Sildenafil Improves Exercise Capacity in Patients with Chronic Heart Failure

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SUMMARY

Background
Phosphodiesterase type 5 inhibitors, as sildenafil, are moderate vasodilators widely used for erectile dysfunction. The evidence currently available establishes that they are potentially useful to treat other conditions like pulmonary hypertension, endothelial dysfunction and chronic heart failure.

Objective
To evaluate whether sildenafil is useful to improve exercise capacity compared to placebo in patients with chronic heart failure in functional class II-III.

Material and Methods
A total of 70 patients with chronic heart failure of any etiology, excluding valvular heart disease, were randomly selected. All patients were receiving optimal medical treatment. Patients were included if they had a left ventricular-diastolic diameter of 55 mm, an ejection fraction <35% systolic blood pressure >90 mm Hg. Patients with anemia, an indication of surgery due to any cause, and those unable to undergo a 6-minute walk test were excluded from the study. After the 6-minute walk test, the patients were randomly assigned to receive 50 mg of sildenafil (sildenafil group) or placebo (placebo group); each group had 35 patients. A second 6-minute walk test was performed 2 hours after the drug was administered. The following variables were evaluated before and after each test: systolic blood pressure, heart rate and the distance walked in meters in each test.

Results
General characteristic, placebo group versus sildenafil group: men: 74% vs. 88%, ischemic dilated cardiomyopathy: 71% vs. 77%, functional class II: 37% vs. 34%, functional class III: 63% vs. 66%, age: 68±10 vs. 68±12 years, ejection fraction: 26.5%±7.8% vs. 26.5%±6.5%, left ventricular end-diastolic diameter: 65±6 vs. 66±9 mm (all p = ns). Before the first 6-minute walk test, the following variables were measured in the placebo versus the sildenafil group: systolic blood pressure: 115±15 vs. 115±21 mm Hg; diastolic blood pressure: 71±10.5 vs. 68±13 mm Hg (both p = ns); heart rate: 74±13 vs. 64±6 (p <0.001). After the first test and before drug administration: systolic blood pressure: 126±20 vs. 133±26 mm Hg, diastolic blood pressure: 68±11 vs. 72±15 mm Hg; heart rate 84±2 vs. 80±9 (all p = ns). Before the second test and after drug administration, placebo versus sildenafil: systolic blood pressure: 112±14 vs. 95±18 mm Hg; diastolic blood pressure: 69±8 vs. 57±12 mm Hg (both p <0.001); heart rate: 73±11 vs. 75±10 (p = ns). Finally, after the second walk test: systolic blood pressure: 123±17 vs. 115±26 mm Hg (p <0.05), diastolic blood pressure: 65±7 vs. 60±12 mm Hg (p <0.02) and heart rate: 84±13 vs. 86±12 (p = ns). The incidence of headache was 11% (4 patients) in the sildenafil group and 0% in the placebo group. No major events were reported. The sildenafil group walked 222±69 and 313±76 meters before and after drug administration, respectively; the difference was 91±19 meters. The placebo group walked 233±67 and 242±67 meters before and after drug administration, respectively; the difference was 9±5 meters. The difference in the distance walked was greater in the sildenafil group: 91±19 vs. 9±5 (p <0.0001).

Conclusions
In patients with heart failure in functional class II-III under optimal medical therapy, sildenafil improved exercise capacity compared to placebo.

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Key words > Heart Failure - Exercise - Functional residual capacity

Abbreviations >

cAMP	Cyclic adenosine monophosphate	**CHF**	Chronic heart failure
ARB	Angiotensin II receptor blocker	**ACFI**	Angiotensin-converting enzyme inhibitor
LVDD	Left ventricular diastolic diameter	**NYHA**	New York Heart Association
EF	Ejection fraction	**PDF**	Phosphodiesterase family
cGMP	Cyclic guanosine monophosphate	**PDE5**	Type 5 Phosphodiesterase

BACKGROUND

Phosphodiesterase family (PDE) comprises a group of enzymes that hydrolyze adenosine and guanosine cyclic nucleotides. Nitric oxide activates guanylyl and adenylyl cyclases, the enzymes that degrades guanosine triphosphate and adenosine thriphosphate and converts them to cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Both cyclic nucleotides act as second messengers. cGMP promotes decrease in intracellular calcium concentrations, leading to smooth muscle relaxation. (1) Sildenafil, a selective inhibitor of type 5 phosphodiesterase (PDE5), produces coronary artery vasodilation and was originally investigated to determine its potential use as an anti-ischemic agent. Currently, sildenafil is used for the treatment of erectile dysfunction. The evidence available establishes that it is potentially useful to treat other conditions like pulmonary hypertension, endothelial dysfunction and chronic heart failure (CHF). (1-3)

Exercise capacity in CHF is (4) determined by several central and peripheral mechanisms. Thus, pulmonary resistance and right ventricular performance influence exercise capacity and prognosis of patients with CHF and right ventricular systolic dysfunction. (5-9) Around 68% to 78% of patients with severe left ventricular dysfunction have pulmonary hypertension that produces right ventricular dysfunction. In addition, pulmonary hypertension is considered an important predictor of low functional capacity in CHF. (5, 6, 10, 11)

Endothelial dysfunction also plays a role in CHF and is associated with the clinical presentation and prognosis. (12-15) Endothelial dysfunction is an abnormal response of the endothelium that reduces the bioavailability of vascular nitric oxide and impairs vasodilation. (16) The inhibition of 5-PDE with sildenafil has proved to be useful in different condition with impaired endothelial function and vascular tone. (17) This favorable effect is partially mediated by increased bioavailability of nitric oxide in the vascular bed. (18) The loss of vasodilator capacity induces changes which increase peripheral vascular resistance, and thus contributes to reducing cardiac performance, producing changes in pulmonary hemodynamics that lead to the development of pulmonary hypertension. (12) Finally, in CHF vasoconstriction generates elevation in aortic impedance which, in turn, increases left ventricular afterload, wall stress and oxygen uptake. The inhibition of PDE5 improves cardiac performance in patients with CHF, probably due to reduction in afterload components: peripheral resistance, stiffness of the aorta and great vessels and peripheral wave reflection. Recent publications have reported improvement in exercise capacity in patients with CHF after the administration of a single dose of sildenafil. (19-23)

The goal of the present study was to determine the effect of a single dose of 50 mg of sildenafil on exercise capacity compared to placebo, evaluated by a 6-minute walk test, in patients with New York Heart Association (NYHA) functional class (FC) II-III chronic heart failure.

MATERIAL AND METHODS

We conducted a randomized, double-blind, controlled trial to evaluate whether a singe dose of 50 mg of sildenafil is useful to improve exercise capacity compared to placebo in patients with CHF.

Patients were enrolled in a single center and were randomly assigned to sildenafil or placebo in a double-blind fashion. The goal of the study was to evaluate whether sildenafil, in a single dose of 50 mg, improves the physical performance of patients with CHF.

CHF patients with NYHA FC II-III were prospectively and consecutively enrolled. All patients gave their consent to be included in the study and signed an informed consent form. All patients had been attending the heart failure clinic for at least 6 months are were receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), beta blockers and spironolactone in optimal or maximal tolerated dose. Each participant underwent a thorough physical examination, laboratory tests, 2D-echocardiograhy and radionuclide ventriculography to determine ejection fraction. Myocardial perfusion tests were ordered to patients with a history of ischemic cardiomyopathy to rule out the presence of ischemia that might benefit from revascularization treatment.

Patients were included if they were > 21 years, had left ventricular-diastolic diameter (LVDD) > 55 mm, ejection fraction (EF) < 35% systolic blood pressure >90 mm Hg.

Patients were excluded from the study if they were under treatment with nitrates, had intolerance to sildenafil, an indication of surgery due to any cause, were waiting for revascularization surgery, had anemia, valvular heart disease or hypertrophic cardiomyopathy, or were unable to undergo a 6-minute walk test. A total of 178 patients were attending the heart failure clinic; 70 were eligible to be included in the study. Before the test, and after a 15-minute rest period, blood pressure, heart rate and oxygen saturation were controlled by the same operator. The patients were

then asked to walk quickly along a 30-m hallway for 6 minutes. The same variables were controlled after the test ended. Fifteen minutes after the test ended, one tablet containing sildenafil or placebo was administered. Identical, consecutively numbered envelopes containing either active drug or placebo were used for allocation concealment. The envelopes were assigned using a lottery drum, so that the evaluator was not aware of the treatment assigned when the results were retrieved.

Sixty minutes after taking the tablet, the same operator invited the participant to undergo a second 6-minute walk test. Blood pressure, heart rate and oxygen saturation were controlled after and before the test by the operator. The distance walked in meters in each test, and the difference walked in meters between both tests, were recorded. Patients were asked to stay within the same premises the tests were performed to evaluate potential drug-related adverse effects. Two groups were established after the tests ended and unblinding: sildenafil and placebo, with 35 patients each. Figure 1 illustrates the study design.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage. Shapiro-Wilk test was used to analyze whether the distribution followed the normal curve. Student's test or Wilcoxon test were used to compare continuous variables, and the association of categorical variables was determined by chi square test or Fisher's exact test. A two-tailed p value ≥ 0.05 was considered statistically significant.

The number of patients necessary to be included was calculated from the information –distance walked in meters- of previous 6-minute walk tests performed in our clinic.
We considered that drug should improve the reference values by 30%. According to this premise, our calculations demonstrated that an adequate sample should include 20 patients in each group for an alpha level of 0.05 and a power of 95%.

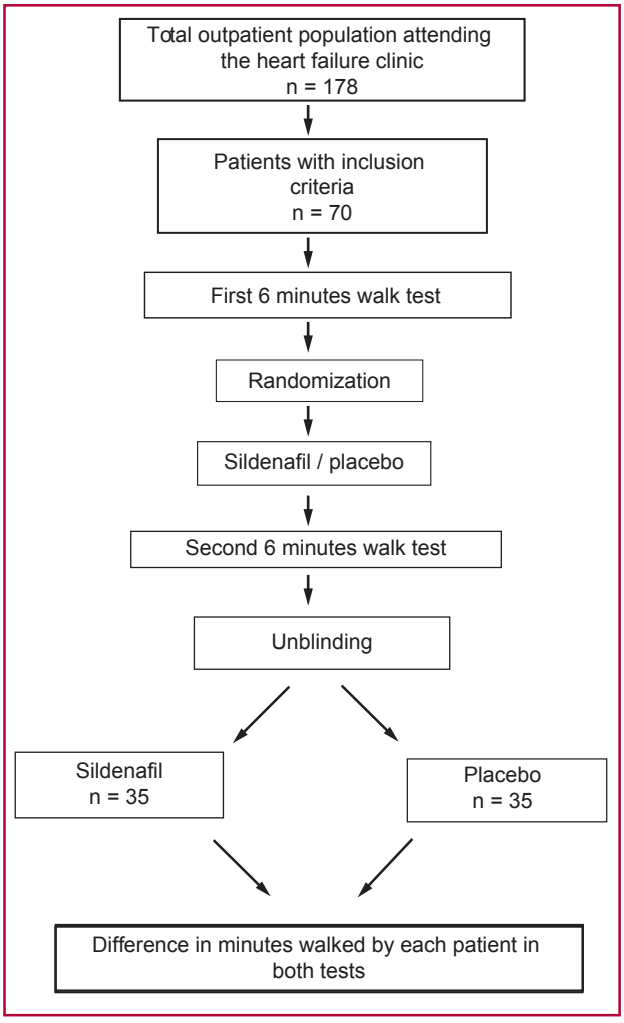

Fig. 1. Study design.

RESULTS

After unblinding, two groups were established. When baseline characteristics of patients were compared (Table 1) there were no differences between both groups.

There were more men than women; mean age was 68 years and 2/3 of patients were in FC III. Heart failure was more frequently due to ischemic heart disease and mean EF was 26.5%. All the participants were receiving ACEIs or ARBs, beta blockers and spironolactone in optimal or maximal tolerated dose.
The clinical variables controlled in both groups before and after the initiation of the 6 minute-walk test are shown in Table 2. No medication was administered during the test. There were no significant differences in systolic and diastolic pressure before the first walk; differences in heart rate were observed. After the first walk, the three variables presented changes in both groups; however there were no significant differences between both groups.

Table 3 describes the clinical variables after the randomization and the administration of the corresponding drug, before and after the second 6-minute walk test.

After the administration of sildenafil, and with the patient at rest, systolic and diastolic blood pressure presented significant reduction in the sildenafil group without changes in heart rate. After the second walk, heart rate increased in both groups without significant differences. On the contrary, systolic and diastolic blood pressure decreased significantly in the sildenafil group compared to the placebo group.

Table 4 shows the average walked, in meters, for each group. Patients in the sildenafil group walked 222 ± 69 and 313 ± 76 meters in the first and second walk, respectively, with a difference of 91 ± 19 meters. The placebo group walked ± and 242 ± 67 meters in the first and second walk, respectively; the difference was 9 ± 5 meters. There were no significant differences in the distance walked by each group in the first test; however, the distance walked by patients in the sildenafil group in the second test was significantly greater compared to the control group.

Two hours after the second walk patients left the hospital. None of the participants complained of major

Table 1. Clinical characteristics in both groups

	Sildenafil (n = 35)	Placebo (n = 35)	p
Age (years)	68 ± 12	68 ± 10	ns
Men (%)	88	74	ns
Coronary artery disease (%)	77	71	ns
Functional class (NYHA) (%)			
II	34	37	ns
III	66	63	ns
LVDD (mm)	66 ± 9	65 ± 6	ns
LVEF (%)	26.5 ± 6.5	26.5 ± 7.8	ns
Treatment (%)			
Diuretics	78	80	ns
Beta blockers	88	90	ns
ACEI	95	93	ns
ARB	3	4	ns
Spironolactone	60	58	ns

n: Number of cases. ns: Non significant.

Table 2. Clinical variables before and after the first walk

	Blood pressure systolic	Blood pressure diastolic	Heart rate
Before 1st walk			
Sildenafil group	115 ± 21	68 ± 13	64 ± 6
Placebo group	115 ± 15	71 ± 10.5	74 ± 13
p	ns	ns	< 0.001
After 1st walk			
Sildenafil group	133 ± 26	72 ± 15	80 ± 9
Placebo group	126 ± 20	68 ± 11	84 ± 2
(t Student) p	ns	ns	ns

n: Number of cases. ns: Non significant.

side effects requiring a medical intervention; yet, four patients (11%) in the sildenafil group presented headache.

DISCUSSION

Previous studies have reported an average blood pressure reduction of 6 to 8 mm Hg in healthy subjects in the supine position two hours after the administration of 50 mg of sildenafil. This reduction is not greater in the erect position, even with greater dose. (24, 25) Blood pressure reduction produces reflex tachycardia. (26, 27)

In patients with FC II chronic heart failure, a single dose of sildenafil improved significantly the outcomes of six-minute walk test on treadmill, compared to placebo (23) These results are similar to other study using fixed dose of 50 mg/day during 6 weeks, which reported improvement on functional capacity without significant changes in blood pressure or heart rate. (28)

Lewis et al. demonstrated that, in patients with CHF, a single dose of sildenafil improves exercise capacity. (21) Another study by the same group included patients with CHF and pulmonary hypertension, and reported that treatment with sildenafil for 12 weeks increased the distance in meters walked during the 6-minute walk test compared to placebo. (29)

Recently, Behling et al. showed that the administration of sildenafil for 4 weeks improved the functional capacity compared to placebo. (30)

Several mechanisms may be involved with the improvement in functional capacity in these patients. Sildenafil increases right ventricular ejection fraction, probably due to a reduction in afterload as a consequence of decreased pulmonary vascular resistance. (31-33) Probably, improvement in right ventricular function during exercise increases stroke volume due to increased left ventricular filling volume. The improvement of the vasodilator capacity of sildenafil might reduce pulmonary and

	Blood pressure systolic	Blood pressure diastolic	Heart rate
Before 2nd walk			
Sildenafil group	95 ± 18	57 ± 12	75 ± 10
Placebo group	112 ± 14	69 ± 8	73 ± 13
p	< 0.001	< 0.001	ns
After 2nd walk			
Sildenafil group	115 ± 26	60 ± 12	86 ± 12
Placebo group	123 ± 17	65 ± 7	84 ± 13
(t Student) p	< 0.05	< 0.02	ns

n: Number of cases. ns: Non significant.

Table 3. Clinical variables before and after the second walk

Group	First walk	Second walk	Difference in meters
Sildenafil	222 ± 69	313 ± 76	91 ± 19
Placebo	233 ± 67	242 ± 67	9 ± 5
(t Student) p	ns		< 0.001

n: Number of cases. ns: Non significant.

Table 4. Distance walked in meters by patients in both groups

systemic vascular resistance and thus increase cardiac performance. (12-16)It is also possible that a reduction in left ventricular overload due to decreased systemic vascular resistance increases contractility and left ventricular systolic stroke. (22)

We have demonstrated that a single dose of 50 mg of sildenafil improves exercise capacity of patients with NYHA FC II-III CHF evaluate by the six-minute walk test. Sildenafil was well tolerated and was associated with minimal adverse effects; however, compared to placebo, it produced significant reduction of systolic and diastolic blood pressure without increasing heart rate. Yet, these variable presented normal changes during exercise.

As opposed to previous reports, we found a pronounced increase in the distance walked in six minutes - mean distance: 90 meters - in the sildenafil group. Probably, this might be due to the fact that we included more patients in FC III who walked a shorter distance in the first test compared to patients in other studies. Left ventricular function might have been more deteriorated in our patients.

Clinical implications

Few particular subgroups of patients with CHF might beneficiate from inhibition of PDE5; for example, patients with limited exercise capacity despite optimal medical treatment. In addition, PDE5 inhibition might be used before cardiac resynchronization therapy or when this therapy does not improve symptoms or functional class. Patients on waiting list for a heart transplant might also beneficiate from this treatment. These potential indications should be examined with studies designed to demonstrate a maximal benefit.

Study limitations

We used two-dimensional echocardiography without Doppler examination to measure cardiac chambers; thus, we did not evaluate pulmonary pressure. Therefore, we do not know if the effect obtained in the active group corresponds to patients with pulmonary hypertension. Although our study includes a small number of patients, the magnitude of the difference makes it highly reliable. These results need to be confirmed by further investigations including a greater number of patients.

CONCLUSIONS

In patients with CHF in FC II-III, the administration of sildenafil produces a significant improvement in exercise capacity compared to placebo. In addition, the rate of adverse effects was very low.

RESUMEN

El Sildenafil mejora la capacidad de ejercicio en pacientes con insuficiencia cardíaca crónica

Antecedentes

Los agentes inhibidores de la fosfodiesterasa 5, como el sildenafil, son vasodilatadores moderados ampliamente utilizados para el tratamiento de la disfunción eréctil. En la actualidad, la evidencia disponible establece su potencial aplicación en otras patologías, como la hipertensión pulmonar, la disfunción endotelial y la insuficiencia cardíaca crónica.

Objetivo

El presente estudio fue diseñado para comprobar si la administración de sildenafil en pacientes con insuficiencia cardíaca crónica en clase funcional II-III mejora la capacidad de ejercicio en comparación con placebo.

Material y métodos

Se seleccionaron en forma aleatoria 70 pacientes portadores de insuficiencia cardíaca crónica de cualquier etiología, excepto valvulares, todos con tratamiento óptimo. Para su inclusión en el estudio, los pacientes debían tener un diámetro diastólico ventricular izquierdo > 55 mm, una fracción de eyección < 35% y una presión arterial sistólica > 90 mm Hg. Se excluyeron los que se encontraban anémicos, aquellos con indicación de cirugía por cualquier causa o los que por diversos motivos no pudieran realizar una caminata de seis minutos. Luego de una caminata de seis minutos fueron aleatorizados para recibir 50 mg de sildenafil o placebo, conformándose dos grupos, placebo y sildenafil, ambos con 35 participantes. Luego de 1 hora de la ingestión de las drogas se realizó una nueva caminata de seis minutos. Antes y después de cada caminata se controlaron las siguientes variables: presión arterial sistólica, diastólica y frecuencia cardíaca; se registraron también los metros caminados en cada prueba.

Resultados

Características generales, grupo placebo versus grupo sildenafil: hombres: 74% vs 88%, etiología isquémico-necrótica: 71% vs 77%, clase funcional II: 37% vs 34%, clase funcional III: 63% vs 66%, edad: 68 ± 10 vs 68 ± 12 años, fracción de eyección: 26,5% ± 7,8% vs 26,5% ± 6,5%, diámetro diastólico ventricular izquierdo: 65 ± 6 vs 66 ± 9 mm (todas p = ns). Las variables del grupo placebo versus sildenafil antes de la primera caminata fueron: presión arterial sistólica: 115 ± 15 vs 115 ± 21 mm Hg y diastólica: 71 ± 10,5 vs 68 ± 13 mm Hg (ambas p = ns) y frecuencia cardíaca: 74 ± 13 vs 64 ± 6 (p < 0,001). Luego de la primera caminata y antes de la administración de las drogas: presión arterial sistólica: 126 ± 20 vs 133 ± 26 mm Hg, diastólica: 68 ± 11 vs 72 ± 15 mm Hg y frecuencia cardíaca 84 ± 2 vs 80 ± 9 (todas p = ns). Antes de la segunda caminata y luego de la administración de las drogas, grupo placebo versus sildenafil: presión arterial sistólica: 112 ± 14 vs 95 ± 18 mm Hg, diastólica: 69 ± 8 vs 57 ± 12 mm Hg (ambas p < 0,001) y frecuencia cardíaca: 73 ± 11 vs 75 ± 10 (p = ns). Finalmente, luego de la segunda caminata: presión arterial sistólica: 123 ± 17 vs 115 ± 26 mm Hg (p < 0,05), diastólica: 65 ± 7 vs 60 ± 12 mm Hg (p < 0,02) y frecuencia cardíaca: 84 ± 13 vs 86 ± 12 (p = ns). Cuatro pacientes (11%) en el grupo sildenafil presentaron cefalea y ninguno en el grupo placebo. No se registraron eventos mayores. El grupo sildenafil caminó 222 ± 69 metros antes y 313 ± 76 luego de la administración de la droga; la diferencia en metros fue de 91 ± 19. El grupo placebo caminó 233 ± 67 metros antes y 242 ± 67 luego de la administración de la droga; la diferencia en metros fue de 9 ± 5. Al comparar estos resultados, la diferencia en metros recorridos resultó significativa a favor del grupo sildenafil: 91 ± 19 vs 9 ± 5 (p < 0,0001).

Conclusiones

En pacientes con insuficiencia cardíaca en clase funcional II-III bajo tratamiento óptimo, el sildenafil mejoró la capacidad de ejercicio en comparación con placebo.

Palabras clave > Insuficiencia cardíaca - Ejercicio - Capacidad residual funcional

BIBLIOGRAPHY

1. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. Physiol Rev 1995;75:725-48.

2. Reffelmann T, Kloner RA. Therapeutic potential of phosphodiesterase 5 inhibition for cardiovascular disease. Circulation 2003;108:239-44.

3. Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil: review of the literature. Eur J Med Res 2002;7:435-46.

4. Florea VG, Mareyev VY, Achilov AA, Popovici MI, Coats AJ, Belenkov YN. Central and peripheral components of chronic heart failure: determinants of exercise tolerance. Int J Cardiol 1999;70:51-6.

5. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183-8.

6. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143-53.

7. Polak JF, Holman BL, Wynne J, Colucci W. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. J Am Coll Cardiol 1983;2:217-24.

8. Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. Am J Cardiol 1984;54:596-9.

9. Meluzin J, Spinarova L, Hude P, Krejci J, Dusek L, Vitovec J, et al. Combined right ventricular systolic and diastolic dysfunction represents a strong determinant of poor prognosis in patients with symptomatic heart failure. Int J Cardiol 2005;105:164-73.

10. Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 1992;19:48-54.

11. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 1999;34:1802-6.

12. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000;102:1718-23.

13. Esper RJ, Nordaby RA, Vilariño JO, Paragano A, Cacharrón JL, Machado RA. Endothelial dysfunction: a comprehensive appraisal. Cardiovascular Diabetology 2006,5:4.

14. Katz SD, Hryniewicz K, Hriljac I, Balidemaj K, Dimayuga C, Hudaihed A, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005;111:310-4.

15. Nakamura M, Ishikawa M, Funakoshi T, Hashimoto K, Chiba M, Hiramori K, et al. Attenuated endothelium-dependent peripheral vasodilation and clinical characteristics in patients with chronic heart failure. Am Heart J 1994;128:1164-9.

16. Katz SD, Schwarz M, Yuen J, Lejemtel TH. Impaired acetylcholine mediated vasodilation in patients with congestive heart failure: role of endothelium-derived vasodilating and vasoconstricting factors. Circulation 1993;88:55-61.

17. Halcox JPJ, Nour KR, Zalos G, Mincemoyer RA, Waclawiw M, Rivera CE, et al. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. J Am Coll Cardiol 2002;40:1232-40.

18. Burnett AL. Phosphodiesterase 5 mechanisms and therapeutic applications. Am J Cardiol 2005;96:29M-31M.

19. Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S. Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 2000;36:845-51.

20. Guazzi M, Tumminello G, Marco FD, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. J Am Coll Cardiol 2004;44:2339-48.

21. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 2007;115:59-66.

22. Hirata K, Adji A, Vlachopoulos C, O'Rourke M. Effect of sildenafil on cardiac performance in patients with heart failure. Am J Cardiol 2005;96:1436-40.

23. Bocchi EA, Guimaraes G, Mocelin A, Bacal F, Bellotti G, Ramires JF. 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. Circulation 2002;106:1097-103.

24. Jackson G, Benjamin N, Jackson N, Allen MJ. Effects of sildenafil citrate on human hemodynamics. Am J Cardiol 1999;83:13C-20C.

25. Gillies HC, Roblin D, Jackson G. Coronary and systemic hemodynamic effects of sildenafil citrate: from basic science to clinical studies in patients with cardiovascular disease. Int J Cardiol 2002;86:131-41.

26. Zusman RM, Morales A, Glasser DB, Osterloh IH. Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 1999;83:35C-44C.

27. Kloner RA. Sex and the patient with cardiovascular risk factors: focus on sildenafil. Am J Med 2000;109:13S-21S.

28. Webster LJ, Michelakis, Davis T, Archer SL. 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. Arch Intern Med 2004;164:514-20.

29. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555-62.

30. Behling A, Rohde L, Colombo F, Goldraich L, Stein R, Clausell N. Effects of 5'- phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. J Cardiac Fail 2008;14:189-97.

31. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148-57.

32. Nagendran J, Archer SL, Soliman D, Gurtu V, Moudgil R, Haromy A, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation 2007;116:238-48.

33. Lepore JJ, Maroo A, Bigatello LM, Dec GW, Zapol WM, Bloch KD, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest 2005;127:1647-53.

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Competing interests

None declared.