Sildenafil Effects on Exercise, Neurohormonal Activation, and Erectile Dysfunction in Congestive Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Study Followed by a Prospective Treatment for Erectile Dysfunction

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A Double-Blind, Placebo-Controlled, Randomized Study Followed by a Prospective Treatment for Erectile Dysfunction

Edimar Alcides Bocchi, MD; Guilherme Guimarães, PhD; Amilcar Mocelin, MD; Fernando Bacal, MD; Giovanni Bellotti, MD; José Franchini Ramires, MD

Background—Erectile dysfunction (ED) is common in patients with congestive heart failure (CHF). ED reduces quality of life, and it may affect compliance, thereby impairing the success of CHF treatment.

Methods and Results—In the first phase (fixed-dose double-blind, randomized, placebo-controlled, two-way crossover study), we studied in 23 men with CHF the effects of 50 mg sildenafil on exercise and neurohormonal activation. Patients underwent a treadmill 6-minute cardiopulmonary walking (6′WT) test followed by a maximal cardiopulmonary exercise test (ET). In the second phase, patients received sildenafil, taken as required for ED. Sildenafil reduced the heart rate (HR) (bpm) before the 6′WT (from 75±15 to 71±14, $P=0.02$) and ET (from 75±15 to 71±15, $P=0.02$); the systolic blood pressure (mm Hg) before the 6′WT (from 116±18 to 108±18, $P=0.004$) and ET (from 116±15 to 108±17, $P=0.001$); the diastolic blood pressure before the 6′WT (from 69±9 to 63±11, $P=0.01$) and ET (from 70±8 to 65±10, $P=0.004$); and the Ve/V_{CO_2} slope during the 6′WT (from 32±7 to 31±6, $P=0.04$) and ET (from 33±8 to 31±5, $P=0.03$). Sildenafil attenuated the HR increment during the 6′WT ($P=0.003$) and ET ($P=0.000$). Sildenafil increased the peak $\dot{V}_{O_2}$ from 16.6±3.4 to 17.7±3.4 mL/kg per min ($P=0.025$) and the exercise time from 12.3±3.4 to 13.7±3.2 minutes ($P=0.003$). Sildenafil improved most scores of International Index of Erectile Function.

Conclusions—Sildenafil was tolerated and effective for ED treatment in CHF, and improved the exercise capacity. The reduction of HR during exercise with sildenafil could theoretically decrease the myocardial oxygen consumption during sexual activity. **(*Circulation*. 2002;106:1097-1103.)**

Key Words: heart failure ■ exercise ■ nitric oxide

The prevalence of congestive heart failure (CHF) and left ventricular systolic dysfunction is estimated to be as high as 8.8% and 11.3%, respectively.[1] CHF may result in marked changes in libido and ability to perform sexually. Erectile dysfunction (ED) affects 60% to 70% of heart failure clinic outpatients.[2] To retain sexual activity, patients may become noncompliant with CHF treatment that they feel causes or aggravates their ED. Most CHF patients place greater importance on improved symptoms rather than longer survival.[3]

Sildenafil inhibits phosphodiesterase type 5 (PDE5) found mainly within the corporea cavernosa, vascular and visceral muscles, tracheal smooth muscles, and platelets, increasing cyclic guanosine-3′,5-monophosphate (cGMP), which mediates many of the biological effects of NO.[4,5] Concerns have been raised about the safety of sildenafil in CHF and the risk of sexual activity triggering cardiovascular events. Evidence-based guidelines about sildenafil use by patients with CHF are lacking.[6]

We investigated in CHF with ED the sildenafil acute effects on exercise, neurohormonal activation, and clinical status. The efficacy and safety of sildenafil for ED treatment were evaluated in a 1-month follow-up in the same patients who were taking multiple concomitant medications in a home setting.

Methods

Study Subjects

The study population was comprised of 24 heterosexual male CHF outpatients, 50±10 years of age, who were referred for ED treatment (Table 1). ED was defined as the inability to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse.[7] Patients were included if they had ED for at least 4 months and present interest in sex and were in a stable relationship. Their ED also had to appear concomitant to new symptoms of CHF, worsening of clinical status, or a change in specific medication for CHF.

All patients were in stable clinical condition without required changes in treatment within the last 3 months. The treatment was continued as clinically indicated. The protocol was approved by the Ethical Review Committee of the Heart Institute (InCor). All subjects provided written informed consent before participation.

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TABLE 1. Characteristics of Patients With ED

Characteristics	No. of Patients (%), or Value, or Dose
Pathogenesis	
Ischemic	5 (22)
Chagasic	5 (22)
Idiopathic dilated cardiomyopathy	6 (26)
Hypertensive	6 (26)
Valvar	1 (4)
LV ejection fraction (echo), %	23±7
LV end-diastolic diameter (echo), mm	72±16
NYHA functional class	
II	19 (83)
III	3 (13)
IV	1 (4)
Previous NYHA functional class	
II	5 (22)
III	5 (22)
IV	13 (57)
Diuretics	21 (91)
ACE inhibitor	19 (67)
Angiotensin II AT_1 receptor antagonists	2 (8)
β-Adrenergic receptor blocker	14 (61)
Spironolactone	14 (61)
Amiodarone	4 (17)
Isosorbide 5-mononitrate (40 mg)	2 (9)
Hypothyroidism/hyperthyroidism	2 (9)/2 (9)
Serum total testosterone, ng/dL (normal 200–950)	604±203
Prolactin, ng/mL (normal 2.5–11.5)	4.2±2.3
Luteinizing hormone, IU/L (normal 1.4–9.2)	3.6±1.9
Follicle-stimulating hormone, IU/L (normal 1–12)	4.2±2.8
Total cholesterol, mg/dL	203±49
HDL cholesterol, mg/dL	46±13
LDL cholesterol, mg/dL	130±41
Triglycerides, mg/dL	155±145
Duration of ED symptoms, mo	24±19
Duration of CHF symptoms, mo	61±49
Resting norepinephrine, pg/mL (normal 40–268)	448±214

Values are mean±SD or n (%). LV indicates left ventricular; RV, right ventricular.

Study Design

Phase 1 was a prospective fixed-dose randomized, double-blind, placebo-controlled, two-way crossover study with a washout period of at least 24 hours to ensure clearance of sildenafil between consecutive treatment periods. The men took their usual medication before the tests. Patients were randomized to receive either a single oral dose of sildenafil (50 mg) or placebo. On day 0, patients underwent a 6-minute treadmill-walking test (6′WT) followed by a maximal exercise test (ET) to get familiarized with the protocol and to detect any contraindication to exercise. On day 1, patients underwent exercise tests ≈1 hour after sildenafil or placebo intake. On day 2, patients crossed over to the second treatment (sildenafil or placebo) and followed the same protocol. Sildenafil (Viagra) was supplied by Pfizer Inc. The placebo was supplied by our institution pharmacy.

The second phase was an open-label, home-based clinical prospective study using a flexible dose of sildenafil during 1 month and included patients who tolerated the drug in the first phase. Patients were instructed to take sildenafil 1 to 2 hours before they were likely to have an opportunity of sexual activity. The starting dose was 50 mg, and the maximal recommended frequency was once per week. On the basis of effectiveness and side effects, the dose could be doubled or increased up to 150 mg or reduced to 25 mg to determine the effective dose of sildenafil in CHF. Patients kept a record of adverse events, and the erections were graded on a 5-point scale. At the end the treatment period, patients were interviewed for an overall assessment of their ED treatment.

The efficacy of sildenafil in ED was evaluated by the 15 questions of the International Index of Erectile Function (IIEF).[8] The responses to IIEF questions were rated on a scale of 1 (almost never or never) to 5 (almost always or always). A score of 0 indicated no attempt of sexual intercourse. Overall scores were computed by adding the scores for the individual questions in each domain. The satisfaction with the ED treatment was evaluated by using the 11 questions of the Index of Satisfaction of ED Treatment.[9]

Exclusion Criteria

Men were excluded if they had ED considered secondary to causes other than heart failure, previous therapy for ED, recent use of PDE inhibitors, severe systemic disease, visual disturbances, psychiatric or psychological disorder, unstable angina or myocardial infarction within the previous 3 months, syncope, angina, heart rate (HR) <55 bpm, high-risk arrhythmias, new atrial tachycardia/fibrillation/flutter or uncontrolled high ventricular response, new or high degree of atrioventricular block, hypertrophic cardiomyopathy, valvular disease, symptomatic hypotension or systolic blood pressure <85 mm Hg, unstable CHF, low systemic perfusion, or venous or pulmonary congestion.

Exercise Protocol: The 6′WT and ET

We measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) and determined plasma norepinephrine blood levels in upright position immediately before each exercise test, at the last minute of the 6′WT, at ET peak, and at 1-minute recovery. ECG was continuously monitored. Pulmonary ventilation and gas exchange data were determined on a breath-by-breath basis with a computerized system (model V_{max} 229 Sensormedics).

The 6′WT was performed using a programmable treadmill without inclination and with patient-controlled velocity (Series 2000, Marquette Electronics) at least 2 hours after a light meal and with controlled room temperature (21°C to 23°C). The patients were oriented to walk according to Borg's scale, with exertion level ranging from light to somewhat hard, from 11 to 13.[10]

After return of HR, SBP, DBP, and symptoms to basal condition, patients underwent a progressive ET using a modified Naughton protocol.[11] They were encouraged to maximal exercise until exhaustion or the onset of nontolerated symptoms occurred and the respiratory exchange ratio exceeded 1.0. The peak oxygen consumption (peak $\dot{V}O_2$) was considered to be the maximum reached $\dot{V}O_2$ value.

Statistical Analysis

Variables are expressed as mean±1 SD. All data were analyzed with SPSS statistical software (SPSS). The criterion for statistical significance was $P<0.05$. The Student's paired t test was used for normally distributed variables and the Wilcoxon signed ranks test for variables that were not distributed normally.

The peak curve statistical model was used for the analysis of differences between sildenafil and placebo effects on serial measurements during 6′WT and ET until the 8th minute and in the recovery phases of both 6′WT and ET.[12] We calculated for each test the AUC plotting time (minutes) versus HR (bpm). The growth curve statistical model was used for the analysis of differences between sildenafil and placebo effects on serial measurements during the ET.

TABLE 2. Effects of 50 mg Sildenafil During Rest and Exercise in Patients With CHF

	6′WT			ET		
Variable	Basal	6th Minute	Recovery	Basal	Peak	Recovery
HR, bpm						
Placebo	75±15	97±21	83±17	75±15	118±23	105±23
Sildenafil	71±14	90±19	79±16	71±15	118±23	103±21
P	0.016	0.000	0.042	0.022	NS	NS
SBP, mm Hg						
Placebo	116±18	126±21	123±17	116±15	132±20	128±20
Sildenafil	108±18	120±21	121±20	108±17	129±26	124±26
P	0.004	NS	NS	0.001	NS	NS
DBP, mm Hg						
Placebo	69±9	70±13	70±113	70±8	74±13	74±14
Sildenafil	63±11	69±13	67±13	65±10	68±15	71±12
P	0.01	NS	NS	0.004	NS	NS
Ve, L/min						
Placebo	11±2	26±6	18±4	11±2	46±11	37±10
Sildenafil	11±2	25±6	19±4	11±2	46±10	38±9
P	NS	NS	NS	NS	NS	NS
V_{O_2}, mL/kg per minute						
Placebo	4.0±0.6	10.9±2.7	7.6±1.6	3.9±0.6	16.6±3.4	12.9±2.4
Sildenafil	3.9±0.5	11.1±2.4	7.7±1.6	4.0±0.4	17.7±3.4	13.6±2.5
P	NS	NS	NS	NS	0.025	NS
Ve/V_{CO_2}						
Placebo	46±9	37±5	37±5	50±11	39±15	39±13
Sildenafil	49±11	36±5	38±8	52±12	34±6	35±5
P	NS	0.056	NS	NS	0.002	NS
VD/VT, %						
Placebo	32±6	25±3	26±4	33±7	21±4	23±5
Sildenafil	33±6	25±4	26±6	34±6	22±4	22±4
P	NS	NS	NS	NS	NS	NS
Slope Ve/V_{CO_2}						
Placebo	...	32±7	...	...	33±8	...
Sildenafil	...	31±6	...	...	31±5	...
P		0.04			0.027	
Distance/exercise time						
Placebo	...	0.204±.038	...	...	12.3±3.4	...
Sildenafil	...	0.200±.029	...	...	13.7±3.2	...
P		NS			0.003	
Norepinephrine, pg/mL						
Placebo	1210±1211	1604±1922	...	620±448	2890±3198	...
Sildenafil	1116±1012	1759±1501	...	624±268	2557±2555	...
P	NS	NS		NS	NS	

Values are mean±SD. Ve indicates pulmonary ventilation; V_{O_2}, oxygen consumption; basal, upright position immediately before the exercise; recovery, 1 minute after stopping the exercise; distance in 6′WT (miles); exercise time in minutes; V_{CO_2}, carbon dioxide production; Slope Ve/V_{CO_2}, the regression coefficient of the linear regression between the Ve and V_{CO_2}; VD/VT, a functional estimate of dead space described as a fraction of tidal volume (estimates the degree of matching of ventilation to perfusion during exercise); Ve/V_{CO_2}, ventilatory equivalent for CO_2, used for noninvasive guide to pulmonary VA/Q (ventilation/perfusion) unevenness; Ve/V_{O_2}, ventilatory equivalent for O_2, used for noninvasive guide to pulmonary VA/Q unevenness.

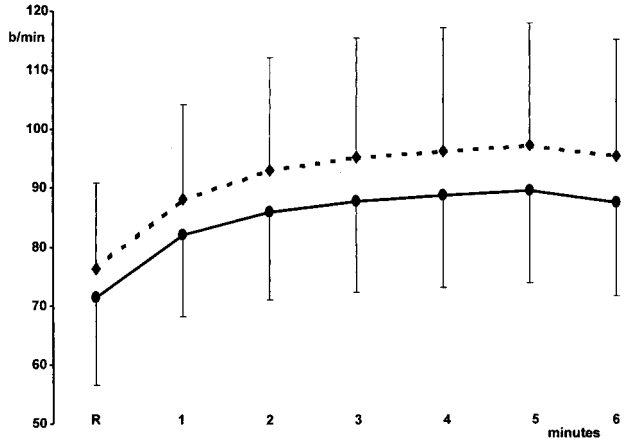

Figure 1. Sildenafil (solid line) attenuated the HR increment during the 6′WT ($P=0.003$) (solid line) versus placebo (dashed line). R indicates resting upright position before the exercise.

It estimates each test's regression coefficients and *y* intersections from linear regression curves plotting time versus HR.

Results

Patients underwent the 6′WT 75±23 minutes after placebo and 76±20 minutes after sildenafil (P=NS). The ETs were performed 105±21 minutes after placebo and 114±32 minutes after sildenafil (P=NS). One patient presented syncope and hypotension during the initial ET, and he was excluded. Three patients did not use sildenafil in the second phase because of CHF decompensation not related to sildenafil exercise test (1), wife's fear of cardiac events (1), and a new relationship problem (1).

HR, SBP, and DBP

Sildenafil reduced the HR at rest and at the first minute of the 6′WT recovery phase (Table 2). Sildenafil attenuated the increment of the HR during the 6′WT (Figure 1) ($P=0.003$) (95% CI of the difference, −50.15 to −11.58) and recovery period ($P=0.007$) (Figure 2) and during the ET until the 8th minute ($P<0.0001$) (95% CI of the difference, −64.57 to −23.43) (Figure 3).

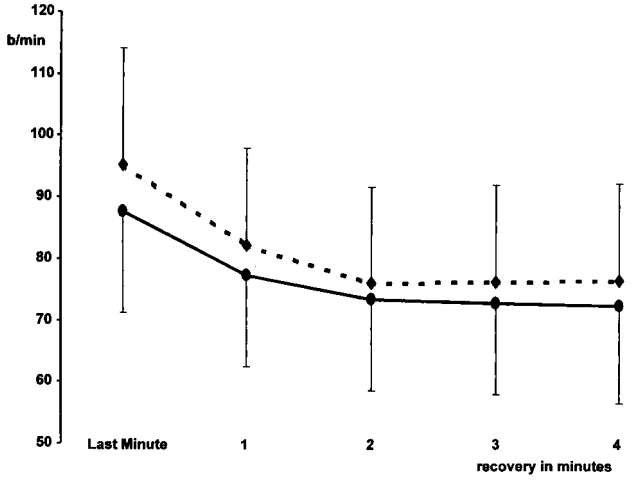

Figure 2. HR was lower during the 6′WT recovery period with sildenafil ($P=0.007$) (solid line) versus placebo (dashed line). Last minute indicates 6th minute of the 6′WT.

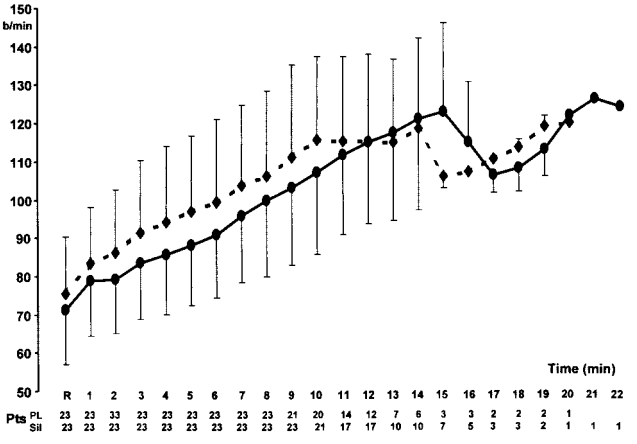

Figure 3. Sildenafil attenuated the HR increment until the 8th minute of the ET ($P<0001$). sil indicates sildenafil treatment (solid line); pl, placebo treatment (dashed line).

No differences were demonstrated in the regression coefficients between sildenafil and placebo (3.63±1.42 and 3.62±1.42, respectively, P=NS) by plotting time of exercise versus HR of ET. Sildenafil reduced the *y* intersection from 79.3±15.6 to 73.8±15.5 ($P<0.0001$) (95% CI of the difference, −7.66 to −3.25), demonstrating parallelism between sildenafil and placebo curves. It is evidence of a persistent sildenafil effect during the ET.

Sildenafil reduced the resting SBP and DBP. Sildenafil treatment did not result in greater reduction in systemic blood pressure in patients receiving nitrates for pulmonary congestion.

Exercise Effects

Sildenafil reduced the Ve/VCO_2 slope during the 6′WT and ET (Table 2). Sildenafil also reduced the Ve/VCO_2 at the ET peak, and a tendency for reduction was observed in the last minute of the 6′WT. Sildenafil increased the ET peak VO_2 and exercise time. No differences were demonstrated in plasma norepinephrine levels during sildenafil and placebo protocols.

Efficacy of Sildenafil in ED

The effective dose of sildenafil for a appropriated erection was 58±30 mg (from 16.3 to 150 mg). In 2 patients, the 50 and 100 mg sildenafil dosages were not effective, and the patients did not increase the dosage.

Use of sildenafil was associated with significantly higher mean scores for most questions of the IIEF except for questions 6, 11, and 12 (Figure 4). The ED Inventory of Treatment Satisfaction results, with a high percentage (≥80%) of A and B answers in all questions with the exception of question 11, suggest a relevant beneficial effect of sildenafil in the satisfaction with ED treatment (Figure 5).

Adverse Effects of Sildenafil and Placebo

The sildenafil ET was stopped because of atypical thoracic pain (1), pain in legs (1), dyspnea (3), fatigue (3), dyspnea associated with discomfort in legs (1), and nonspecific

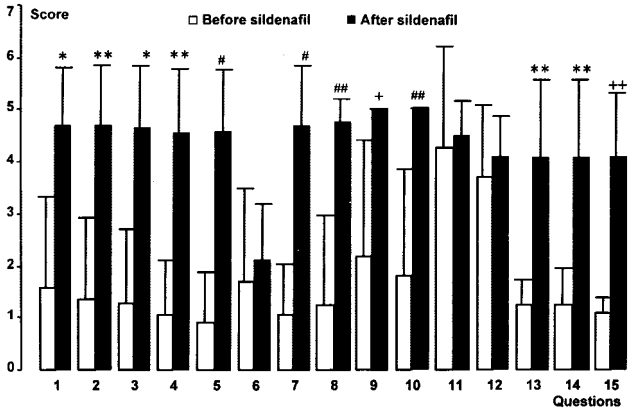

Figure 4. Scores rates of the 15-question IIEF before and with sildenafil use. Sildenafil improved the scores for each question except for questions 6, 11, and 12 (P=NS). *P=0.005; **P=0.004; #P=0.002; ##P=0.10; +P=0.16; ++P=0.003.

tiredness (14) (Table 3). The placebo ET was stopped because of dizziness (1), atypical thoracic pain (1), dyspnea (6), fatigue (2), dyspnea and discomfort in legs (2), discomfort in legs (3), pain in legs (1), and nonspecific tiredness (7).

Discussion

In patients with CHF, sildenafil reduces HR and systemic blood pressure at standing position. Sildenafil attenuated the HR increment and reduced the Ve/V_{CO_2} slope during exercise. Sildenafil increased the maximal exercise capacity, but it was associated with more adverse symptoms, none of which resulted in discontinuation from the study. Sildenafil was well tolerated and effective in improving ED in patients with CHF under multiregimen drugs. Sildenafil did not change the neurohormonal sympathetic activation.

Effects on HR, SBP, and DBP

The resting HR reduction and attenuation of the HR increment during exercise after sildenafil confirm that the L-arginine/nitric oxide/cGMP pathway modulates the pacemaker activity of sinoatrial node cells in CHF patients.[13] Multiple mechanisms can be involved, including the following: (1) NO-cGMP pathway activity reducing norepinephrine release from intracardiac sympathetic neurons; (2) NO-cGMP pathway activity facilitating acetylcholine release and bradycardia[14]; (3) activation by sildenafil of central nervous system NO-cGMP pathway producing prominent dose-related depressor and bradycardic effects and reducing sympathetic nerve activity[15]; (4) increase of cGMP levels by sildenafil acting in the myocardium[16]; cGMP mediates inhibition of Ca^{2+} influx by means of L-type sarcolemmal voltage-dependent Ca^{2+} channels[17,18]; and (5) sildenafil inhibition of the positive chronotropic response to β-adrenergic stimulation during exercise through reduction of β-receptor density and increment in levels of G_i proteins. A direct cardiac and electrophysiological effect of sildenafil was demonstrated only in several-fold higher plasma concentrations than those encountered in clinical practice.[19] Also, myocardial expression of PDE5 has not been shown in radiolabeled histological myocardial tissue preparations.[20–22] However, a direct cardiac effect of sildenafil in remodeled human myocardium in CHF has not been investigated.

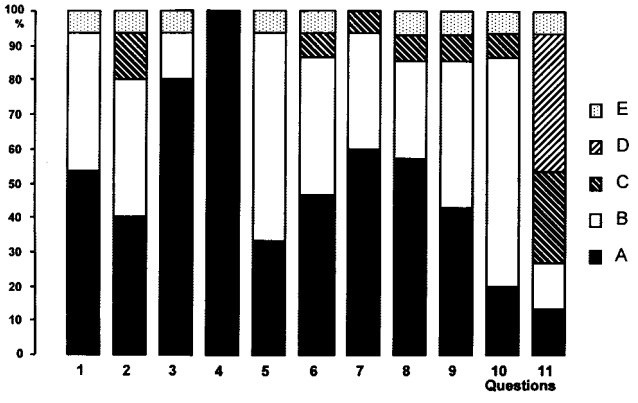

Figure 5. Satisfaction rate after ED treatment with sildenafil assessed using the answers to 11 questions of the Index of Satisfaction of ED Treatment. The results were shown in percent of patients in each question, with answer from A (best) to E (worst).

TABLE 3. Effects, Symptoms, and Adverse Effects After Sildenadil Versus Placebo

Symptoms or Adverse Effect	Placebo (n=12)	Sildenafil (n=22)
First phase		
Maximal exercise	n=10	n=16
Tolerated dizziness	2	2
Tolerated facial flushing	2	3
Atypical thoracic pain	3	3
Inappropriate erection	1	1
Nausea	2	1
Myalgia	3	1
Dyspnea	...	3
Fatigue in legs or respiration	3	...
Fatigue in legs	...	3
Headache	...	2
Pain in legs	...	1
Abnormal vision	1	1
Increment in general fatigue	...	2
Dyspepsia	1	...
Six-minute walking test	n=2	n=3
Nausea	2	2
Fatigue	...	1
During 24 hours after tests	n=1	n=8
Inappropriate erection	...	4
Nocturnal erection	1	3
Abnormal vision	...	1
Second phase	...	n=3
Tolerated facial flushing	...	1
Tolerated headache	...	1
Transient arm paresthesia	...	1

Some patients had >1 adverse effect or symptom. n indicates total of patients. The symptoms during the second phase were transitory and nonrepetitive.

The modest asymptomatic reduction in resting systemic arterial pressure after sildenafil could be explained by an increase in vascular c-GMP as a consequence of a PDE5 inhibition.[23] The sildenafil effects on heart rate could limit the expected compensatory increase in cardiac output in response to vasodilatation.[24,25] Normalization of blood pressure during exercise could be explained by exertional responses, including cardiac output and heart rate. Then, hypotension as an adverse effect of sildenafil during sexual activity is unlikely. Sildenafil had no direct synergistic interaction with nitrates in two cases; however, additional studies are necessary to clarify the interaction between nitrates and sildenafil in CHF.

Effects on Exercise

The improvement in maximal exercise capacity could be explained by an increment in muscular blood flow attributable to arterial vasodilatation associated to an increase in cardiac output as demonstrated in primary pulmonary hypertension and after L-arginine infusion in CHF.[13,26] An isolated sildenafil action in pulmonary NO-cGMP pathway is unlikely based on absence of improvement in exercise capacity during NO inhalation.[27,28]

PDE5 inhibition seems not to influence the 6′WT, or, alternatively, the beneficial vasodilatation was counterbalanced by the attenuation of HR increment limiting the expected increase in cardiac output. In general, sexual activity with an exercise workload of 3 to 4 METs is similar to mild to moderate intensity exercise.[29] Therefore, the sildenafil use in CHF seems safe during exercise approximating the sexual activity.

The decrease of Ve/V_{CO_2} slope could be explained by reduction of pulmonary physiological dead space during exercise by pulmonary vascular sildenafil effects through the NO-cGMP pathway, as demonstrated with NO inhalation.[28]

Erectile Dysfunction

The improvement in ED demonstrated that sildenafil can change the hemodynamic and endothelial factors involved in erection in CHF under the control of the autonomic nervous system and influenced by multiregimen drugs.[30] Sildenafil was an effective and well-tolerated treatment, with results comparable to those reported in placebo-controlled clinical trials with a broad range of concomitant conditions, where efficacy rates were reported as 63% to 82%.[31]

Limitation of the Study

It was not possible to include during the exercise tests the neuroendocrine sympathetic response achieved in arousal and coitus in a patient real-life setting.[32] However, the arousal/erection per se causes little stress on the cardiovascular system in healthy volunteers, and any experimental or model of research will be by definition an unnatural setting.[33] The observed V_{O_2} during the 6′WT was comparable to the estimated peak V_{O_2} rate during the sexual activity, corresponding to 60% of the subject's maximum achieved V_{O_2}, or 11.7 mL O_2/kg per min.[34] Our data may not be true for extramarital sexual activity, but this sexual activity is not the most common.

Clinical Implications

Our results suggest that it is feasible to apply the exercise testing on clinical basis to determine whether CHF patients with ED can achieve the physiological workload associated with sexual intercourse to improve the assessment of the adverse event risk after sildenafil intake, especially to guide physicians in high-risk conditions. The sildenafil stress test could prevent and distinguish potential causes of sildenafil adverse effects, such as coincidental, reporting bias, exercise enabler effect, excitement enabler effect, a precipitous drop in blood pressure in multidrug treatment, synergistic decreases in blood pressure with NO donors, and a coronary steal phenomenon.

The successful treatment of ED in CHF could not only improve sexual relationships but overall quality and success of CHF treatment. The advent of this effective treatment allows most men with stable CHF and ED to tentatively resume sexual activity.

Conclusion

The reduction of heart rate could decrease the myocardial oxygen consumption during exercise with intensity similar to sexual activity that could be important for ischemic cardiomyopathy. The acute effect of oral sildenafil on resting blood pressure and heart rate is not likely to be clinically significant in patients with stable CHF taking concomitant multiregimen drugs, and it was normalized during the exercise.

Sildenafil can become an important tool to resolve the challenge of concomitant improvement in relevant aspects of quality of life without changes in multiregimen drugs necessary to improve prognosis in CHF.

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