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**PDE5 Inhibition With Sildenafil Improves Left Ventricular Diastolic Function, Cardiac Geometry, and Clinical Status in Patients With Stable Systolic Heart Failure : Results of a 1-Year, Prospective, Randomized, Placebo-Controlled Study**

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## PDE5 Inhibition With Sildenafil Improves Left Ventricular Diastolic Function, Cardiac Geometry, and Clinical Status in Patients With Stable Systolic Heart Failure

### Results of a 1-Year, Prospective, Randomized, Placebo-Controlled Study

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**Background**—In heart failure (HF), a defective nitric oxide signaling is involved in left ventricular (LV) diastolic abnormalities and remodeling. PDE5 inhibition, by blocking degradation of nitric oxide second-messenger cyclic guanosine monophosphate, might be beneficial. In a cohort of systolic HF patients, we tested the effects of PDE5 inhibition (sildenafil) on LV ejection fraction, diastolic function, cardiac geometry, and clinical status.

**Methods and Results**—Forty-five HF patients (New York Heart Association class II-III) were randomly assigned to placebo or sildenafil (50 mg three times per day) for 1 year, with assessment (6 months and 1 year) of LV ejection fraction, diastolic function, geometry, cardiopulmonary exercise performance, and quality of life. In the sildenafil group only, at 6 months and 1 year, LV ejection fraction, early diastolic tissue Doppler velocities (E') at the mitral lateral (from 4.62 to 5.20 and 5.19 m/s) and septal (from 4.71 to 5.23 and 5.24 m/s) annuli significantly increased, whereas the ratio of early transmitral (E) to E' lateral decreased (from 13.1 to 9.8 to 9.4) ( $P < 0.01$ ). Changes were accompanied by a reverse remodeling of left atrial volume index (from 32.0 to 29.0 and 29.1 mL/m<sup>2</sup>;  $P < 0.01$ ) and LV mass index (from 148.0 to 130.0 and 128.0 g/m<sup>2</sup>;  $P < 0.01$ ). Furthermore, sildenafil improved exercise performance (peak VO<sub>2</sub>), ventilation efficiency (ventilation to CO<sub>2</sub> production slope), and quality of life ( $P < 0.01$ ). Minor adverse effects were noted: flushing in 4 and headache in 2 treated patients.

**Conclusions**—Findings confirm that in HF, sildenafil improves functional capacity and clinical status and provide the first human evidence that LV diastolic function and cardiac geometry are additional targets of benefits related to chronic PDE5 inhibition.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00975494. (*Circ Heart Fail.* 2011;4:8-17.)

**Key Words:** PDE5 inhibition ■ heart failure ■ diastolic function ■ cardiac remodeling

Heart failure (HF) is a significant health care concern that is evolving to epidemic proportions.<sup>1</sup> Development of new forms of interventions remains a challenging task. An abnormal nitric oxide (NO) pathway is involved in several pathophysiological abnormalities encountered in HF syndrome,<sup>2</sup> and NO overexpression may represent a desirable therapeutic target.

#### Editorial see p 2 Clinical Perspective on p 17

PDE5 inhibition is an intriguing pharmacological strategy that enhances in vivo NO signaling by increasing the cyclic guanosine monophosphate (cGMP) availability. A number of theoretical backgrounds support the use of PDE5 inhibitors in HF, and several recent clinical studies have tested its clinical

viability as a potential adjunct in the pharmacological management of HF.<sup>3</sup> Because PDE5 is highly expressed in the pulmonary circulation, studies have primarily focused on the drug efficacy on pulmonary hemodynamics and alveolar gas exchange of patients with HF and left-sided pulmonary hypertension.<sup>4-9</sup> Examination of important clinical correlates has also demonstrated the positive effects of acute and chronic PDE5 inhibition on functional capacity and exercise ventilation efficiency,<sup>4-8</sup> systemic endothelial function,<sup>10</sup> and quality of life (QOL).<sup>6,11</sup>

In failing hearts of animal models, PDE5 inhibition has also shown the attractive therapeutic property of reversing left ventricular (LV) chamber remodeling by preventing and reversing LV hypertrophy and fibrosis<sup>12,13</sup> and by protecting myocardium from ischemia-reperfusion injury<sup>14</sup> and apopto-

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sis.<sup>15</sup> There is also evidence that abnormal NO activity plays an important role in the excitation-relaxation process of the failing heart, an effect explained by a defective cGMP-induced phosphorylation of troponin I, which facilitates calcium-independent diastolic cross-bridge cycling and concomitant myocardium diastolic stiffening.<sup>16</sup>

No report has thus far investigated whether cardiac function and, primarily, diastolic LV function, may be a target of chronic PDE5 inhibition, and any improvement in diastolic function is associated with an effect on cardiac geometry. Accordingly, the primary end points of our study were the assessment of a drug-induced beneficial effect on LV diastolic function, chamber dimensions, and mass. Furthermore, because it is undefined whether a favorable activity on cardiac performance may be involved in the reported changes in important clinical correlates, such as functional capacity and QOL, we tested these additional hypotheses as secondary end points.

## Methods

### Study and Control Patients

Patients were referred to the outpatient Cardiopulmonary Unit at San Paolo Hospital, Milan, Italy, and to the Department of Physical Therapy at Virginia University, Richmond, Virginia, for HF evaluation. They were enrolled over a 12-month period. The average duration of HF disease was  $28 \pm 6$  months. HF eligibility criteria were consent to participate in the study after detailed information about benefits and risks; clinical stable conditions defined as no changes in HF regimens or hospitalization since 6 months before study entry; negative exercise stress test before study initiation; forced expiratory volume in 1 second/forced vital capacity ratio  $>70\%$ ; LV ejection fraction (LVEF)  $<40\%$ , and presence of LV diastolic dysfunction determined by Doppler analysis with documentation of a mitral inflow early (E) velocity to mitral annulus early velocity (E')  $>10$ .<sup>17</sup> Patients were not recruited if they were unable to complete a maximal exercise test, had resting systolic blood pressure  $<110$  mm Hg, therapy with nitrate preparations, LV assist devices, history of sildenafil intolerance, significant lung or valvular diseases, neuromuscular disorders, or peripheral vascular disease. Of the 60 HF patients originally screened, 8 were excluded for concomitant nitrate intake, 5 for LV assist devices, and 2 declined to participate. None presented with significant renal insufficiency (serum creatinine concentration  $>1.5$  mg/dL).

Because diabetic cardiomyopathy is considered a distinct disease process that involves peculiar molecular pathways,<sup>18</sup> the effects of chronic PDE inhibition in this setting might be distinct from nondiabetic failing hearts. On the basis of this rationale, diabetic patients were excluded. Participants were not involved in any physical training program for at least 6 months before study initiation; all were symptomatic during exercise and limited by breathlessness and muscle fatigue; their current drug HF treatment was stable and adherent to guidelines.<sup>19</sup>

Thirty-six percent of patients in the placebo group and 42% in the sildenafil group had previously used a PDE5 inhibitor for erectile dysfunction and did not report any side effects. All subjects gave their written consent to the study after detailed information. The trial was approved by the local ethics committees.

### Echocardiography

An expert echocardiographer observer performed the echocardiographic analysis by transthoracic echocardiography accomplished with an IE33, Philips ultrasound machine, equipped with a software for tissue Doppler (TD), using a 2.5- to 5.0-MHz probe (S5). Standard M-mode, 2D, and Doppler blood flow measurements were performed according to the current American Society of Echocardiography Guidelines.<sup>20</sup> Chamber dimensions were obtained using

standard procedures including left atrial volume index (LAVI) and LV mass index (LVMI).<sup>21</sup>

Septal and posterior wall thickness, LA, and LV end-systolic and end-diastolic dimensions were obtained from the parasternal long-axis view. LVEF, end-diastolic volume index (LVEDVI), and end-systolic volume index were evaluated with the Simpson method.

### Conventional Doppler and TD Measurements

The TD images of the mitral annulus movement were obtained from the apical 4-chamber view. A 1.5-mm sample volume was placed sequentially at the lateral and septal annular sites.<sup>20</sup> Analysis was performed for the systolic (S') and the early (E') and late (A') diastolic peak velocities. Pulsed-wave Doppler echocardiography was used to assess mitral peak early (E) and late (A) wave flow velocity, E-wave deceleration slope, and isovolumic relaxation time. Mitral early-to-late velocity (E/A) was considered as a parameter of diastolic function. The ratio of early transmitral flow velocity to annular velocity (E/E') was considered as an index of end-diastolic pressure, whereas the time interval between E and E' (T E-E') was regarded as an indicator of LV relaxation rate.<sup>22</sup> Adequate mitral and TD signals were recorded in all patients.

### Pulmonary Artery Systolic Pressure Measure

Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient using the modified Bernoulli equation. Right atrial pressure (clinically assessed jugular venous pressure) was added to the calculated gradient to yield PASP.<sup>23</sup> No subjects had significant right ventricular outflow tract obstruction.

The reviewer who performed the reading was a cardiologist with extensive experience in the echo laboratory who was blinded to drug treatment and performed a double reading on a sample of 5 patients in each group after 1 week to 10 days from the first reading to test the intraobserver variability. This variability was 3% and 4% for patients treated with placebo and sildenafil, respectively. A second expert echocardiographer independently reviewed 10 randomly selected cases in each group. Interobserver variability was 3.5% for ultrasound and 4.7% for Doppler variables.

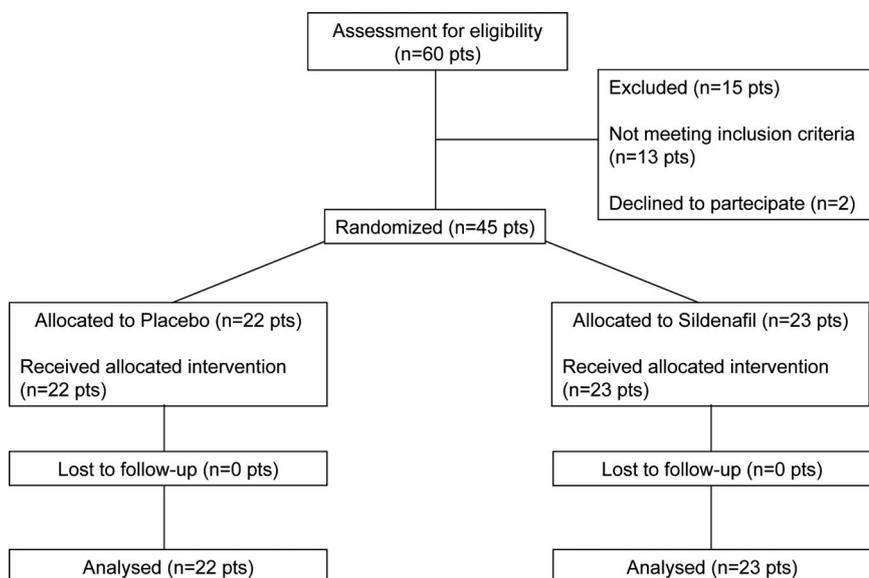
### Cardiopulmonary Exercise Testing

Patients performed a progressively increasing (personalized ramp protocol) work rate cardiopulmonary exercise testing (CPET) to maximal tolerance on an electromagnetically braked cycle ergometer (Carnival 906900, Lode, Holland) in upright position. Gas exchange analysis (Cardiopulmonary Metabolic Cart, Sensormedics Vmax Spectra) was performed at rest (3 minutes), throughout exercise (8 to 10 minutes), and during 3 minutes of recovery. A 12-lead ECG and cuff blood pressure were recorded. Respiratory gases were sampled continuously from a mouthpiece: Oxygen consumption ( $\dot{V}O_2$ ) at peak exercise and at anaerobic threshold, carbon dioxide output ( $\dot{V}CO_2$ ), minute ventilation ( $\dot{V}E$ ), and other exercise variables were computer-calculated breath by breath, interpolated second by second, and averaged over a 10-second interval. Test termination criteria consisted of symptoms (ie, dyspnea and/or fatigue), ventricular tachycardia,  $>2$  mm of horizontal or downsloping ST-segment depression, or drop in systolic blood pressure  $>20$  mm Hg during progressive exercise.

### Study Protocol

This was a double-blind, randomized, placebo-controlled trial. Eligible patients were randomly assigned to receive placebo or oral sildenafil 50 mg 3 times per day<sup>6</sup> in addition to their baseline treatment.

The trial duration was 1 year. Symptoms were recorded and QOL was questioned,<sup>24</sup> and the current therapy prescribed by the referring physician was maintained. After routine laboratory work, including N-terminal pro-brain natriuretic peptide (NT-pro BNP) measurements and cardiac and pulmonary function evaluation, patients underwent Doppler echocardiography and familiarization with a graded CPET to determine overall exercise performance. On the



**Figure 1.** Flow diagram. Progress through the phases of the trial from enrolment to follow-up and data analysis.

following day, ultrasound examinations and CPET tests were repeated, and results were taken as reference.

On the next morning, the response to sildenafil was acutely assessed in all patients to verify whether the agent was similarly effective in subjects randomly assigned to placebo as in candidates to the active preparation treatment. After an overnight fast, in a quiet room, after 15 minutes' rest, 50 mg sildenafil was administered orally. Two hours later, to coincide with the expected peak in the hemodynamic response, LVEF, PASP, Doppler-derived diastolic data, and CPET variables were reevaluated in that order. No patient was excluded after 1-time administration of sildenafil.

Patients were then discharged, and a 1-year, double-blind trial of sildenafil (25 patients) versus placebo (25 patients) was begun. Pills were provided by a nurse, and the investigators were kept blinded to patient treatment. Patients were monitored clinically every month until the end of the study. In all participants, compliance was assessed by the pill-count method at monthly return visits during which symptoms were recorded, physical examination, ECG and blood pressure measurements were performed and pills were supplied. Doppler echocardiography, NT-proBNP measurements, CPET, and QOL were reassessed at 6 and 12 months in both groups.

### Statistical Analysis

For participant allocation, a computer-generated list of random numbers was used. Assuming a 10% decrease in LVMI, LVEDVI, and E/E' and a 20% increase in peak  $\dot{V}O_2$ , a test with an  $\alpha$  level 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 patients. A flow diagram of the progress through the phases of the trial is reported in Figure 1.

Differences in patient baseline frequencies were compared using Fisher exact test analysis. The Student *t* test for independent samples was used for testing differences in quantitative baseline variables. For non-normal data distribution, the Mann-Whitney test was used.

Responses to acute sildenafil were analyzed using the Student paired *t* test. Comparison of between-group changes with chronic treatments were performed using covariance analysis. Repeated-measures analysis of variance and the Newman-Keuls multiple comparison procedure were used to test within-group differences before and after treatment.

Values are expressed as mean $\pm$ SD. A probability value of  $<0.05$  was considered significant. Statistical analyses were performed by means of STATA 7.0 package (Stata Corp, LP, College Station, Tex).

### Results

The trial included 45 Caucasian male patients between 38 and 80 years of age in stable clinical condition (New York Heart

Association class II-III) with ischemic, idiopathic, or hypertensive cardiomyopathy. All patients completed the double-blind treatment phase.

### Baseline Characteristics

Population characteristics, heart dimensions, CPET data, and therapy distribution are reported in Table 1. All patients were RAS-inhibited (48% were receiving enalapril at an average dose of  $18.0\pm 2.0$  mg/d, 32% ramipril at a dose of  $6.0\pm 4.2$  mg/d, and 20% losartan at a dose of  $65.0\pm 35.0$  mg/d). Ninety percent of patients were receiving  $\beta$ -blockers, 42% patients were given carvedilol at an average dose of  $40.0\pm 8.0$  mg/d, and 38% were treated with bucindolol at an average dose of  $20.0\pm 9.0$  mg/d. Forty-two percent of patients were receiving spironolactone at an average dose of  $32.0\pm 8.0$  mg/d.

The 2 cohorts were similar with respect to age, body mass index, etiology, chronic atrial fibrillation, NT-proBNP levels, heart dimensions, CPET data, QOL, therapy distribution (Table 1), and baseline conventional Doppler and TD indexes of diastolic function (Table 2).

### Acute Sildenafil Response

The acute responsiveness to 50 mg of sildenafil was comparable between the 2 cohorts (Table 3) and consisted of a similar significant decrease in PASP and improvement in exercise aerobic and ventilation efficiency, whereas LVEF and Doppler-derived variables of LV diastolic function did not change.

### Cardiac Dimensions and LV Systolic and Diastolic Functions

Over 12 months, LAVI, LVEDV, and LVMI were unchanged in the placebo group and decreased in the active treatment group, which suggests reverse remodeling with sildenafil involving both the ventricle and the atrium (Figure 2). Over the same time period in the sildenafil group, there was a progressive increase in mean LVEF, from 29.5% at baseline to 34.9% and 36.3% at 6 and 12 months, respectively (all  $P<0.01$ ). Changes observed with sildenafil were significantly different compared with placebo (all  $P<0.01$ ).

**Table 1. Baseline Patient Characteristics**

	Placebo Group (n=22)	Sildenafil Group (n=23)	P
<b>Demographics</b>			
Age, y	61±4	60±4	0.20
BMI, kg/m <sup>2</sup>	27.6±7.5	28.1±7.2	0.22
NYHA functional class II/III, n (%)	9 (41)/13 (59)	10 (43)/13 (57)	0.30
NT-proBNP, pg/mL	2111±2150	2030±2009	0.22
Dilated cardiomyopathy, n	8	9	0.42
Ischemic cardiomyopathy, n	12	11	0.35
Hypertensive cardiomyopathy, n	2	3	0.29
Chronic atrial fibrillation, n	4	3	0.36
<b>Echocardiography</b>			
LVEF, %	30.2±4.0	29.5±3.0	0.35
LA parasternal, mm	41.3±10.4	42.0±9.7	0.19
LAVI, mL/m <sup>2</sup>	30.9±9.9	31.7±11.0	0.24
LVEDD, mm	60.7±9.7	61.3±9.8	0.21
Septum, mm	11.2±2.4	10.9±2.5	0.18
Posterior wall, mm	10.5±3.2	10.9±3.1	0.22
LVMI, g/m <sup>2</sup>	144.3±28.1	147.2±30.2	0.19
LVEDVI, mL/m <sup>2</sup>	111±21	112±20	0.21
PASP, mm Hg	37.7±3.9	37.1±4.3	0.32
<b>CPET variables</b>			
Peak VO <sub>2</sub> , mL/min/kg	12.7±5.0	12.9±6.8	0.29
VO <sub>2</sub> at AT, mL/min/kg	7.3±4.0	7.2±4.9	0.29
VE/VO <sub>2</sub> slope	35.5±3.7	35.1±4.2	0.34
<b>Quality of life</b>			
Breathlessness	23.2±5.4	24.9±4.5	0.26
Fatigue	21.9±5.6	23.2±5.0	0.22
Emotional function	32.0±7.6	31.0±6.0	0.15
<b>Therapies</b>			
β-blockers, n (%)	20 (90)	18 (78)	0.39
ACE inhibitors, n (%)	20 (90)	19 (83)	0.41
AT1 blockers, n (%)	6 (27)	5 (22)	0.35
Antialdosterone agents, n (%)	10 (45)	9 (39)	0.46
Digitalis, n (%)	3 (14)	2 (9)	0.47
Cardiac resynchronization therapy, n (%)	8 (36)	9 (39)	0.29

BMI indicates body mass index; NYHA, New York Heart Association; LVEDD, LV end-diastolic dimension; and AT, anaerobic threshold.

As reported in Table 4, diastolic measures of LV function demonstrated systematic and sustained improvement after both 6 months and 1 year of sildenafil. The transmitral E/A ratio, isovolumic relaxation time, and both lateral and septal E/E' decreased from baseline through 12 months (all *P*<0.01), which indicates an improvement in LV diastolic function and a decrease in LV filling pressure. Furthermore, T E-E' septal was significantly reduced at 6 and 12 months of sildenafil treatment (*P*<0.01). All these changes were consonant with the observed reverse remodeling on LAVI, which is viewed as morphological expression of LV end-diastolic pressure.<sup>25</sup> Changes observed at 6 months and 1 year after sildenafil were significantly different compared with the

**Table 2. Baseline Diastolic Indices of Conventional Doppler and TD Echocardiography**

	Placebo Group (n=22)	Sildenafil Group (n=23)	P
<b>Mitral inflow</b>			
Mitral E velocity, cm/s	61.0±16.0	59.0±17.9	0.10
Mitral A velocity, cm/s	71.9±18.0	71.0±16.0	0.15
Mitral E/mitral A	0.85±0.66	0.83±0.59	0.14
IVRT, ms	93.0±7.60	91.0±6.90	0.20
<b>TD</b>			
S' lateral, m/s	5.76±0.93	5.55±0.91	0.28
E' lateral, m/s	4.79±0.78	4.62±0.80	0.14
E/E' lateral, m/s	13.0±4.6	13.1±4.8	0.32
T E-E' lateral, ms	35.0±4.40	35.9±5.0	0.28
S' septal, m/s	5.94±0.93	5.90±0.88	0.18
E' septal, m/s	4.82±0.76	4.71±0.74	0.28
E/E' septal, m/s	12.6±5.60	12.5±6.10	0.19
T E-E' septal, ms	34.0±5.5	34.6±4.2	0.21

IVRT indicates isovolumic relaxation time.

placebo group (all *P*<0.01). Figure 3 shows a typical case of changes observed over time in transmitral and TD mitral Doppler patterns during PDE5 inhibition.

**Plasma NT-proBNP and PASP Changes**

Plasma NT-proBNP levels rose by a mean of 117 pg/mL over 12 months in the placebo group and fell by a mean of 320 pg/mL with sildenafil. PASP significantly decreased at 6 and 12 months (Table 5).

**CPET Data and QOL Assessment**

In the sildenafil group, CPET data at 6 and 12 months (Table 5) showed a significant improvement versus baseline in peak VO<sub>2</sub> (14% and 17%; *P*<0.01) and VO<sub>2</sub> anaerobic threshold (20% and 32%; *P*<0.01) and a decrease in VE/VO<sub>2</sub> slope (9% and 17%; *P*<0.01). Values observed with sildenafil were significantly different versus placebo (all *P*<0.01). Variations in peak VO<sub>2</sub> and VE/VO<sub>2</sub> slope significantly correlated with changes in E/E' lateral (*r*=−0.38; *P*=0.032; *r*=0.421; *P*=0.036, respectively), T E-E' (*r*=−0.740; *P*=0.010; *r*=0.720; *P*=0.015, respectively), and LVEDVI (*r*=−0.37; *P*=0.04; *r*=0.390; *P*=0.032, respectively). QOL assessment documented a significant and sustained sildenafil-mediated improvement in breathlessness, fatigue, and emotional function (Table 5).

**Hospitalization and Side Effects**

During the trial, there were 3 hospitalizations in the placebo group and 1 in the sildenafil arm, all for new-onset atrial fibrillation. No major side effects were attributable to research procedures and sildenafil treatment. Minor adverse reactions consisted of flushing in 3 cases and headache in 2 cases in the sildenafil group, which disappeared in a few days after drug initiation, and 2 cases of diarrhea in the placebo group. Three patients (2 in the placebo and 1 in the sildenafil group) switched from ACE inhibitors to AT1 blockers, and 2 patients (1 in each group) required a small reduction of their β-blocker dose for bradycardia.

**Table 3. Circulatory and Exercise Data and Diastolic Function at Baseline and After Acute Sildenafil in Patients Randomly Assigned to Placebo and in Patients Randomly Assigned to Sildenafil**

	Placebo Group (n=22)		Sildenafil Group (n=23)	
	Baseline	Sildenafil	Baseline	Sildenafil
<b>Hemodynamics</b>				
LVEF, %	29.0±3.0	30.3±2.9	28.9±2.8	28.4±3.0
Blood pressure, mm Hg				
Systolic	109.0±7.0	105.2±9.5	107.2±7.8	108.4±7.7
Diastolic	72.0±6.9	71.2±7.0	72.2±8.2	71.0±8.6
PASP, mm Hg	38.4±3.0	28.7±2.7†	38.0±5.7	26.7±3.1†
<b>CPET variables</b>				
Peak $\dot{V}O_2$ , mL · min <sup>-1</sup> · kg <sup>-1</sup>	13.9±2.5	15.9±2.8†	14.8±2.3	15.6±1.9†
$\dot{V}O_2$ at AT, mL · min <sup>-1</sup> · kg <sup>-1</sup>	9.2±3.0	10.0±2.7*	9.3±3.2	10.4±3.4†
$\dot{V}E/\dot{V}CO_2$ slope	35.0±3.2	31.7±3.1†	36.4±4.2	33.9±3.7†
<b>Mitral inflow</b>				
Mitral E velocity, cm/s	61.0±15.8	61.2±16.7	58.0±15.9	59.4±16.8
Mitral A velocity, cm/s	71.2±18.1	71.7±16.8	70.9±15.3	70.4±15.6
Mitral E/mitral A	0.86±0.68	0.85±0.66	0.82±0.70	0.84±0.63
IVRT, ms	92.0±7.60	92.4±7.40	91.4±6.20	91.0±5.9
<b>TD</b>				
S' lateral, m/s	6.0±0.94	5.89±0.91	5.88±0.84	5.9±1.0
E' lateral, m/s	4.74±0.78	4.79±0.93	4.59±0.88	5.19±0.92
E/E' lateral, m/s	13.8±4.80	13.9±4.40	13.8±4.80	13.9±5.20
T E-E' lateral, ms	34.0±4.2	34.1±4.15	35.2±4.4	35.4±5.0
S' septal, m/s	5.93±0.94	5.94±0.94	5.88±0.85	5.88±0.89
E' septal, m/s	4.64±0.75	4.66±0.71	4.53±0.72	4.89±0.79
E/E' septal, m/s	12.1±4.91	12.4±4.82	12.5±5.3	12.4±5.1
T E-E' septal, ms	33.3±5.10	33.2±5.4	33.8±4.9	33.2±4.8

AT indicates anaerobic threshold; IVRT, isovolumic relaxation time.

Responses to sildenafil in assigned treatment groups were comparable.

\* $P < 0.05$  versus baseline; † $P < 0.01$  versus baseline value.

## Discussion

In this randomized, double-blind, placebo-controlled study, we found that in stable HF patients with reduced LVEF, long-term treatment with the PDE5 inhibitor sildenafil significantly improved LV diastolic function, altered LA and LV geometry, and improved clinical status. It is noteworthy that these effects were observed in a group of patients treated with a background therapeutic regimen adherent to current guidelines recommendations and that long-term sildenafil therapy was well tolerated, with minor reported adverse effects occurring in a low rate.

### Sildenafil Effects on Diastolic LV Function and Geometry

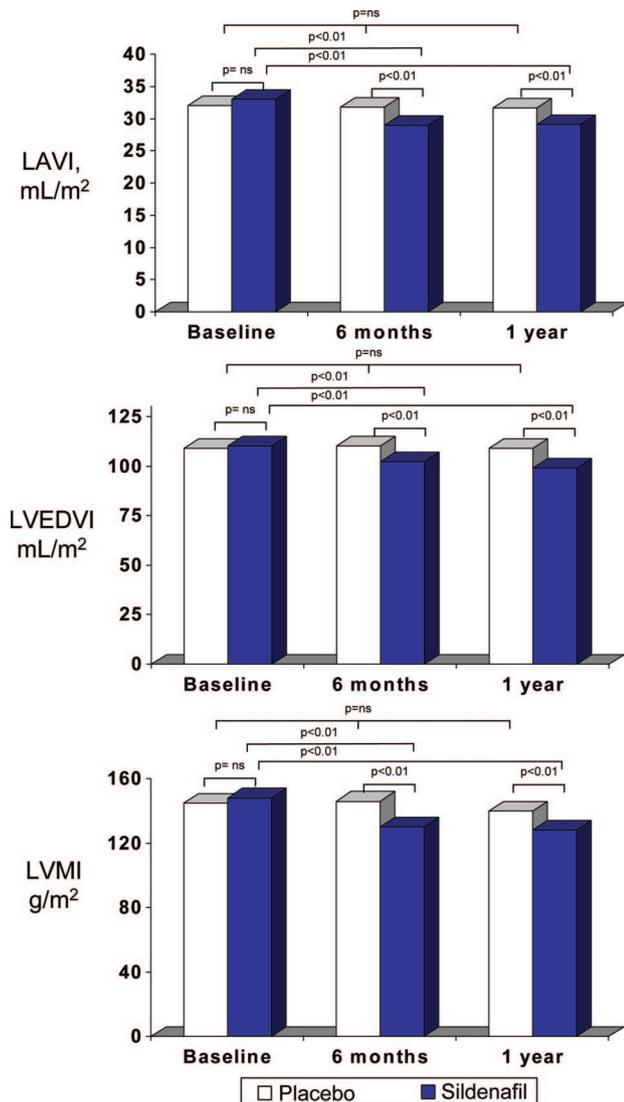
The study primarily focused on the effects of chronic PDE5 inhibition on LV diastolic function and cardiac chamber remodeling, providing the first human evidence that PDE5 inhibition can be beneficial for improving the diastolic and structural properties of the failing LV.

E/E', a variable repeatedly found related to LV filling pressures in a variety of left-sided cardiac disorders,<sup>25</sup> significantly decreased at 6 months and 1 year of active treatment.

Additional study findings that support the hypothesis that PDE5 inhibition may represent a novel and viable therapeutic strategy for improving LV relaxation are (1) the significant shortening in both lateral and septal T E-E', a Doppler-derived index of LV relaxation performance validated against invasively measured negative  $dP/dT^{22}$ ; (2) the reverse remodeling effect on LV mass; and (3) the reduced levels of NT-proBNP over time.

These results raise the intriguing possibility that the NO pathway may be crucially involved in these effects.

An NO-induced, diastolic LV distensibility-increasing effect has been documented in several animal models,<sup>26</sup> with supporting evidence also in the normal and failing human heart.<sup>16,27</sup> Major identified molecular pathways involved in the NO-mediated effect on the diastolic function properties of the cardiomyopathic heart are an NO-induced phosphorylation of troponin I with concomitant reduction of diastolic cross-bridge cycling and an effect on myocardial metabolism by preserving myocardial energetics through its activity on mitochondrial respiration, oxygen consumption, and substrate utilization. Furthermore, LV relaxation may benefit from NO activity through the prevention of endomyocardial fibrosis by



**Figure 2.** Heart dimensions data: LAVI, LVEDVI, and LVMI at baseline and 6-month and 1-year study periods.

blocking the signaling cascade involving endothelin, angiotensin II, aldosterone, and transforming growth factor- $\beta$ .<sup>27</sup>

There is also the recent intriguing suggestion that sildenafil and an increased cGMP activity on protein kinase G may benefit LV cardiomyocyte relaxation because of phosphorylation of the giant protein titin.<sup>28</sup>

Although the cellular bases for the improved diastolic relaxing properties remain undefined, the study provides the first evidence that in the human failing heart, this effect is combined with an antiremodeling activity on the left atrium and ventricle. This raises a number of intriguing questions of whether an effect is a direct consequence of the other, or both, result from a pharmacological or biological activity on similar or complementary pathways.

A considerable number of experimental studies suggest that increasing intracellular cGMP activity by PDE5 inhibition has remarkable positive effects on the myocyte biological properties that may block adrenergic, hypertrophic, and proapoptotic signaling.<sup>29</sup> Landmark experiments by Takimoto et al<sup>12</sup> obtained in animals exposed to sustained pressure

overload have shown that chronic PDE5 inhibition by sildenafil can prevent and reverse cardiac hypertrophy and interstitial fibrosis. Mechanistic insights provided by this set of experiments found that sildenafil could deactivate multiple hypertrophy signaling pathways triggered by pressure overload including calcineurin/NFAT, mitogen activated protein kinase, and Akt pathways. Sildenafil targeting appeared to be upstream of these proteins, as constitutive activation of calcineurin in myocytes or Akt in vivo induced hypertrophy that could not be suppressed by the PDE5 inhibitor. Most recent observations document that transgenic models that overexpress PDE5 in myocytes develop LV dilation and that explanted failing human hearts exhibit a high LV PDE5 expression.<sup>30</sup>

Although the definitive in vivo correlates of these findings remain unexplored and the extent of PDE5 expression and activity in the human failing heart has yet to be fully elucidated across different phenotypes of myocardial hypertrophy and failure, our data well support the bulk of laboratory observations suggesting that an antihypertrophic and antifibrotic effect can occur in vivo as well. Accordingly, it can be inferred that the cellular pathways involved in the observed effects on LA and LV geometry are seemingly complementary or synergistic to those already activated by chronic  $\beta$ -blockers and RAS inhibitors.

Interestingly, the lack of any further effects on LV mass regression at 1 year compared with 6 months may argue for the occurrence of drug tolerance over time.

Another point that must be discussed is the potential role that a sustained NO oversignaling might have on myocardial contractile state. In contrast with the aforementioned evidence of the beneficial effects of NO on the relaxing properties of the failing LV, there is the experimental appraisal of a possible negative NO-mediated effect on the myocyte extent and velocity of shortening of both normal and failing heart models.<sup>31</sup> Information on the effects of chronic PDE5 inhibition on myocardial contractility are lacking. Nonetheless, basic science studies<sup>32</sup> and a preclinical report performed in healthy volunteers<sup>33</sup> have provided evidence of the sildenafil pharmacological property of acutely blunting the contractile response to adrenergic stimulation. The functional potential implications of this effect on the  $\beta$ -adrenergic pathway are unknown. Nonetheless, there is the suggestion that a modulatory protection against sympathetic nervous system activation may be another contributory mechanism that helps to reverse the functional contractile abnormalities of failing myocytes. We did not measure LV contractile state. However, the overall LV performance, as indicated by LVEF, increased over time, an effect that together with the improved cardiac chamber geometry, strongly supports the concept that, as for  $\beta$ -blockers and RAS inhibitor agents, the effects of long-standing PDE5 inhibition are the result of a biological rather than a pharmacological effect. This is further strengthened by the observation that acute administration of sildenafil does not cause improvement in LV relaxation even when catheter-based measures of diastolic function are assessed.<sup>34</sup>

Furthermore, the present findings argue against the justified but unproven theoretical possibility that an increase in cAMP concentration secondary to cGMP accumulation may

**Table 4. Diastolic Function at Baseline and After 6 and 12 Months of Treatment With Placebo or Sildenafil**

	Placebo Group (n=22)					Sildenafil Group (n=23)				
	Baseline	6 Months	Δ	12 Months	Δ	Baseline	6 Months	Δ	12 Months	Δ
<b>Mitral inflow</b>										
Mitral E velocity, cm/s	61.0±16.0	62.0±15.0	+1.0	61.0±16.0	0	59.0±17.9	54.1±17.8*†	-4.9‡	53.0±16.2*†	-6.0‡
Mitral A velocity, cm/s	71.9±18.0	71.3±16.5	-0.6	71.5±15.9	-0.04	71.0±16.0	70.7±14.9	-0.3	71.2±16.0	+0.2
Mitral E/mitral A	0.85±0.66	0.87±0.61	+0.2	0.85±0.61	0	0.93±0.59	0.75±0.59*†	-0.18‡	0.74±0.70*†	-0.19‡
IVRT, ms	93.0±7.60	93.4±6.50	+0.4	94.4±8.80	+1.4	91.0±6.90	86.0±5.0*†	-5.0‡	85.0±6.0*†	-6.0‡
<b>TD</b>										
S' lateral, m/s	5.76±0.93	5.82±0.94	+0.06	5.78±0.95	+0.02	5.55±0.91	6.10±1.2*†	+0.55‡	6.19±1.1*†	+0.64‡
E' lateral, m/s	4.79±0.78	4.75±0.84	-0.04	4.69±0.78	-0.10	4.62±0.80	5.20±0.81*†	+0.58‡	5.19±0.85*†	+0.57‡
E/E' lateral, m/s	13.0±4.6	13.9±4.50	+0.9	13.8±4.80	+0.8	13.1±4.8	9.8±5.1*†	-3.3‡	9.4±5.2*†	-3.7‡
T E-E' lateral, ms	35.0±4.40	35.6±4.15	+0.6	35.5±4.22	+0.5	35.9±5.0	30.0±5.3*†	-5.9‡	31.0±5.1*†	-4.9‡
S' septal, m/s	5.94±0.93	5.96±0.95	+0.02	5.91±0.92	-0.3	5.90±0.88	6.24±0.80*†	+0.34‡	6.30±0.87*†	+0.40‡
E' septal, m/s	4.82±0.76	4.78±0.77	-0.04	4.74±0.75	-0.8	4.71±0.74	5.23±0.82*†	+0.52‡	5.24±0.89*†	+0.53‡
E/E' septal, m/s	12.6±5.60	12.5±5.0	-0.01	12.3±5.2	-0.3	12.5±6.10	9.4±4.85*†	-3.1‡	9.8±5.1*†	-2.7‡
T E-E' septal, ms	34.0±5.5	33.9±5.3	-0.01	33.2±5.4	-0.8	34.6±4.2	29.0±4.42*†	-5.6‡	28.0±4.3*†	-6.6‡

IVRT indicates isovolumic relaxation time.

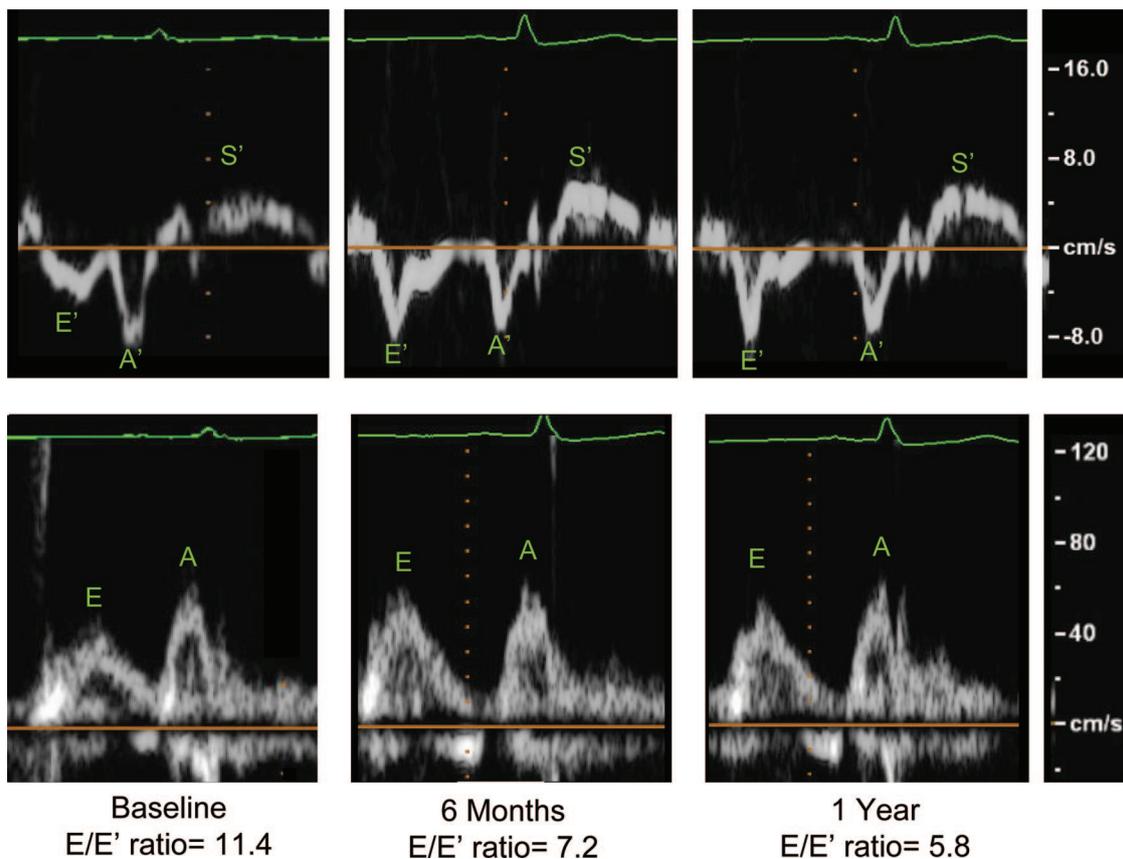
\**P*<0.01 versus corresponding value in the placebo group; †*P*<0.01 versus baseline value; and ‡*P*<0.01 for changes from baseline according to placebo.

be responsible for a positive inotropic “milrinone effect,” with its potential known adverse consequences on the natural history of the disease.<sup>35</sup>

An intriguing question that must be addressed in future studies is the potential for sildenafil to promote cardiac benefits similar to the NO-dependent mechanisms described for exercise training interventions.<sup>36</sup>

**Sildenafil Impact on Functional Capacity and Clinical Status**

Exercise tolerance and symptoms are established measures of efficacy of new therapeutic interventions in HF populations. Consistent with previous reports, sildenafil promoted a sustained beneficial effect on aerobic capacity and ventilatory efficiency. These improvements have previously been ex-



**Figure 3.** TD and mitral flow velocity profile. Example of sildenafil-induced changes in E and E' leading to a progressive reduction in E/E' ratio after 6 months and 1 year of sildenafil treatment.

**Table 5. Neurohumoral, Echocardiographic, CPET, and Quality-of-Life Data at Baseline and After 6 and 12 Months of Treatment With Placebo or Sildenafil**

	Placebo Group (n=22)					Sildenafil Group (n=23)				
	Baseline	6 Months	Δ	12 Months	Δ	Baseline	6 Months	Δ	12 Months	Δ
Hormones										
NT-proBNP, pg/mL	2111±2150	2284±2210	+173	2228±2098	+117	2030±2009	1790±2120*†	-240‡	1710±2021*†	-320‡
Blood pressure, mm Hg										
Systolic	109.0±9.0	110.0±8.5	+0.1	111.0±8.0	+0.2	110.4±7.9	111.3±8.9	+0.9	110.4±9.2	0
Diastolic	72.0±8.0	73.0±8.0	+1.0	74.0±8.1	+2.0	74.1±8.3	72.2±7.7	-1.9	71.1±7.9	-3.0
Echo data										
LVEF, %	30.2±4.0	30.5±3.0	+0.3	31.0±3.2	+0.8	29.5±3.0	34.9±3.2*†	+5.4‡	36.3±3.0*†	+6.8‡
LVEDD, mm	60.7±9.7	61.2±9.2	+0.5	61.6±8.8	+0.9	61.3±9.8	57.9±9.2*†	-3.4‡	57.1±9.8*†	-4.2‡
PASP, mm Hg	37.7±3.9	37.3±3.0	-0.4	37.9±4.0	+0.2	37.1±4.3	24.2±3.0*†	-12.9‡	24.0±3.0*†	-13.1‡
CPET variables										
Peak $\dot{V}O_2$ , mL · min <sup>-1</sup> · kg <sup>-1</sup>	12.7±5.0	12.5±4.7	-0.2	13.0±5.0	+0.3	12.9±6.8	15.0±6.0*†	+2.1‡	15.6±5.8*†	+2.7‡
$\dot{V}O_2$ at AT, mL · min <sup>-1</sup> · kg <sup>-1</sup>	7.3±4.0	7.0±3.7	-0.3	7.2±3.0	-0.1	7.2±4.9	8.9±3.2*†	+1.7‡	10.6±3.7*†	+3.4‡
$\dot{V}E/\dot{V}CO_2$ slope	35.5±3.7	36.0±4.0	+0.5	35.9±4.2	+0.4	35.1±4.2	32.0±3.0*†	-3.1‡	29.1±3.1*†	-6.0‡
QOL										
Breathlessness	23.2±5.4	23.1±5.0	-0.1	22.9±6.0	-0.3	23.9±4.5	31.4±5.2*†	+7.7‡	31.5±4.9*†	+7.8‡
Fatigue	21.9±5.6	22.4±6.1	+0.5	22.0±6.2	+0.1	22.2±5.0	28.4±5.0*†	+6.2‡	29.0±5.0*†	+6.8‡
Emotional function	32.0±7.6	31.7±6.3	-0.3	32.2±7.0	+0.2	31.0±6.0	36.8±6.6*†	+5.8‡	36.1±6.7*†	+5.1‡

AT indicates anaerobic threshold.

\* $P < 0.01$  versus corresponding value in the placebo group; † $P < 0.01$  versus baseline value; and ‡ $P < 0.01$  for changes from baseline according to placebo.

plained by a multilevel drug activity on pulmonary hemodynamics and arterial endothelium.<sup>4–8,10</sup> The correlations of changes in  $E/E'$  and especially in  $T E-E'$  with those in peak  $\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  slope may imply that cardiac changes observed in LV distensibility provide some contribution to variations in exercise performance. In agreement with previous specifically designed trials looking at QOL during sildenafil treatment,<sup>12</sup> daily life symptoms and functional emotion were significantly improved.

### Study Limitations

Some limitations of our study must be recognized. First, although we demonstrated a clear ability of sildenafil of improving Doppler-validated indexes of LV filling pressure and relaxation, a definitive substantiation of PDE5 inhibition as modulator of the ventricular diastolic properties in the human failing heart would derive from a specifically designed catheter-based study. Second, although there is a physiological background for using  $E/E'$  ratio in the noninvasive assessment of LV diastolic properties, a note of caution should be used in HF when interpreting  $E/E'$  changes as an index of increased LV filling pressure, particularly in patients with systolic HF with larger LV volumes, more impaired cardiac index, and in the presence of cardiac resynchronization therapy.<sup>37</sup>

Furthermore, echocardiography-derived measures of cardiac chamber morphological changes, especially when the

number of examined cases is small, does not allow for a significant time course definition of the fine changes occurring in the ongoing remodeling. This precludes an exact definition of when the reverse LA and LV remodeling process starts and of when it coincides with changes in diastolic reserve.

Our findings have an obvious limited generalizability, given that the study population included only men and that diabetic patients were excluded. In addition, a significant portion of our patients had already taken and well tolerated PDE5 inhibitors. Indeed, the study of a pure PDE5 inhibitor population would have provided more convincing data on tolerability. It also must be remarked that this population of systolic HF patients exhibited a low rate of hospitalization, possibly because it was a highly selected one and was tightly monitored (every month) over a 1-year period. Thus, the present subset of patients may substantially differ from the general HF population followed up in the community.

### Conclusions

In summary, in stable HF patients, long-term use of sildenafil was well tolerated. This therapeutic regimen promoted, as first evidence reported in human beings, a sustained significant improvement in LV and diastolic function properties and cardiac geometry. These effects yielded to a better functional capacity and clinical status. Additional work is needed to confirm findings observed with this promising therapeutic

strategy and to further clarify the significance and clinical impact of these effects on the natural history of HF.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

In 45 optimally treated patients with systolic heart failure, we tested the hypothesis that nitric oxide pathway oversignaling through chronic PDE5 inhibition (sildenafil 50 mg 3 times per day) may be beneficial on left ventricular (LV) diastolic function, cardiac remodeling, and functional and clinical status. Patients were randomly assigned to placebo or sildenafil for 1 year, with assessment of LV diastolic function, cardiac geometry, LV ejection fraction, cardiopulmonary exercise performance, and quality of life at 6 months and 1 year. In the sildenafil group, at 6 months and 1 year, diastolic relaxation indexes and LV filling pressure improved compared with placebo, as suggested by a significant increase in early diastolic tissue Doppler velocities ( $E'$ ) at the mitral lateral and septal annuli and by a significant reduction in the ratio of early transmitral ( $E$ ) to  $E'$ , respectively. Changes were accompanied by a reverse remodeling as documented by a significant reduction left atrial volume index and LV mass index compared with placebo. Furthermore, sildenafil improved exercise performance (peak  $VO_2$ ), ventilation efficiency (ventilation to  $CO_2$  production slope) and quality of life. The drug was well tolerated, and minor adverse effects were noted. The present findings suggest, as first evidence reported in human beings, that chronic PDE5 inhibition promotes a sustained significant improvement in LV diastolic function properties, cardiac geometry, and clinical status in patients with systolic heart failure.