Use of Sildenafil for Safe Improvement of Erectile Function and Quality of Life in Men With New York Heart Association Classes II and III Congestive Heart Failure

A Prospective, Placebo-Controlled, Double-blind Crossover Trial

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Background: Erectile dysfunction (ED) is common in patients with congestive heart failure (CHF) and is often associated with symptoms of depression. Although sildenafil citrate, a phosphodiesterase 5 inhibitor, is effective in treating ED, its use is considered a relative contraindication in CHF. We hypothesized that sildenafil is a safe and effective treatment for ED in patients with New York Heart Association classes II and III CHF and that treatment of ED will improve symptoms of depression and enhance perceived quality of life.

Methods: We studied 35 patients in a prospective, placebo-controlled, crossover trial for 12 weeks. Inclusion required a history of chronic ED and absence of ischemia (negative results from exercise stress test or nuclear perfusion scan) or nitrate use. The tolerability of sildenafil citrate was established by monitoring the ambulatory blood pressure for 4 hours after a single 50-mg dose. Improvement in ED, the primary end point, was assessed using the International Index of Erectile Function. The effect of improved erectile function on quality of life and mood was assessed using the Minnesota Living With Heart Failure Questionnaire, the Beck Depression Index, and the Center for Epidemiological Studies–Depression Scale.

Results: Sildenafil caused a mean ± SEM asymptomatic decrease in blood pressure of 6 ± 3 mm Hg, and no patient experienced symptomatic hypotension or other significant adverse effects. Sildenafil improved the International Index for Erectile Function (P < .001) and both sets of depression scores. The Living With Heart Failure Questionnaire index also improved with sildenafil (P = .02).

Conclusion: Sildenafil is a safe and effective treatment for ED in men with New York Heart Association classes II and III CHF and provides relief of depressive symptoms, explaining an improvement in the perception of quality of life.

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Erectile Dysfunction (ED) is the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance. Its prevalence is 52% in men aged 40 to 70 years. Normal erection involves an arousal-induced release of nitric oxide from nonadrenergic-noncholinergic nerves and endothelium. The resulting activation of soluble guanylate cyclase increases cyclic guanosine monophosphate (cGMP) levels in penile arteries and cavernosal smooth muscle cells; cGMP leads to vasodilatation in large part through a protein-phosphokinase G–mediated activation of large-conductance calcium-sensitive potassium channels. Sildenafil citrate enhances erectile function by inhibiting phosphodiesterase 5 (PDE5), which rapidly degrades cGMP as it is formed. The mechanism of normal erection seems to be compromised with ageing and vascular disease. Disruption of the nitric oxide–cGMP system is common in vascular disease, one of the most common underlying mechanisms in ED of organic etiology. The association between vascular disease and ED is so strong that ED has been proposed to be a marker of cardiovascular disease. In a cohort of clinic outpatients with congestive heart failure (CHF), three quarters reported compromised libido and erectile function. A serious relation exists between sexual function and the results of the 6-minute walk (r = 0.32) or New York Heart Association (NYHA) functional class (r = 0.21). This strong association can be explained because, in addition to vascular disease, patients with CHF have other predisposing factors for ED, specifically polypharmacy and depression. Several drugs used in the treatment of CHF, such as β-blockers, are associated with ED.

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poor prognosis and the significant impact of CHF symptoms in everyday life, patients with symptomatic CHF suffer from depression, a well-known predisposing factor of ED.9,10 Conversely, ED itself causes depression, and may further compromise the quality of life in patients with CHF. Depression, ED, and cardiovascular disease have been proposed to form a mutually reinforcing triad.11

Despite the high incidence of ED in patients with CHF, the effectiveness and the impact of ED treatment in this patient population are not known. This is unfortunate because the use of sildenafil has revolutionized the treatment of ED, with efficacy rates exceeding 69%,12,13 in patients without cardiovascular disease. The reports of deaths associated with the use of sildenafil soon after the release of sildenafil14 contributed to the hesitation of physicians to prescribe this drug to patients with significant cardiovascular disease. However, it is now known that sildenafil does not increase cardiovascular disease mortality.15 In patients with stable coronary disease, sildenafil enhances coronary flow reserve16 and does not worsen cardiac function under exercise conditions.17 The main contraindication for the use of sildenafil is the interaction between sildenafil and nitrates. This interaction can lead to profound hypotension and is avoidable by education and by not prescribing sildenafil to patients with evocable ischemia on a conventional exercise stress test. The American College of Cardiology and American Heart Association released statements suggesting that the use of any form of nitrates and the inability to perform 5 metabolic equivalents of exercise without evidence of ischemia are considered absolute contraindications for the use of sildenafil.18 Caution was also raised for the potential interaction, resulting in hypotension, of sildenafil with vasodilators commonly used in the treatment of CHF. In this consensus statement, CHF was listed as a relative contraindication for the use of sildenafil.13 However, a significant percentage of patients with CHF do not have active ischemia and do not require the use of nitrates, and could therefore be candidates for treatment of ED with sildenafil.

We hypothesized that in patients with moderately severe CHF who undergo appropriate screening and selection, sildenafil is safe and effective. To study safety, we used ambulatory blood pressure monitors and observed the patients for several hours after the intake of sildenafil. To study efficacy, we used the standard International Index for Erectile Function (IIEF)18 to compare the effects of sildenafil vs placebo in patients with NYHA classes II and III CHF in a prospective crossover trial. In addition to its effectiveness in treating ED, we also hypothesized that sildenafil would be useful in decreasing symptoms of depression that stem from lack of a satisfactory sex life in these patients. We used 2 different and well-validated indices of depression: the Beck Depression Index (BDI)10-22 and the Center for Epidemiologic Studies–Depression Scale (CES-D).23-26 To determine whether the treatment of ED and decrease in ED-related depressive symptoms in these patients would improve quality of life and lead to an improvement in the perception of their disease, we used the Minnesota Living With Heart Failure Questionnaire (LihFE).27-30

The human ethics board of the University of Alberta, Edmonton, approved the protocol, and each participant signed an informed consent form.

**SCREENING**

Initial contact was made by a letter offering participation to men with NYHA classes II and III CHF who were not taking nitrates in our heart function clinic. The 41 patients who responded underwent further screening and were excluded from the study if they (1) had symptomatic hypotension or systolic blood pressure of less than 80 mm Hg at baseline, (2) had a positive stress test result within the past year or a history consistent with ongoing myocardial ischemia, (3) were receiving psychotropic therapy (anxiolytics or antidepressants), (4) had significant valvular disease, and (5) had a recent history of alcohol and/or other drug abuse. Three patients were excluded based on those criteria. The remaining 38 patients underwent further screening with an exercise stress test (Bruce protocol) to ensure adequate functional capacity (>5 metabolic equivalents, a level of cardiovascular fitness necessary for most sexual activity1) and exclude ischemia. Overall, 3 patients were excluded because they had active ischemia. Four patients failed to achieve the target heart rate (85% of maximal [220 beats/min – age of participant]), and 21 patients had abnormal findings on the baseline electrocardiogram that compromised the interpretation of the exercise electrocardiogram (atrial fibrillation [n=13], left bundle branch block [n=5], and nonspecific ST-T wave changes [n=3]). Among these 25 patients who required further assessment to exclude coronary ischemia, 18 underwent nuclear imaging studies and 7, dobutamine stress echocardiogram (n=7). Evidence of an old myocardial infarction was found in 18 patients, but none had reversible ischemia. Thirty-five patients entered the study.

**STUDY DESIGN**

The study was a 12-week randomized, placebo-controlled, crossover study. The randomization to placebo vs sildenafil followed successful completion of the safety protocol.

**SAFETY PROTOCOL**

After a single 50-mg dose of sildenafil, the patients were observed in the clinic for 5 hours under ambulatory blood pressure monitoring (Del Mar Pressurimeter model P6; Del Mar Avionics, Irvine, Calif). The blood pressure and heart rate were recorded at 15-minute intervals, and data were analyzed at the end of the session. All patients took their morning medications before 8 AM, and all studies were performed from 10 AM and 2 PM. Patients were excluded from the study if they manifested a fall in mean arterial pressure (seated, at rest for 3 minutes) of more than 10% that was sustained for more than 30 minutes or was associated with hypotensive symptoms (dizziness, angina, and diaphoresis).

**EFFICACY PROTOCOL**

Patients were randomized to 1 of the following 2 arms: placebo for the first 6 weeks with a switch to sildenafil citrate (50 mg) at the midpoint, or sildenafil for the first 6 weeks with a switch to placebo thereafter. The appearance of the placebo pills was similar but not identical to that of the sildenafil pills in shape and color, and they were supplied by the pharmacy services of the University of Alberta Hospitals. Patients were instructed to ingest the medication approximately 1 hour before antici-
Previously, the use of sildenafil in CHF patients was limited by concerns regarding the cardiovascular and pulmonary risks of its use, particularly with regard to increased systolic blood pressure and potential exacerbation of heart failure symptoms. However, it has been demonstrated that sildenafil is well tolerated in CHF patients when used in appropriately conservative dosing regimens. It is a selective phosphodiesterase-5 inhibitor that increases intracavernosal tissue cyclic guanosine monophosphate levels, leading to smooth muscle relaxation and increased veno-occlusive pressure, facilitating tumescence and subsequent erectile function.

METHODS

Patients

From March 2000 through August 2001, patients aged 18 to 80 years, meeting the New York Heart Association (NYHA) class II or III criteria for CHF, were recruited from the Cardiovascular Center at Washington University Medical School. The inclusion criteria were a history of CHF for >6 months, NYHA class II or III, left ventricular ejection fraction <35%, and history of nocturnal dyspnea. Exclusion criteria included acute decompensation of CHF within 2 weeks, known or suspected COVID-19, and any medical condition contraindicating the use of sildenafil, such as impaired renal function, bleeding diathesis, severe hypotension, and severe anemia. A total of 28 patients from the Cardiovascular Center were enrolled in this study. All patients gave written informed consent for participation in this study, which was approved by the Washington University Institutional Review Board.

Study Protocol

All patients were instructed to use the drug as needed for sexual activity, and the drug was available in 50-mg tablets. The medication was to be ingested 1 hour before sexual activity and was not to be taken more than once a day. The dosing regimen entailed a 50-mg dose for 2 weeks, followed by a 100-mg dose for 2 weeks. The average time before effect was noted at the first administration of the drug. The following assessments were performed on days 7 and 14 of each dosing period:

- A complete medical history and physical examination
- Echocardiogram
- Serum creatinine level
- Plasma sodium level
- Complete blood count
- Baseline hemodynamic measurements
- Safety assessment

Patient Characteristics

The patient characteristics are shown in the Table. The mean age of the patients was 60 ± 2 years, and the mean weight was 85 ± 2 kg. The mean serum creatinine level was 113 ± 5 mg/dL, and the mean ejection fraction was 26 ± 1%.

Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, mean ± SEM, y</td>
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</tr>
<tr>
<td>Serum creatinine level, mean ± SEM, mg/dL</td>
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</tr>
<tr>
<td>Ejection fraction, mean ± SEM, %</td>
<td>26 ± 1</td>
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<tr>
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<td>25 (71)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>21 (60)</td>
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<tr>
<td>Idiopathic</td>
<td>9 (26)</td>
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<tr>
<td>Other</td>
<td>5 (14)</td>
</tr>
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<td>Hypertension</td>
<td>24 (69)</td>
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<tr>
<td>Diabetes</td>
<td>9 (26)</td>
</tr>
<tr>
<td>ACE</td>
<td>33 (94)</td>
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<tr>
<td>Diuretic</td>
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<td>ASA</td>
<td>23 (66)</td>
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<tr>
<td>Coumadin</td>
<td>22 (63)</td>
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<tr>
<td>Digoxin</td>
<td>22 (63)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
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<tr>
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<td>9 ± 1</td>
</tr>
<tr>
<td>BDI</td>
<td>9 ± 1</td>
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<td>CES-D</td>
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<tr>
<td>LihFE</td>
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†Indicates erectile function domain (questions 1-5 and 15).

RESULTS

Results of power calculations indicated that a sample size of 24 would be needed to detect a difference in the primary outcome measure of 1 point on the IIEF with a power of 0.80 and a 2-sided type I error of 0.05. The mean hemodynamic data (heart rate and blood pressure) for 4 hours after a 50-mg dose of sildenafil citrate are shown in Figure 1. Mean heart rate and blood pressure did not decrease significantly after the ingestion of sildenafil. At no time did the mean arterial pressure decrease.

Figure 1. Mean heart rate and blood pressure for 4 hours after a 50-mg dose of sildenafil citrate.

CLINICAL CHARACTERISTICS

All participants completed the 12-week protocol. The baseline hemodynamic measurements, basic clinical variables, and baseline scores in all indices used are outlined in the Table.

SAFETY

The mean hemodynamic data (heart rate and blood pressure) for 4 hours after a 50-mg dose of sildenafil citrate are shown in Figure 1. Mean heart rate and blood pressure did not decrease significantly after the ingestion of sildenafil. At no time did the mean arterial pressure decrease.
crease more than 10% from the baseline level. Furthermore, the heart rate did not significantly change during the 4 hours after the ingestion of the initial dose of sildenafil. No patient reported any adverse effects, including dizziness, weakness, nausea, hot flushes, or visual and color vision disturbances.

EFFICACY

Erectile Function

The erectile function scores at baseline and 6 and 12 weeks for the placebo-sildenafil crossover protocol are shown in Figure 2. Erectile function significantly improved at week 4 for those who first received sildenafil (P < .001). With the crossover to placebo, their scores returned to baseline. The group that received placebo initially did not show statistically significant improvement of their erectile function scores (P = .67) until they received sildenafil during the latter part of the study (P < .001). The overall response to sildenafil did not differ between the 2 groups (sildenafil first vs placebo first; P = .98).

Depression

Figure 3A illustrates the scores measured using 2 separate indices. All indices showed improvement during the period that sildenafil was used, in contrast to placebo.

Quality of Life

Figure 3B shows the scores using the LihFE index at baseline and after sildenafil and placebo treatments. In the sildenafil-first group, the use of sildenafil caused a significant decrease in the score (P = .008), and switching to placebo caused an increase in the score (P = .04) that reached the baseline levels. In the placebo-first group, there was no change in the score until the patients received sildenafil in week 4, which again caused a decrease in the score (P = .003 vs baseline; P = .02 vs placebo). Again, there was no difference in the responses to the LihFE questionnaire, whether the patients received placebo or sildenafil first.

ADVERSE EVENTS

There were no significant hemodynamic effects during the course of the study. No participant was hospitalized during their participation in the study or during the 30 days after participation. Two deaths were reported to study personnel, one 4 months and the second 5 months after the end of the patient’s participation in this study. Atrial fibrillation developed in 2 patients during the trial period, and neither was taking sildenafil at the time the arrhythmia was detected. These dysrhythmias were noted at 2 and 4 weeks of the placebo phase of the study. The atrial fibrillation was asymptomatic on both occasions and was discovered only on electrocardiograms obtained at routine visits. One patient experienced worsening symptoms of heart failure (dyspnea and limited exercise tolerance) during the fifth week of the placebo phase (placebo-first group), thought to be due to volume overload.

COMMENT

The major finding of this study is that sildenafil is safe and effective in treating ED in men with moderate (NYHA classes II-III) heart failure who undergo appropriate screening. There was also a remarkably clear beneficial effect of treating ED for symptoms of depression and quality of life in this CHF cohort. To our knowledge, this is the first report on the safety and efficacy of this commonly used drug in a population with moderately severe CHF. It is also one of few studies to examine the potentially beneficial effect of treating ED in patients with advanced cardiovascular disease. Although the use of sildenafil in patients with CHF at present is considered a relative contraindication, our findings suggest that this drug can be prescribed in patients with moderately severe CHF, provided that they are not taking nitrates and they have no evidence of active myocardial ischemia.

SAFETY IN NYHA CLASSES II AND III CHF

The primary safety end point used to ensure that these patients could tolerate sildenafil, a weak vasodilator, was the absence of hypotension for 4 hours after a single ingestion of 50 mg of sildenafil citrate. Using an ambulatory recording system, we were able to measure blood pressure and heart rate at multiple points. We showed that at no point did the blood pressure drop more than 10% from baseline, although there was a small decrease at 60 minutes that was not associated with any symptoms.

Our findings are in agreement with those reported by Vardi et al, who used ambulatory blood pressure monitoring for 6 hours after sildenafil use in 22 hypertensive and 27 normotensive patients. These authors reported a small and asymptomatic decrease in the mean arterial pressure (mean decrease, –5.3 mm Hg) that did not differ between the normotensive and hypertensive
groups. Arruda-Olson et al\textsuperscript{17} studied the hemodynamic effects of sildenafil in 105 men with known or probable coronary artery disease. They reported a small and asymptomatic decrease in the systolic blood pressure measured once, 1 hour after oral sildenafil citrate administration (50 or 100 mg) (mean change of $-7$ vs $-2$ mm Hg in the placebo group; $P < .001$) but not in the diastolic blood pressure ($P < .16$) or the heart rate ($P < .08$). In that study, the mean ejection fraction of the patients studied was 60\%, and thus the results could not be extrapolated in patients with significant left ventricular dysfunction.

The decrease in blood pressure that we reported was associated with a small increase in heart rate (Figure 1). This increase in heart rate is likely due to the decrease in blood pressure. Alternatively, sildenafil can cause an increase in heart rate because it has been proposed to cause an increase in sympathetic activation. Phillips et al\textsuperscript{34} recently reported that in 14 healthy volunteers, a single oral dose of sildenafil citrate (100 mg) caused a significant increase in muscle sympathetic nerve activity and plasma norepinephrine levels. Despite this sympathetic activation, the blood pressure, heart rate, and forearm vascular resistance did not change in these healthy volunteers. Senzaki et al\textsuperscript{15} have shown that the cGMP modulation of $\beta$-adrenergic stimulation in healthy dog myocardium is blunted in dogs with heart failure, perhaps due to alterations in PDE5 localization and reduced synthesis. Whether the PDE5 expression and function are altered in the hearts of humans with CHF remains unknown.

The peak biological and hemodynamic effects of sildenafil are known to occur from 50 to 60 minutes, and this has been confirmed in several recent studies by our group\textsuperscript{36} (REF) and others (REF—the circulation coro

Finally, the minimal hemodynamic effects that we report may also be a result of the expected action of background CHF medications, because all of the studies were performed in the morning, and at a time coinciding with the peak effect times of antihypertensive therapy and diuretics (2–3 hours). This is important because in many studies, the medications are held the morning of the study. Our study suggests that sildenafil is safe to prescribe to patients taking all the currently indicated medications for CHF (Table).

**EFFECTIVENESS IN TREATING ED IN PATIENTS WITH CHF**

The efficacy of treatment was shown by the improvement of the IIEF scores during the sildenafil arm of the trial (Figure 2). The efficacy of sildenafil in treating ED in the general population exceeds 80\%,\textsuperscript{12,38,39} but this has never been studied in CHF. In our study, only 1 patient had no response at all to sildenafil (Figure 2).

The IIEF scores were not significantly altered by placebo in either of our study groups. This is in agreement with recent large trials showing that placebo did not alter the erectile function domain of the IIEF.\textsuperscript{32} We do not know what percentage of our study patients had mainly organic vs mainly psychogenic ED, because invasive erectile function studies were not performed. However, given the very high prevalence of endothelial dysfunction and overt vascular disease in CHF, it is likely that most of our study participants had a major organic component in their ED.

Although the placebo pill was not identical to the sildenafil pill, it was very similar in shape and color. Because sildenafil has been reported to cause hot flashes, it is possible that patients aware of this adverse effect would be able to identify the sildenafil pill. However, none of the patients reported hot flashes in the sildenafil group, and only 2 patients in our study had previously used sildenafil.

Furthermore, the crossover design of our study strengthens our interpretation of the data and limits potential weaknesses in the randomization and blinding process. As expected, the IIEF scores after sildenafil ingestion returned to baseline during the placebo phase of the study (Figure 2). In addition to the IIEF, this return to baseline after the placebo phase was observed in all of the indices used (ie, the CES, BDI, and LihFE) (Figure 3).

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**Figure 3.** Depression (A) and quality-of-life scores (B) at baseline and 6 and 12 weeks for the placebo–sildenafil citrate crossover protocol. BDI indicates Beck Depression Inventory; CES-D, Center for Epidemiological Studies–Depression Scale; LihFE, Minnesota Living With Heart Failure Questionnaire.
The assessment of the initial hemodynamic variables in combination with the erectile improvement indicates that the vasodilatory effect of sildenafil primarily affects the penile circulation during arousal, without significant impact on the systemic blood pressure.

DECREASE IN DEPRESSIVE SYMPTOMS AND IMPROVEMENT IN QUALITY OF LIFE

A potentially important benefit of effective treatment of ED in these older, chronically ill patients with CHF is the observed improvement of quality of life and relief of depressive symptoms. Indices assessing depression and perceptions of quality of life of those living with heart failure showed significant improvement in scores during the period of sildenafil treatment and reversion to basal levels during the placebo phase of the study (Figure 3). The beneficial effects of treatment of ED with sildenafil in regard to depressive symptoms are in agreement with previously reported studies, using the same and different depression indices. In a placebo-controlled study, Seidman et al reported that sildenafil effectively treated ED, and this was associated with improvements in depression and quality-of-life indices. These authors used the Hamilton Depression Rating Scale. We used 2 separate self-reported instruments to study depression in our study, both of which have been well validated in multiple patient groups, including elderly patients, outpatients, and populations with chronic disease. To our knowledge, our study is the first to study the association between the treatment of ED and depression.

Phosphodiesterase inhibitors have been used in the treatment of depression. For example, rolipram, a PDE4 inhibitor, has been used to treat depression, perhaps a reflection of the high expression of PDE4 in the brain. Although PDE5 is also expressed in the brain, only limited data suggest any effects of sildenafil on brain function.

Although the effects on the depression and quality-of-life indices are interesting and cited as a secondary endpoint in our study, it should not be assumed that the effective treatment of ED cures depression. Depression in this population subsides and exacerbates with the natural progression of heart failure symptoms. The etiology of depression is often multifactorial, and the effective treatment of ED in these patients addresses but one cause. Nonetheless, there was a clear correlation between effective treatment of ED and perceived quality of life.

Effective treatment of ED with sildenafil has been shown to improve several indices of quality of life in the general population and in patients with chronic illness such as spinal cord injury. We show that quality of life improved by treating ED in patients with CHF, one of the most common chronic diseases, by using the LibHE, an index developed to assess quality of life specifically in CHF. We speculate that the mechanism for this improvement is the decrease in depressive symptoms.

In conclusion, this study provides new evidence that it is safe and effective to treat men with ED and moderate heart failure with sildenafil. It is necessary to complete baseline safety measurements to ensure adequate physical fitness for sexual activity and absence of myocardial ischemia that would necessitate nitrate use. Sildenafil is a reasonable alternative to the invasive solutions of the past (e.g., penile implants, intracavernosal injections of vaso-dilators) for many CHF patients with ED.

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