Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 50, No. 22, 2007
ISSN 0735-1097/07/$34.00
doi:10.1016/j.jacc.2007.07.078

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

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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 (PDE_5) inhibitor.

Background In CHF, endothelial dysfunction is involved in muscle underperfusion, ergoreflex oversignaling, and exercise ventilation inefficiency. Inhibition of PDE_5 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 $l \cdot min^{-1}$ and 1.9 $l \cdot min^{-1}$), ventilation to CO_2 production slope (V_E/Vco_2, 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 Vo_2 (from 14.8 to 18.5 $ml \cdot min^{-1} \cdot kg^{-1}$ and 18.7 $ml \cdot min^{-1} \cdot kg^{-1}$), and ratio of Vo_2 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 Vo_2 and V_E/Vco_2 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).

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Manuscript received April 16, 2007; revised manuscript received July 6, 2007, accepted July 23, 2007.

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).

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Sildenafil is a specific inhibitor of type 5 phosphodiesterase (PDE_5) 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 PDE_5 inhibition in CHF.

Abbreviations and Acronyms

CHF = chronic heart failure
CPET = cardiopulmonary exercise testing
FMD = flow-mediated dilation
PDE_5 = type 5 phosphodiesterase
V_{CO_2} = carbon dioxide production
V_D/V_T = dead space/tidal volume ratio
V_E = ventilation
V_{O_2} = oxygen uptake
WR = work rate

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

	Placebo Group	Sildenafil Group
n	23	23
Age, yrs	63 ± 4	62 ± 3
Gender, male/female	23/0	23/0
Body mass index, kg/m^2	27 ± 2	26 ± 1
Etiology, IHD/DCM	10/13	11/12
Quality of life		
Breathlessness	21.4 ± 4.3	23.6 ± 5.2
Fatigue	22.1 ± 6.4	19.6 ± 5.0
Emotional function	30.8 ± 7.1	32.6 ± 8.4
Blood tests		
Total cholesterol, mmol·l^{-1}	5.5 ± 0.3	5.7 ± 0.5
Triglycerides, mmol·l^{-1}	1.9 ± 0.2	2.0 ± 0.3

Drug Therapy	Average Daily Dose (mg)		
Digoxin	0.25	7	5
Furosemide	50	15	16
Aldactone	25	12	12
ACE inhibitors			
Enalapril	10	10	12
Ramipril	5	8	7
Angiotensin-1 receptor blockers			
Losartan	75	4	4
Beta-blockers			
Metoprolol	83	6	6
Carvedilol	16	10	8

ACE = angiotensin-converting enzyme; DCM = dilated cardiomyopathy; IHD = ischemic heart disease.

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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 V_{max} 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_E), oxygen uptake (V_{O_2}), carbon dioxide output (V_{CO_2}), dead space/tidal volume ratio (V_D/V_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 (V_{CO_2}/V_{O_2} >1.1) and stopped exercise as a result of breathlessness and/or fatigue. The slope of the relationship between V_E and V_{CO_2} (V_E/V_{CO_2}) was calculated, by simple regression of data collected throughout exercise, as an established index of ventilatory efficiency (23). We also assessed the V_{O_2} at AT and the rate at which V_{O_2} increased per WR ($\Delta V_{O_2}/\Delta WR$) as an indicator of aerobic efficiency (24). Peak V_{O_2} was computed as the average V_{O_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_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_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 V_{O_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,

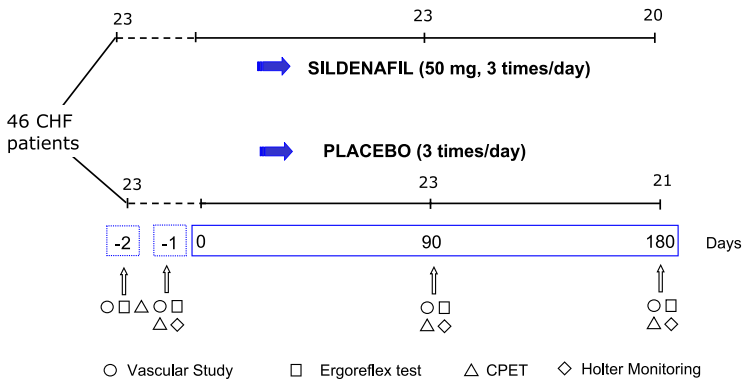

Figure 1 **Study Design**

Measurements at day −2 were performed at baseline, and those at day −1 were performed after a single oral dose of sildenafil (50 mg) in all participants. CHF = chronic heart failure; CPET = cardiopulmonary exercise testing.

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 V_E/V_{CO_2} slope and a 20% increase in peak V_{O_2} (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 V_E/V_{CO_2} slope and peak V_{O_2}, 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 (V_{O_2} at AT and peak V_{O_2}), ventilatory efficiency (V_E/V_{CO_2} slope), V_D/V_T, aerobic efficiency ($\Delta V_{O_2}/\Delta WR$), brachial artery FMD, and ergoreflex effect on V_E. 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 V_{O_2} and V_{O_2} at AT, and aerobic efficiency, and of a significant decrease of the pulmonary artery systolic pressure (SPP), ergoreflex effect on V_E, and V_D/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%), V_E/V_{CO_2} slope (−14.0%), peak V_D/V_T (−17.3%), breathlessness (−29.6%), and emotional function (−19.3%). A parallel increase of brachial

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Table 2 Circulatory and Respiratory Variables at Baseline and After Acute Sildenafil in Patients Randomized to Placebo and in Patients Randomized to Sildenafil

	Placebo Group		Sildenafil Group	
	Baseline	Sildenafil	Baseline	Sildenafil
Hemodynamics				
Heart rate, beats/min	71.9 ± 2.6	72.7 ± 4.6	73.2 ± 2.1	72.1 ± 5.5
LV ejection fraction, %	31.9 ± 3.3	33.0 ± 2.5	30.6 ± 3.0	32.8 ± 2.7
Systemic arterial pressure, mm Hg				
Systolic	124.8 ± 6.2	121.4 ± 7.0	126.7 ± 5.4	121.3 ± 7.6
Diastolic	75.2 ± 2.8	72.8 ± 4.0	76.7 ± 3.3	73.2 ± 5.7
Pulmonary artery systolic pressure, mm Hg	31.9 ± 2.7	25.4 ± 3.0*	33.7 ± 3.1	26.8 ± 3.2*
Vascular assessment				
Brachial artery FMD, %	7.8 ± 0.7	11.6 ± 0.8*	8.5 ± 0.6	12.7 ± 0.7*
Brachial artery reactive hyperemia, ml·min^{-1}	261.0 ± 18.0	273.0 ± 15.0	272.0 ± 16.0	284.0 ± 12.0
CPET variables				
Peak Vo_2, ml·min^{-1}·kg^{-1}	15.3 ± 1.8	19.2 ± 1.4*	14.8 ± 1.5	18.3 ± 1.7*
Vo_2 at AT, ml·min^{-1}·kg^{-1}	8.9 ± 3.1	12.5 ± 3.7*	9.2 ± 3.3	13.3 ± 2.9*
V_E/Vco_2 slope	34.4 ± 2.7	31.0 ± 3.9*	35.5 ± 4.7	32.3 ± 3.6*
Peak RER	1.16 ± 0.09	1.15 ± 0.07	1.14 ± 0.07	1.15 ± 0.08
Peak V_D/V_T	0.22 ± 0.03	0.19 ± 0.01*	0.23 ± 0.01	0.20 ± 0.02*
$\Delta Vo_2\Delta WR$	7.9 ± 2.0	9.4 ± 1.8*	7.7 ± 1.8	9.1 ± 1.9*
Arterial O_2 saturation, %	97.8 ± 0.6	98.3 ± 0.5	98.1 ± 0.4	98.0 ± 0.5
Ergoreflex effect on V_E, l·min^{-1}	7.3 ± 1.4	2.4 ± 0.5*	6.9 ± 1.2	2.2 ± 0.6*

*$p < 0.01$ versus baseline.

AT = anaerobic threshold; CPET = cardiopulmonary exercise testing; FMD = flow-mediated dilation; LV = left ventricular; RER = respiratory exchange ratio; V_D/V_T = dead space to tidal volume ratio; Vo_2 = oxygen uptake; WR = work rate.

artery FMD (+57.6%), peak Vo_2 (+25.0%), Vo_2 at AT (+38.1%), and $\Delta Vo_2/\Delta WR$ (+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, V_E/Vco_2 slope, FMD, peak Vo_2, and $\Delta Vo_2/\Delta WR$ 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, V_E/Vco_2 slope, and $\Delta Vo_2/\Delta WR$ were consistently better ($p < 0.01$). Heart rate and systemic arterial pressure did not vary significantly during the trial in the 2 groups.

Figure 2 is a graphic expression of V_E in both the study patients and control patients, at rest, during handgrip and metaboreflex test, in the baseline and during follow-up.

Baseline brachial artery FMD, in patients in the active treatment group as well as in those in the placebo group, was inversely related with the baseline ergoreflex component of the ventilatory response to handgrip (Fig. 3). On the contrary, FMD changes at 3 and 6 months were inversely related with changes in ergoreflex in the sildenafil group only (Fig. 3). In this group, and not in that receiving placebo, changes in ergoreflex were inversely related with those in peak Vo_2 and positively related with those in V_E/Vco_2 slope, at 3 and 6 months (Fig. 4).

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.

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

	Placebo Group			Sildenafil Group		
	Baseline	3 Months	6 Months	Baseline	3 Months	6 Months
Hemodynamics						
Heart rate, beats/min	71.9 ± 2.6	71.5 ± 2.9	73.8 ± 3.1	73.2 ± 2.1	74.3 ± 4.2	72.4 ± 3.8
LV ejection fraction, %	31.9 ± 3.3	30.8 ± 2.6	30.4 ± 3.6	30.6 ± 3.0	33.6 ± 3.2	34.7 ± 2.8
Systemic arterial pressure, mm Hg						
Systolic	124.8 ± 6.2	123.1 ± 4.2	122.2 ± 5.8	126.7 ± 5.4	122.3 ± 5.6	124.4 ± 4.5
Diastolic	75.2 ± 2.8	74.0 ± 3.2	74.1 ± 3.7	76.7 ± 3.3	74.7 ± 3.2	75.2 ± 3.0*
Pulmonary artery systolic pressure, mm Hg	31.9 ± 2.7	34.5 ± 2.8	33.7 ± 3.1	33.7 ± 3.1	25.2 ± 2.4*†	23.9 ± 3.1*†
Vascular assessment						
Brachial artery FMD, %	7.8 ± 0.7	7.6 ± 0.6	8.1 ± 0.8	8.5 ± 0.6	13.4 ± 0.7*†	14.2 ± 0.5*†
Brachial artery reactive hyperemia, ml·min^{-1}	261.0 ± 18.0	274 ± 31.0	269 ± 26.0	272.0 ± 16.0	286 ± 21.0	291.0 ± 18.0
CPET variables						
Peak Vo_2, ml·min^{-1}·kg^{-1}	15.3 ± 1.8	14.9 ± 1.8	15.1 ± 1.5	14.8 ± 1.5	18.5 ± 1.6*†	18.7 ± 1.7*†
Vo_2 at AT, ml·min^{-1}·kg^{-1}	8.9 ± 3.1	9.0 ± 2.8	8.8 ± 3.1	9.2 ± 3.3	12.9 ± 2.8	13.1 ± 3.2
V_E/Vco_2 slope	34.4 ± 2.7	34.2 ± 2.6	34.5 ± 3.7	35.5 ± 4.7	32.1 ± 3.5	29.8 ± 2.7*
Peak RER	1.16 ± 0.09	1.14 ± 0.09	1.15 ± 0.07	1.14 ± 0.07	1.15 ± 0.06	1.16 ± 0.08
Peak V_D/V_T	0.22 ± 0.03	0.23 ± 0.01	0.22 ± 0.01	0.23 ± 0.01	0.19 ± 0.02*†	0.20 ± 0.01*
$\Delta Vo_2\Delta WR$	7.9 ± 2.0	7.7 ± 2.0	7.8 ± 1.9	7.7 ± 1.8	9.3 ± 1.9*†	10.1 ± 1.8*†
Arterial O_2 saturation, %	97.8 ± 0.6	97.9 ± 0.5	98.1 ± 0.6	98.1 ± 0.4	98.4 ± 0.3	98.2 ± 0.4
Ergoreflex effect on V_E, l·min^{-1}	7.3 ± 1.4	7.2 ± 1.2	7.5 ± 0.9	6.9 ± 1.2	2.3 ± 1.3*†	1.9 ± 1.5*†
Quality of life						
Breathlessness	21.4 ± 4.3	22.2 ± 5.0	24.1 ± 5.2	23.6 ± 5.2	16.6 ± 5.3*†	17.2 ± 4.5*†
Fatigue	22.1 ± 6.4	22.8 ± 6.0	21.5 ± 5.4	19.6 ± 5.0	18.6 ± 4.8	20.7 ± 6.2
Emotional function	30.8 ± 7.1	32.1 ± 6.9	34.1 ± 7.8	32.6 ± 8.4	26.3 ± 7.7*†	25.0 ± 8.4*†

*$p < 0.01$ versus baseline value. †$p < 0.01$ versus corresponding value in the placebo group.
Vco_2 = carbon dioxide production; V_E = ventilation; other abbreviations as in Table 2.

In the active treatment arm, breathlessness and pulmonary artery pressure were attenuated and exercise performance and ventilatory efficiency were improved both at 3 and at 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 PDE_5 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 PDE_5 inhibition may become greater with continuous application.

PDE_5 inhibition and exercise ventilatory efficiency. An excessive ventilatory response to exercise is objectively detected by an increase in the V_E/Vco_2 slope and is perceived as breathlessness. Increased V_E might help to keep normal O_2 alveolar tension, at the price, however, of premature exhaustion of the ventilatory reserve. The pathogenesis of inefficient V_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 amend 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 PDE_5 inhibition may temper breathlessness not only by improving

JACC Vol. 50, No. 22, 2007
November 27, 2007:2136–44

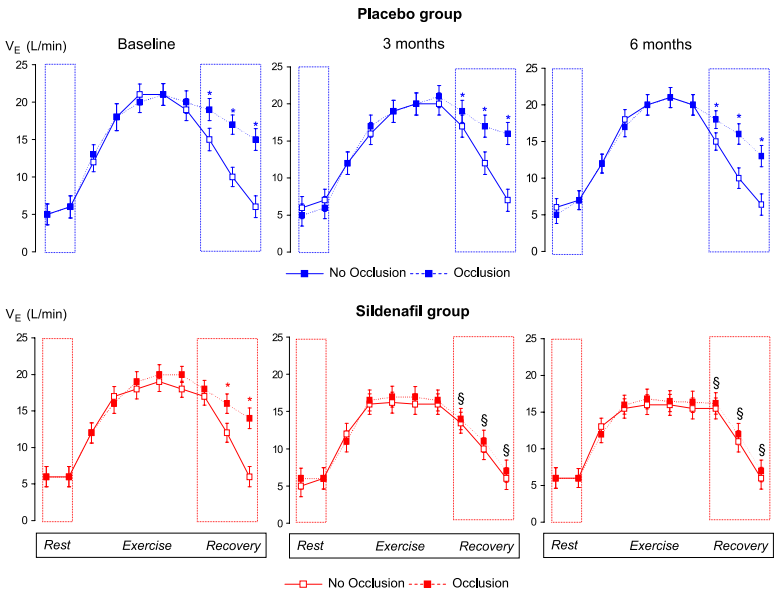

Figure 2 **Ergoreflex Assessment**

Graphic expression of ventilation (V_E) at rest (2 min), during handgrip (5 min), and during recovery (3 min) of metaboreflex test, in the baseline and after 3- and 6-month treatment in patients receiving placebo and in patients receiving sildenafil. *p < 0.01 versus no occlusion. §p < 0.01 versus patients receiving placebo.

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 V_E was decreased by more than 80%. 4) The amount of O_2 utilized per unit increase in work rate ($\Delta V_{O_2}/\Delta WR$) 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 V_E/V_{CO_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 PDE_5 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 V_E to exercise and those in peak V_{O_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 PDE_5 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

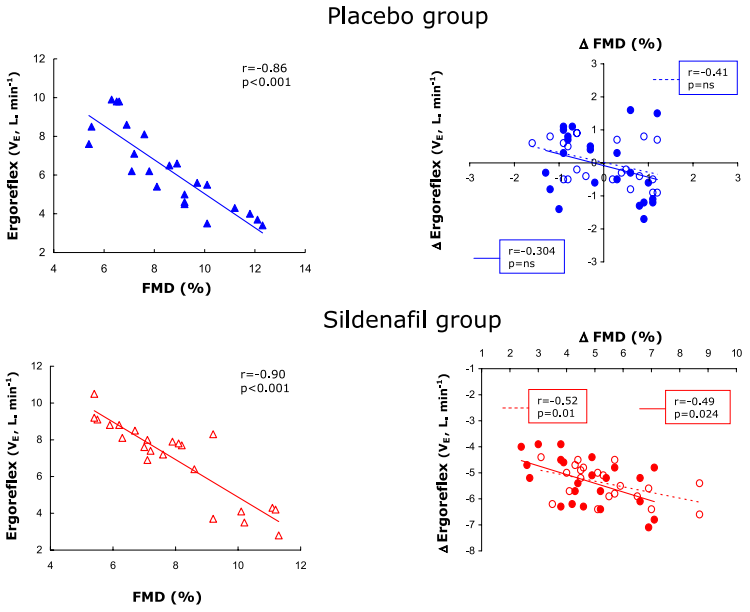

Figure 3 **Correlation Analyses**

Correlation analyses between brachial artery flow-mediated dilatation (FMD) and the ergoreflex component of the ventilatory response to handgrip at baseline in the placebo group **(solid triangles)** and in the sildenafil group **(open triangles)** as well as between changes of the 2 variables at 3- **(open circles)** and 6-month **(solid circles)** treatment. V_E = ventilation.

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.

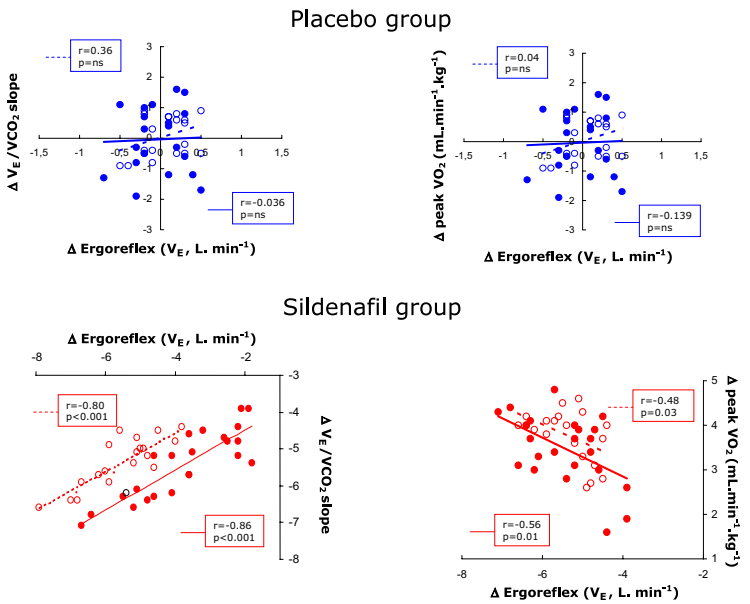

Figure 4 **Correlation Analyses**

Correlation analyses between changes from baseline in the ergoreflex component of the ventilatory response to handgrip and those in V_E/Vco_2 slope and peak oxygen uptake (Vo_2) in the placebo and sildenafil groups at 3- **(open circles)** and 6-month **(solid circles)** treatment. Vco_2 = carbon dioxide production; V_E = ventilation.

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 PDE_5 inhibition should be considered.

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