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Original Article

Effect of sildenafil on stable chronic heart failure: a prospective randomized-controlled clinical trial

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Abstract

Background
Patients with systolic heart failure (HF) who develop secondary pulmonary hypertension have reduced exercise capacity and increased mortality compared with HF patients without pulmonary hypertension. A defective nitric oxide signaling is involved in left ventricular (LV) diastolic abnormalities and remodeling. Phosphodiesterase type 5 inhibition, by blocking degradation of nitric oxide second-messenger cyclic guanosine monophosphate, might be beneficial.

Aim of the study
In our study, we tested the effects of phosphodiesterase type 5 inhibition (sildenafil) on LV ejection fraction, diastolic function, pulmonary artery pressure, and clinical status.

Patients, methods, and results
One hundred HF patients (New York Heart Association classes II–IV) were assigned randomly to placebo or sildenafil (50 mg three times per day) for 6 months, with assessment at the first and 6 months of LV ejection fraction, diastolic function, pulmonary artery systolic pressure, and exercise performance (using 6 min walk test). The two groups studied were similar in terms of age, sex distribution, etiology of cardiomyopathy, the prevalence of chronic atrial fibrillation, LVEDD, LA dimensions, and pulmonary artery pressure as well as drug therapy is given to each group all through the study period ($P > 0.05$). After 1 month of therapy, there was a significant increase in LV ejection fraction and a decrease in pulmonary artery systolic pressure in the sildenafil group ($P < 0.01$ and <0.001). In the placebo group, there was no significant change in the LV ejection fraction and pulmonary artery systolic pressure ($P > 0.05$). Doppler-derived variables of LV diastolic function improved significantly in the sildenafil group ($P < 0.05$), whereas in the placebo group, there was no significant change in the Doppler-derived diastolic parameters ($P > 0.05$). Over 6 months of therapy and follow-up, LV ejection fraction increased from 31.5 ± 5.4 to 36.4 ± 3.5 and the difference was not significant between the two groups ($P > 0.05$), whereas in the sildenafil group, ejection fraction % increased significantly from 30.6 ± 4.5% at baseline to 45.6 ± 5.4% ($P < 0.001$). There was no significant change in the placebo group in the pulmonary artery systolic pressure (PASP) ($P > 0.05$), whereas in the sildenafil group, it decreased significantly from 48.3 ± 17.7 to 28.4 ± 6.4 mmHg ($P < 0.001$). Diastolic measures of LV function showed a sustained improvement after 6 months of sildenafil. The transmitral E wave velocity, A wave velocity, E/A ratio, and isovolumic relaxation time decreased from baseline through 6 months (all $P < 0.01$), which indicates an improvement in LV diastolic function and a decrease in LV filling pressure. Changes observed at 6 months after sildenafil were significantly different compared with the placebo group (all $P < 0.01$). The 6 min walking distance showed sustained improvement after 6 months of sildenafil therapy. Also, in the placebo group, there was a significant increase in the walking distance for 6 min. However, the walking distance in the sildenafil group was significantly higher than that of the placebo group, P value less than 0.001.

Conclusion
In patients with HF, long-term use of sildenafil was well tolerated. This therapeutic regimen (50 mg three times per day) promoted a sustained significant improvement in LV systolic and diastolic function properties in comparison with placebo.

Keywords: Chronic heart failure, secondary pulmonary hypertension, sildenafil

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Introduction

Heart failure (HF) is a significant health care concern that is evolving to epidemic proportions [1]. 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 [2], and NO overexpression may represent a desirable therapeutic target.

Very few studies have investigated whether cardiac function and diastolic left ventricular (LV) function may be a target of chronic phosphodiesterase type 5 (PDE5) inhibition, and any improvement in diastolic function is associated with an effect on the clinical and symptomatic improvement of HF. Accordingly, the primary endpoints of our study were the assessment of a drug-induced beneficial effect on LV diastolic function and chamber dimensions as an objective measurement of the beneficial effect.

Aim of the study

This study aimed to evaluate the effect of the PDE5 inhibitor (sildenafil) on systolic and diastolic LV function in patients with chronic HF.

Patients and methods

Study and control patients

Patients who attended the outpatient clinic at the National Heart Institute, Giza, Egypt, were enrolled. A total of 100 patients with systolic HF (ejection fraction ≤40%) were enrolled over a 6-month period. The average duration of HF disease was 24 ± 6 months.

Inclusion criteria

(1) Provision of consent to participate in the study after detailed information on benefits and risks.
(2) Clinical stable conditions defined as no changes in HF regimens or hospitalization for 6 months before study entry.
(3) Presence of LV diastolic dysfunction determined by Doppler analysis.

Exclusion criteria

Patients were not recruited if they could not perform a 6 min walk test, had resting systolic blood pressure less than 110 mmHg, had received therapy with nitrate preparations, used LV assist devices, had a history of sildenafil intolerance, and had significant lung or valvular diseases, neuromuscular disorders, or peripheral vascular disease. Participants were not involved in any physical training program for at least 6 months before study initiation; all patients were symptomatic during exercise and limited by breathlessness and muscle fatigue; and their current drug HF treatment was stable and adherent to guidelines. Thirty percent of the patients in the placebo group and 35% of the patients in the sildenafil group had previously used a PDE5 inhibitor occasionally for erectile dysfunction and did not report any side effects. All participants provided their written consent to the study after detailed information was provided.

Echocardiography

An expert echocardiographer carried out the echocardiographic analysis by transthoracic echocardiography with a GE, GE Healthcare, United states, Georgia Vivid 5 ultrasound machine using a 2.5–5.0 MHz probe. Standard M-mode, 2D, and Doppler blood flow measurements were performed according to the current American Society of Echocardiography Guidelines 20 Chamber dimensions were obtained using standard procedures [3].

Septal and posterior wall thickness, LA, and LV end-systolic and end-diastolic dimensions were obtained from the parasternal long-axis view. LV ejection fraction, the end-diastolic volume index, and the end-systolic volume index were evaluated using the Simpson method.

6 mi walking distance

Following a standardized protocol (3–5, 6, 14), participants walked up and down a 50 m hallway for 6 min on the basis of instructions to cover as much distance as possible. The distance completed after 6 min was recorded.

Study protocol

This was a randomized, placebo-controlled trial. Eligible patients were assigned randomly to receive placebo or oral sildenafil 50 mg three times per day in addition to their baseline treatment.

The trial duration was 6 months. Symptoms were recorded, and the current therapy prescribed by the referring physician was maintained. After routine laboratory work, patients underwent Doppler echocardiography. After 1 month, the echocardiographic examination was repeated and the results were recorded.

After 48 h, patients were asked to visit the hospital for evaluation of the side effects of sildenafil or intolerance to the prescribed doses. No patient was excluded after 48 h of administration of sildenafil.

Patients were followed up monthly for 6 months; clinical, echocardiographic study, and 6 min walking distance were assessed at the end of the follow-up period.

Statistical analysis

Differences in patient baseline frequencies were compared using the χ^2 test and Fisher exact test analysis. Values are expressed as mean ± SD. A P value of less than 0.05 was considered significant.

Results

The trial included 100 patients aged between 38 and 65 years, with a mean of 56 ± 10.9 years, in stable clinical condition (New York Heart Association classes II–III) with ischemic, idiopathic, or hypertensive cardiomyopathy. All patients completed the clinical trial treatment phase. The study was carried out in the period from February 2014 to September 2015.

Over 6 months of therapy and follow-up, the LV ejection fraction increased from 31.5 ± 5.4 to 36.4 ± 3.5 and the difference was not significant between the two groups ($P > 0.05$), whereas in the sildenafil group, ejection fraction % increased significantly from 30.6 ± 4.5% at baseline to 45.6 ± 5.4% ($P < 0.001$). There was no significant change in the placebo group in the PASP ($P > 0.05$), whereas in the sildenafil group, it decreased significantly from 48.3 ± 17.7 to 28.4 ± 6.4 mmHg ($P < 0.001$) (Table 1).

As shown in Table 1, diastolic measures of LV function showed systematic and sustained improvement after 6 months of sildenafil therapy. The transmitral E wave velocity, A wave velocity, E/A ratio, and isovolumic relaxation time decreased from baseline through 6 months (all $P < 0.01$), which indicates an improvement in LV diastolic function and a decrease in LV filling pressure. Changes observed at 6 months after sildenafil were significantly different compared with the placebo group (all $P < 0.01$).

As shown in Table 2, the 6 min walking distance showed sustained improvement after 6 months of sildenafil therapy. In addition, in the placebo group, there was a significant increase in the walking distance for 6 min. However, the walking distance in the sildenafil group was significantly higher than that of the placebo group ($P < 0.001$).

Hospitalization and side effects

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

Discussion

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

E/A, a variable repeatedly found related to LV filling pressures in a variety of left-sided cardiac disorders [4], increased significantly at 6 months of active treatment. Our results showed that the diastolic measures of LV function indicated systematic and sustained improvements after 6 months of sildenafil. The transmitral E wave velocity, A wave velocity, E/A ratio, and isovolumic relaxation time decreased from baseline through 6 months (all $P < 0.01$), which indicates an improvement in LV diastolic function and a decrease in LV filling pressure. Changes observed at 6 months after sildenafil were significantly different compared with the placebo group (all $P < 0.01$).

The results of our study raise the intriguing possibility that the NO pathway may be crucially involved in these effects. A NO-induced, diastolic LV dispensability-increasing effect has been documented in several animal models [5], with supporting evidence also in the normal and failing human heart [6,7]. The major identified molecular pathways involved in the NO-mediated effect on the diastolic function properties of the cardiomyopathic heart are 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

Table 1: Left ventricular ejection fraction, pulmonary artery systolic pressure, and Doppler-derived diastolic indices in the two groups before and 1 month after therapy

	Placebo group ($n=50$)		Sildenafil group ($n=50$)		*P* between before and after in placebo	*P* between before and after in sildenafil
	Before	After 6 months	Baseline	After 6 months		
LVEF (%)	31.5±5.4	36.4±3.5	30.6±4.5	45.6±5.4	>0.05	<0.001
PASP (mmHg)	49.7±19.7	45.6±14.7	48.3±17.7	28.4±6.4	>0.05	<0.001
Diastolic parameters						
Mitral E	65.2±16.0	69.6±12.8	63.9±19.7	72.4±8.5	>0.05	<0.01
Mitral A	76.7±19.8	74.3±16.5	77.9±18.5	67.9±11.4	>0.05	<0.01
Mitral E/A	0.8±0.64	0.93±0.34	0.82±0.69	1.1±0.16	>0.05	<0.01
IVRT (ms)	93.0±7.60	94.0±5.4	91.0±6.90	95.2±3.8	>0.05	<0.05

LVEF, left ventricular ejection fraction.

Table 2: 6 min walking distance in the two groups at baseline and after 6 months of therapy

	Placebo group ($n=50$)		Sildenafil group ($n=50$)		*P* between before and after in placebo	*P* between before and after in sildenafil
	Before	After 6 months	Baseline	After 6 months		
Walking distance (m)	167±25.5	235±45.5	171±29.5	450±65	<0.01	<0.001

P value less than 0.001 (highly significant) between the sildenafil and the placebo group after 6 months of follow-up.

respiration, oxygen consumption, and substrate utilization. Furthermore, LV relaxation may benefit from NO activity through the prevention of endomyocardial fibrosis by blocking the signaling cascade involving endothelin, angiotensin II, aldosterone, and transforming growth factor-β [7].

The results of the current study showed that the 6 min walking distance showed sustained improvement after 6 months of sildenafil therapy. In addition, in the placebo group, there was a significant increase in the walking distance for 6 min. However, the walking distance in the sildenafil group was significantly higher than that of the placebo group ($P < 0.001$). Our results indicated that 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. Multilevel drug activity has previously explained [3,8–10]. In agreement with previous specifically designed trials looking at QOL during sildenafil treatment, nine daily life symptoms and functional emotion were significantly improved.

The results of this study on the beneficial therapeutic effect of sildenafil in patients with stable HF are in agreement with those reported by Guazzi *et al.* [11], who stated that in HF, a defective NO signaling is involved in LV diastolic abnormalities and remodeling. PDE5 inhibition, by blocking degradation of NO second-messenger cyclic guanosine monophosphate, might be beneficial. They tested the effects of PDE5 inhibition (sildenafil) on LV ejection fraction, diastolic function, cardiac geometry, and clinical status. Their findings confirmed 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 [12].

Conclusion

In patients with HF, long-term use of sildenafil was well tolerated. This therapeutic regimen (50 mg three times per day) promoted a sustained significant improvement in LV and diastolic function properties in comparison with placebo. These effects yielded better functional capacity and clinical status. Additional work is needed to confirm the 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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Nil.

Conflicts of interest

There are no conflicts of interest.

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