exercise performance, echocardiography, and ECG Holter monitoring reassessed at 3 and 6 months in both groups (Fig. 1). Physical examination and ECG were performed, symptoms were recorded, and QOL was evaluated. For each patient, compliance was assessed by the pill count method at monthly return visits.

Statistical analysis. Randomization was performed on the basis of computer-generated random numbers. Assuming a 10% decrease of VE/VCO2 slope and a 20% increase in peak VO2 (16), a test with an alpha of 0.05 and a power of 0.90 would require a sample size of 19 patients. Including a 20% safety margin for patients lost to follow-up, we aimed at the recruitment of 23 study patients. An equal number of similar patients were enrolled as control patients. Values are expressed as mean ± SD. Patient characteristics at baseline were compared using chi-square analysis.

The acute incremental changes from baseline with sildenafil were analyzed using a paired t test. Repeated-measures analysis of variance and the Neuman-Keuls multiple comparison procedure were used to test differences between pre- and post-treatment evaluations. The relationship of changes in FMD versus those in ergoreflex, as well as those between ergoreflex and VE/VCO2 slope and peak VO2, were assessed using the Pearson correlation coefficient. Comparisons of the various phases of the ergoreflex test (resting phase, handgrip exercise, recovery) between the 2 groups, and within the same group between with and without circulatory occlusion, were performed using the paired and unpaired t test as appropriate.

A value of p < 0.05 was considered significant. Statistical analyses were performed by the STATA 7.0 package (Stata Corp., College Station, Texas).

Results

None of the patients was withdrawn for major adverse events. Twenty patients in the placebo group and 21 in the sildenafil group completed the trial (Fig. 1). Three and 2 patients in group 1 and group 2, respectively, were lost to follow-up during the last 3 months (Fig. 1), for family reasons or because they moved from the town. The 2 cohorts were similar regarding age, gender, body mass index, drug therapies, cholesterol and triglyceride plasma concentrations, and QOL (Table 1). Cohorts were also homogeneous with respect to left ventricular ejection fraction, systemic and pulmonary artery pressures, and brachial artery FMD. No significant difference was evidenced in exercise performance (VO2 at AT and peak VO2), ventilatory efficiency (VE/VCO2 slope), VD/VT, aerobic efficiency (ΔVO2/ΔWR), brachial artery FMD, and ergoreflex effect on VE. Values of these functions are reported in Table 2.

After randomization, the acute responses to sildenafil were evaluated in all participants to test sensitivity to the drug. The responsiveness was comparable between the 2 cohorts (Table 2), and consisted of a similar significant increase in ventilation efficiency, brachial artery FMD, peak VO2 and VO2 at AT, and aerobic efficiency, and of a significant decrease of the pulmonary artery systolic pressure (SPP), ergoreflex effect on VE, and VD/V T. Heart rate, systemic arterial pressure, left ventricular ejection fraction, and reactive hyperemia to brachial artery occlusion were not significantly affected.

Table 3 reports values of the aforementioned variables and QOL score at baseline and with the active drug and placebo, at 3 and 6 months of follow-up. Compared with baseline, measurements performed after 3 months of active treatment showed a significant reduction of SPP (−25.2%), ergoreflex (−66.6%), VE/VCO2 slope (−14.0%), peak VD/V T (−17.3%), breathlessness (−29.6%), and emotional function (−19.3%). A parallel increase of brachial
artery FMD (+57.6%), peak VO$_2$ (+25.0%), VO$_2$ at AT (+38.1%), and ΔVO$_2$/ΔWR (+20.7%) was observed. Absolute values at 3 months were similar to those achieved in the acute study after a single oral dose of sildenafil (Table 2). In the group receiving placebo, no significant change from baseline was observed in any of these functions after 3 months.

At 6 months, compared with the 3-month assessments, there were no variations with placebo, and a trend of SPP, ergoreflex, VE/VCO$_2$ slope, FMD, peak VO$_2$, and ΔVO$_2$/ΔWR toward a further improvement with sildenafil. Variations observed at 6 months did not reach statistical significance when compared with those at 3 months; however, when compared with acute sildenafil, SPP, brachial artery FMD, VE/VCO$_2$ slope, and ΔVO$_2$/ΔWR were consistently better (p < 0.01). Heart rate and systemic arterial pressure did not vary significantly during the trial in the 2 groups.

Table 2

<table>
<thead>
<tr>
<th>Vascular assessment</th>
<th>Placebo Group</th>
<th>Sildenafil Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery FMD, %</td>
<td>7.8 ± 0.7</td>
<td>11.6 ± 0.8*</td>
</tr>
<tr>
<td>Brachial artery reactive hyperemia, ml·min$^{-1}$</td>
<td>261.0 ± 18.0</td>
<td>273.0 ± 15.0</td>
</tr>
<tr>
<td>Peak VO$_2$, ml·min$^{-1}$·kg$^{-1}$</td>
<td>15.3 ± 1.8</td>
<td>19.2 ± 1.4*</td>
</tr>
<tr>
<td>VO$_2$ at AT, ml·min$^{-1}$·kg$^{-1}$</td>
<td>8.9 ± 3.1</td>
<td>12.5 ± 3.7*</td>
</tr>
<tr>
<td>VE/VCO$_2$ slope</td>
<td>34.4 ± 2.7</td>
<td>31.0 ± 3.9*</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.16 ± 0.09</td>
<td>1.15 ± 0.07</td>
</tr>
<tr>
<td>Peak VO$_2$/Vr</td>
<td>0.22 ± 0.03</td>
<td>0.19 ± 0.01*</td>
</tr>
<tr>
<td>ΔVO$_2$/ΔWR</td>
<td>7.9 ± 2.0</td>
<td>9.4 ± 1.8*</td>
</tr>
<tr>
<td>Arterial O$_2$ saturation, %</td>
<td>97.8 ± 0.6</td>
<td>98.3 ± 0.5</td>
</tr>
<tr>
<td>Ergoreflex effect on VO$_2$, l·min$^{-1}$</td>
<td>7.3 ± 1.4</td>
<td>2.4 ± 0.5*</td>
</tr>
</tbody>
</table>

*p < 0.01 versus baseline.

AT = anaerobic threshold; CPET = cardiopulmonary exercise testing; FMD = flow-mediated dilation; LV = left ventricular; RER = respiratory exchange ratio; VO$_2$/Vr = dead space to tidal volume ratio; VO$_2$ = oxygen uptake; WR = work rate.

In 7 patients at the end of the 6-month sildenafil prescription, withdrawal assessments at 24 h did not document significant differences in any variable from values while on treatment. The exact durability of effect, however, remains to be defined.

We did not observe any major adverse effect attributable to the research procedures or to sildenafil. In particular, Holter monitoring ruled out development of hyperkinetic arrhythmias in patients receiving the PDE$_5$ inhibitor, no visual abnormalities (blurred vision or color vision abnormalities) were reported during follow-up, and liver enzymes and creatinine levels remained unchanged for the duration of the study. Minor adverse reactions consisted of flushing in 3 patients in group 1 and in 4 patients in group 2. No patient developed initial dose hypotension or headache or showed sexual disturbances. During the trial there were no deaths in either group; there were 2 hospitalizations in the placebo group, both because of atrial fibrillation, and no hospitalizations in the active treatment arm.

**Discussion**

The aims of the present investigation were: 1) to give evidence that the ability of sildenafil to improve CHF symptoms and exercise performance (17–19) is persistent during chronic utilization; 2) to probe whether modulation of exercising muscle oversignaling (ergoreflex) may be a mechanism; and 3) to provide a rational basis for larger long-term therapeutic trials with PDE$_5$ inhibitors in CHF patients.
In the active treatment arm, breathlessness and pulmonary artery pressure were attenuated and exercise performance and ventilatory efficiency were improved both at 3 and 6 months. Compared with baseline, these variables were steady in the placebo arm, and this discrepancy was not explained by different drug responsiveness. Group assignment was performed randomly, the trial was double blind, and the cohorts were fairly homogeneous with respect to age, gender, somatic characteristics, and current drug therapy. The evidence is convincing that improvement of CHF symptoms and of the underlying pathophysiology in the sildenafil group is attributable to the drug, and that such an ability persists during chronic treatment. This is consonant with results of PDE5 inhibition in pulmonary hypertension, showing that efficacy persists as long as the application is continued (27–31). At 6 months, compared with 3 months, the trend of symptoms and physiological variables was toward further improvement, without reaching statistical significance. Nonetheless, the trend was uniform, and notably, improvement was significant when values at 6 months were compared with those in the acute study, suggesting that the responsiveness to PDE5 inhibition may become greater with continuous application.

**PDE5 inhibition and exercise ventilatory efficiency.** An excessive ventilatory response to exercise is objectively detected by an increase in the V\textsubscript{E}/V\textsubscript{CO2} slope and is perceived as breathlessness. Increased V\textsubscript{E} might help to keep normal O\textsubscript{2} alveolar tension, at the price, however, of premature exhaustion of the ventilatory reserve. The pathogenesis of inefficient V\textsubscript{E} may be: reduced perfusion of ventilated lung, early acidosis, lung interstitial space distension and J-receptor activation, abnormal chemoreflex and baroreflex control, overactive skeletal muscle signaling, excessive pulmonary capillary pressure increase, and interstitial fluid transition on exercise (1,2,32,33). It can be inferred that improved pulmonary hemodynamics and cardiac output could ameliorate many of these disorders, thus augmenting exercise capacity and reducing ventilation.

A hallmark of CHF is an increase in impedance to right and left ventricular ejection due to increased pulmonary and systemic vascular resistances. A therapeutic goal in CHF to improve overall cardiac performance is reduction in pulmonary vascular resistance (34). Sildenafil in CHF acts predominantly as a pulmonary vasodilator during exercise (21). Reduction in pulmonary vascular resistance leads to improved ventricular ejection fraction, cardiac output, exercise performance (18), and diminished fluid flux transition to the alveolar interstitium (17). On the other hand, heightened systemic vascular tone contributes to diminished skeletal muscle perfusion that facilitates early anaerobic metabolism on exercise (5).

We explored the hypothesis that endothelial dysfunction in CHF may promote muscle oversignaling and PDE5 inhibition may temper breathlessness not only by improving

**Table 3**

| Table 3: Circulatory and Respiratory Variables and Quality of Life at Baseline and After 3 and 6 Months of Treatment With Placebo or Active Drug |

<table>
<thead>
<tr>
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<th>Placebo Group</th>
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<td></td>
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<td>6 Months</td>
<td>Baseline</td>
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<td>Hemodynamics</td>
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<td>Heart rate, beats/min</td>
<td>71.9 ± 2.6</td>
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<td>LV ejection fraction</td>
<td>31.9 ± 3.3</td>
<td>30.8 ± 2.6</td>
<td>30.4 ± 3.6</td>
<td>30.6 ± 3.0</td>
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<td>Systolic</td>
<td>124.8 ± 6.2</td>
<td>123.1 ± 4.2</td>
<td>122.2 ± 5.8</td>
<td>126.7 ± 5.4</td>
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<td>Diastolic</td>
<td>75.2 ± 2.8</td>
<td>74.0 ± 3.2</td>
<td>74.1 ± 3.7</td>
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<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>31.9 ± 2.7</td>
<td>34.5 ± 2.8</td>
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<tr>
<td>Brachial artery reactive hyperemia, ml·min(^{-1})</td>
<td>261.0 ± 18.0</td>
<td>274 ± 31.0</td>
<td>269 ± 26.0</td>
<td>272.0 ± 16.0</td>
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<tr>
<td>CPET variables</td>
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<tr>
<td>Peak V\textsubscript{CO2}, ml·min(^{-1})·kg(^{-1})</td>
<td>15.3 ± 1.8</td>
<td>14.9 ± 1.8</td>
<td>15.1 ± 1.5</td>
<td>14.8 ± 1.5</td>
</tr>
<tr>
<td>VO\textsubscript{2} at AT, ml·min(^{-1})·kg(^{-1})</td>
<td>8.9 ± 3.1</td>
<td>9.0 ± 2.8</td>
<td>8.8 ± 3.1</td>
<td>9.2 ± 3.3</td>
</tr>
<tr>
<td>V\textsubscript{E}/V\textsubscript{CO2} slope</td>
<td>34.4 ± 2.7</td>
<td>34.2 ± 2.6</td>
<td>34.5 ± 3.7</td>
<td>35.5 ± 4.7</td>
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<tr>
<td>Peak RER</td>
<td>1.16 ± 0.09</td>
<td>1.14 ± 0.09</td>
<td>1.15 ± 0.07</td>
<td>1.14 ± 0.07</td>
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<tr>
<td>Peak V\textsubscript{CO2}/V\textsubscript{E}</td>
<td>0.22 ± 0.03</td>
<td>0.23 ± 0.01</td>
<td>0.22 ± 0.01</td>
<td>0.23 ± 0.01</td>
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<tr>
<td>∆VO\textsubscript{2}∆WR</td>
<td>7.9 ± 2.0</td>
<td>7.7 ± 2.0</td>
<td>7.8 ± 1.9</td>
<td>7.7 ± 1.8</td>
</tr>
<tr>
<td>Arterial O\textsubscript{2} saturation, %</td>
<td>97.8 ± 0.6</td>
<td>97.9 ± 0.5</td>
<td>98.1 ± 0.6</td>
<td>98.1 ± 0.4</td>
</tr>
<tr>
<td>Ergoreflex effect on V\textsubscript{E}, ml·min(^{-1})</td>
<td>7.3 ± 1.4</td>
<td>7.2 ± 1.2</td>
<td>7.5 ± 0.9</td>
<td>6.9 ± 1.2</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td>21.4 ± 4.3</td>
<td>22.2 ± 5.0</td>
<td>24.1 ± 5.2</td>
<td>23.6 ± 5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22.1 ± 6.4</td>
<td>22.8 ± 6.0</td>
<td>21.5 ± 5.4</td>
<td>19.6 ± 5.0</td>
</tr>
<tr>
<td>Emotional function</td>
<td>30.8 ± 7.1</td>
<td>32.1 ± 6.9</td>
<td>34.1 ± 7.8</td>
<td>32.6 ± 8.4</td>
</tr>
</tbody>
</table>

\(^{*}p < 0.01 \text{ versus baseline value.} \quad ^{†}p < 0.01 \text{ versus corresponding value in the placebo group.} \quad \text{VCO}_{2} = \text{carbon dioxide production; V}_{E} = \text{ventilation; other abbreviations as in Table 2.}\)
cardiac and pulmonary hemodynamics, but also by influencing signaling from the periphery. Several facts strengthen this hypothesis: 1) Baseline FMD in the study patients was lower than values recorded by the same methods in normal subjects (35), and was similar to that observed in hypertension and diabetes (13), diseases with well-established endothelial dysfunction. 2) Brachial artery endothelial function was persistently increased with sildenafil (FMD was increased by more than 50% and 60% at 3 and 6 months, respectively). 3) The ergoreflex effect on VE was decreased by more than 80%. 4) The amount of $O_2$ utilized per unit increase in work rate ($\Delta VO_2/\Delta WR$) was increased, suggesting an improved $O_2$ diffusion from the capillary to mitochondria or a facilitated working muscle perfusion. 5) There was an inverse baseline correlation of brachial artery FMD with the ergoreflex component of the ventilatory response to exercise, as well as of changes of the former with changes of the latter after sildenafil. 6) The variations in the ergoreflex ventilatory component significantly correlated with those in the $VE/VCO_2$ slope.

This interpretation provides a reasonable explanation for the enduring efficacy of the compound on breathlessness, the dominant symptom in patients with CHF. It is conceivable, but so far unproven, that other basic mechanisms evidenced in acute studies, such as increased myocardial contractility (15), improved pulmonary hemodynamics and right ventricular function (18), enhanced alveolar gas diffusing capacity (17), and beta-adrenergic modulation (36), may also be involved in benefits of chronic PDE5 inhibition. Confirmatory studies, however, are needed.

A better exercising muscle perfusion, a delayed exhaustion of the ventilatory reserve that postpones exercise interruption, and a reduced impedance to left ventricular ejection (16) may well explain the correlation observed, both at 3 and 6 months, between changes in the ergoreflex component of VE to exercise and those in peak VO$_2$.

Another aim of this study was to define whether a prolonged use of sildenafil produces adverse effects. The possibility of an inadequate gas exchange and arterial oxygen desaturation with PDE5 inhibition (37), an event that might be undesired in CHF patients, has been reported. Our results, however, are not consistent with the occurrence of some oxygen desaturation (38). Sildenafil was well tolerated, and development of hyperkinetic arrhythmias, or significant changes in heart rate and blood pressure, were not observed. The more frequently reported side effect was flushing, and its incidence was similar to that reported in other controlled trials (9).

**Study limitations.** Some limitations should be critically discussed. Cardiovascular drugs were not titrated during the study, and maximal tolerated doses of beta-receptor blockers or renin-angiotensin system inhibitors were possibly not achieved. The study, however, was not aimed at providing patients with the best medical treatment, but at probing whether sildenafil adds benefits when combined with the current drug treatment, and an endothelial dysfunction modulating effect may be a mechanism. All investigated patients were men. This may represent an additional shortcoming. Another issue was the exclusion of patients taking statins or aspirin, drugs that are known...
to reduce mortality in ischemic cardiomyopathy. Because they can affect endothelium or the ergoreflex, and possibly conceal the effects of sildenafil, we judged it ethically more acceptable to enroll patients whose current treatment did not include these compounds rather than to withdraw them for the trial.
Conclusions

In CHF, prolonged use of sildenafil improved the nitric oxide-mediated vasodilation, tempered the peripheral stimulus to hyperventilation, heightened ventilatory efficiency and exercise performance, and was associated with the aforementioned side effects. These results, along with the work of several other investigators (39), suggest that larger long-term trials in CHF patients with utilization of PDE5 inhibition should be considered.

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EDITORIAL COMMENT

Type 5 Phosphodiesterase Inhibition in Heart Failure
The Next Step*

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Those who cannot remember the past are condemned to repeat it.
—George Santayana (1)

The possibility that selective inhibition of type 5 phosphodiesterase (PDE5) might be helpful in heart failure (HF) is currently receiving attention. This approach consistently and significantly reduces pulmonary vascular resistance (PVR) by inhibiting the hydrolysis of cyclic guanosine monophosphate in the pulmonary vasculature (2). As a result, right ventricular (RV) function and exercise capacity improve in patients with pulmonary hypertension (3,4). Based on the efficacy and safety of these compounds in that setting, several investigators have begun to study this class of therapy in patients with HF caused by left ventricular (LV) systolic heart failure (SHF). The creative and well-conducted study by Guazzi et al. (5) in this issue of the Journal represents the latest of these investigations. The purpose of this Editorial Comment is to review this study, place it in the context of current knowledge, and suggest a possible next step in the investigation of the therapeutic potential of these interesting compounds for SHF.

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Guazzi et al. (5) studied the effects of sildenafil in patients with chronic stable SHF on contemporary neurohormonal inhibitory therapy and diuretics. They set out 3 goals for their study: 1) to show that acute effects of sildenafil on a number of physiological parameters could be safely maintained with up to 6 months of treatment; 2) to investigate the possibility that a novel mechanism, namely improving the sensitivity of the ergo-ventilatory reflex, might contribute to any benefits seen; and 3) to establish a rational basis for further study of this compound in heart failure. How well did they succeed?

In my opinion, the first goal was clearly met. Compared with placebo, 6 months of administration of sildenafil (50 mg twice daily) reduced pulmonary artery pressure (estimated from echocardiographic Doppler study), improved ventilatory efficiency and peak oxygen consumption, improved flow-mediated vasodilation in the brachial artery, and improved the sensitivity of the ergo-ventilatory reflex (a reflex that couples mechanoreceptors and/or chemoreceptors in exercising skeletal muscle to the control of ventilation) (6,7). Findings present in acute experiments were reproduced at 3 and 6 months in the active treatment group. In addition, one component of an unspecified quality-of-life questionnaire, breathlessness, was improved with active treatment. There were no untoward effects of therapy.

These findings are impressive. The acute experiments confirm results from other acute studies in SHF (8,9). An important feature of the current study design was the assessment of the response of all variables (other than those assessed on the heart failure questionnaire) to active therapy in all subjects before randomization to minimize the chance that differences in response between groups could have been caused by intrinsic differences in responsiveness. In fact, both groups responded identically to acute therapy, whereas only the sildenafil-treated group showed similar responses at 3 and 6 months. Interestingly, there was little difference in the magnitude of the response of any variable between acute administration and 3 months of therapy with sildenafil, and only trends toward any additional improvement at 6 months. The implication of the time course of these responses is clearly that whatever the mechanism responsible for the improvements, the effect is likely to be pharmacological rather than biological because the results of major changes in gene expression or structure would presumably take longer to become evident.

Sildenafil therefore may be an effective agent in patients with chronic SHF by reducing pulmonary artery pressure and by improving ventilatory efficiency and exercise capacity and the associated symptom of breathlessness. The next issue is the nature of the mechanism producing these effects and the implications of this mechanism or mechanisms for further investigation. This leads to the examination of how well the investigators succeeded in meeting their second goal, namely investigating the possibility that improvements in ergo-ventilatory reflex function contribute significantly to the hemodynamic and ventilatory effects seen. In my opinion, although the study shows a clear effect of sildenafil on this reflex, any speculation about cause and effect is premature. This is an interesting reflex that has been shown to be abnormal in patients with HF (6,7), but little is known about factors influencing its function. It is tempting to assume that improved nitric oxide donation (presumptively the mechanism of the improved flow-mediated vasodilation shown in the forearm circulation) also improved the function of this reflex. Proof would require future experiments with an inhibitor of nitric oxide generation or effect. But
whatever the mechanism by which the reflex function improved, it is entirely plausible that the improvement occurred in parallel with the other responses shown. Nothing in the data allows any conclusion about causality in either direction (i.e., from the reflex to the ventilatory and hemodynamic responses, or vice versa). Therefore, although these data are novel and intriguing, the most that can really be said is that improvements in this reflex represent another possible mechanism by which this class of agents might improve exercise capacity and ventilatory function in patients with SHF. Simply improving pulmonary perfusion as a result of lowered pulmonary vascular resistance could have had a major effect on physiological dead space and possibly on other receptors and reflexes originating within the pulmonary circulation. These effects could also have led to improvements in ventilatory efficiency, exercise capacity, and the sensation of breathlessness.

What then should we do in view of this study, which nicely extends acute experiments by their own group and those of others working in this field (8,9)? This question relates to their third goal, that of providing a rational basis for further study. Here, in my opinion, although providing important data that may be useful in future studies, they have not made a compelling case showing that such study is yet warranted. My concern follows from important mechanistic questions that are not yet resolved, and that I think need to be resolved if we are not to find ourselves ruefully pondering Santayana several years hence. Should we proceed without more and crucial information about how these drugs work in SHF?

The most consistent effect of these drugs is to lower PVR. Little if any effect is seen on systemic vascular tone (although the observation on improved flow-mediated vasodilation certainly suggests activity in the peripheral circulation). Cardiac output, however, frequently increases, both in patients with primary pulmonary hypertension and in those with SHF (4,8–10). Furthermore, in patients with predominantly RV dysfunction, cardiac output increases with sildenafil but not the inhalation of nitric oxide at comparable reductions in the pulmonary vascular resistance (10). These observations, of course, strongly suggest an inotropic effect of inhibiting PDE5. Yet it has been difficult to demonstrate PDE5 in human myocardium (11), and cardiac output does not increase when PDE5 is inhibited in normal humans or those with coronary disease (12,13). Other experiments in normal myocardium have shown that PDE5 inhibition actually blunts the inotropic response to adrenergic agonists (14). At a minimum, one would have to conclude that the actions of PDE5 and its inhibition in normal myocardium are unclear, and may depend on whether effects are assessed under basal conditions or with adrenergic stimulation.

A recent and important investigation by Nagendran et al. (15), however, extends our knowledge of this physiology by studying PDE5 effects in abnormal human myocardium. These investigators confirmed that although PDE5 was not found in normal human RV myocardium, it was found in diseased, hypertrophied RV myocardium, and it was possible to show an inotropic effect of PDE5 inhibition in this tissue. The proposed mechanism is indirect inhibition of PDE3 as a result of increased guanosine monophosphate signaling, with subsequent cyclic adenosine monophosphate-mediated effects as would be expected. In the accompanying editorial, Kass (16) notes that although these findings conflict to some extent with other reported data and will require confirmation, the data are intriguing and may help to reconcile the apparent paradox of an inotropic effect of PDE5 inhibition in patients with RV dysfunction, but not in normal subjects. Nagendran et al. (15) laud this finding as yet another reason that this type of therapy might be effective in primary pulmonary hypertension with abnormal RV function. However, if the same type of response were to be demonstrable in diseased, hypertrophied left ventricular tissue (and as Kass [16] notes, this seems more likely than not), there would be significant cause for concern about the safety of long-term administration of these agents in patients with SHF. We have learned, painfully and repeatedly, that inotropic intervention in HF, including that based on PDE3 inhibition, is dangerous (17).

In view of these considerations, I believe the next step in the development of PDE5 inhibitory therapy for SHF should be to repeat the experiments of Nagendran et al. (15) in human LV myocardial tissue. If the results are negative, in view of the promising signals from the small clinical series reported to date, a larger outcomes trial would be reasonable. However, if PDE5 is found in LV tissue, and if an inotropic effect is shown as a result of its inhibition, then a very hard look would have to be taken at the possible clinical relevance of such findings. A possible increase in mortality caused by chronic inotropic stimulation would have to be set against the likelihood of symptomatic improvement from the effects of PDE5 inhibition in the lung. It is true, of course, that the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, adrenergic antagonists, and defibrillators might diminish the risks of chronic low-dose PDE3 inhibition in SHF. But we do not know that, whereas we do have the tools and techniques at our disposal to learn whether such concerns should enter into consideration of future development of these compounds. In other words, we have the ability not only to remember our past history with other agents that inhibit phosphodiesterase in chronic SHF, but also to avoid repeating previous mistakes. I believe we should make every attempt to do so before embarking on larger trials in SHF with these interesting and potentially useful compounds.

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