Brief Comments

Pressure Response in Chagasic Cardiomyopathy Patients After Using Sildenafil

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Summary

Objective: To accurately verify the effect of Sildenafil on blood pressure (BP) and heart rate (HR) in individuals with Chagasic myocardiopathy (CMC) and severe systolic ventricular dysfunction (EF<40%) submitted to physical activity.

Methods: Twelve men with ejection fractions <40% and CMC confirmed by a serological test were assessed. The six-minute walk test (6MWT) was performed before and after administration of 50 mg of Sildenafil, with a 30 minute interval. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure were taken and compared before and after each 6MWT. For statistical analysis purposes, the study was divided into four stages: before the 6MWT and administration of Sildenafil (S1); after the 6MWT but before the administration of Sildenafil (S2); after the administration of Sildenafil but before the 6MWT (S3); and after the administration of Sildenafil and the 6MWT (S4).

Results: Participant ages ranged from 47 to 68 years (57.6 ± 6.4). SBP and DBP after the 6MWT and the administration of Sildenafil (S4) were lower than before taking the drug (S2): 134.2 ± 15.1 versus 125.5 ± 14.0 and 88.4 ± 12.4 versus 83.0 ± 10.8, respectively. None of the patients reported any symptoms during the 6MWT. There were no differences in the distances walked during the 6MWT before or after taking Sildenafil (487.5±15.22 versus 505.3±18.45 meters, respectively)–p=0.056, or in HR (before Sildenafil 75.5 ± 8.79 and 96.8 ± 10.36 bpm and after 77.1 ± 9.81 and 96.1 ± 12.97 bpm).

Conclusion: A significant reduction in BP after physical activity while using Sildenafil was observed. However, during the six-minute walk test, the patients did not report any symptoms, indicating that this effect is not sufficient to cause clinical manifestations in CMC and heart failure patients.

Key words: Cardiac output, low; Chagas disease; sildenafil; Chagas cardiomyopathy.

Introduction

Based on data from national studies on the epidemiology of erectile dysfunction (ED), it is estimated that there are currently approximately 25 million men over the age of 18 in Brazil who suffer from some degree of ED and that 11.3 million have moderate to serious dysfunction. This prevalence is much higher in heart failure patients due to specific characteristics such as endothelial dysfunction, low cardiac output, use of drugs that cause sexual impotence and a greater possibility to suffer thromboembolytic events[1].

Recently, a new class of drugs called phosphodiesterase type 5 inhibitors (nafil) has proven effective in the treatment of ED for the population in general. Even though these inhibitors are specifically indicated for phosphodiesterase type 5 (PDE5) that has a closer relationship with sexual function than systemic blood pressure, studies have shown that Sildenafil causes slight, but statistically significant blood pressure reductions. Its association with high blood pressure and vasodilator drugs can cause synergic hypotensive effects and endanger the

patient's life.

Studies that demonstrate not only the efficacy but especially the safety of PDE5 inhibitors are required for the population with heart failure due to the distinctive characteristics of low cardiac output and the use of drugs with potential synergic vasodilatation effects[2]. This is even more relevant when analyzing particular distinct characteristics of the Brazilian population where there is a high prevalence of individuals with the Chagas myocardiopathy that usually present some specific events in relation to systolic dysfunction that are also present with other heart failure etiologies. In Chagasic patients there is a higher incidence of cardiac electrical conduction alterations such as bundle branch and atrioventricular blocks, extrasystoles and complex arrhythmias, such as ventricular tachycardia.

New studies have demonstrated a significant nitric oxide involvement in the Chagasic myocardiopathy physiopathology. The infection caused by the *Trypanossoma cruzi* induces an iNOS expression, greatly increasing the release of nitric oxide causing an inflammatory process that destroys the myocytes. The phosphodiesterase type 5 inhibitors regulate nitric oxide production and could be a therapeutic option for these patients in the future.

The objective of the study is to accurately verify the hemodynamic effects of Sildenafil on blood pressure and

heart rate during physical exercise in patients with Chagasic myocardiopathy and severe ventricular dysfunction.

Methods

The participants in the study were male patients over the age of 18 with Chagas disease, confirmed by ELISA or immunofluorescence, or systolic heart failure with ejection fractions less than 40%, confirmed by an echocardiogram using the Simpson formula. Exclusion criteria included the use of nitrate, presence of ischemic heart disease symptoms and NYHA functional class III or IV.

Interviews and medical chart information were used to collect data on prior medical histories, current symptoms and treatments. The IIEF (International Index of Erectile Dysfunction) questionnaire was used to assess erectile dysfunction. Heart rate and systemic blood pressure readings for the study participants were taken before and after the two six-minute walk tests (6MWT). The 6MWT was conducted according to the American Thoracic Association protocol[3].

After the first 6MWT[3], the patients were given a 50mg oral dose of Sildenafil and rested for 30 minutes. After this interval they underwent the second 6MWT.

For statistical analysis purposes, the study was divided in four stages: Before the 6MWT and administration of Sildenafil (S1); after the 6MWT but before the administration of Sildenafil (S2); after the administration of Sildenafil but before the 6MWT (S3); and after the administration of Sildenafil, and the 6MWT (S4). Data comparison was performed with the SPSS software SPSS program. The chi-square test was used for nominal variables and the Student's t-test for continuous variables. Statistical significance was determined as $p < 0.05$.

Results

The study included twelve patients with an average age of 57.5 ± 6.3 years. In relation to race, 25.0% were white, 41.7% mulattos and 33.3% negroes. The majority of the patients were functional class I (91.7%). According to the IIEF questionnaire,

75% of the study participants had erectile dysfunction. In relation to the use of drugs, 100% used ACE inhibitors, 66% digitalis, 58% diuretics, 41% beta-blockers and 50% class 3 antiarrhythmic agents (amiodarone).

There was no statistically significant difference in the total distance walked during the six-minute walk test (6MWT) before and after the use of Sildenafil (487.5 ± 15.22 versus 505.3 ± 18.45 meters, respectively) – $p = 0.056$ (Graphic 1).
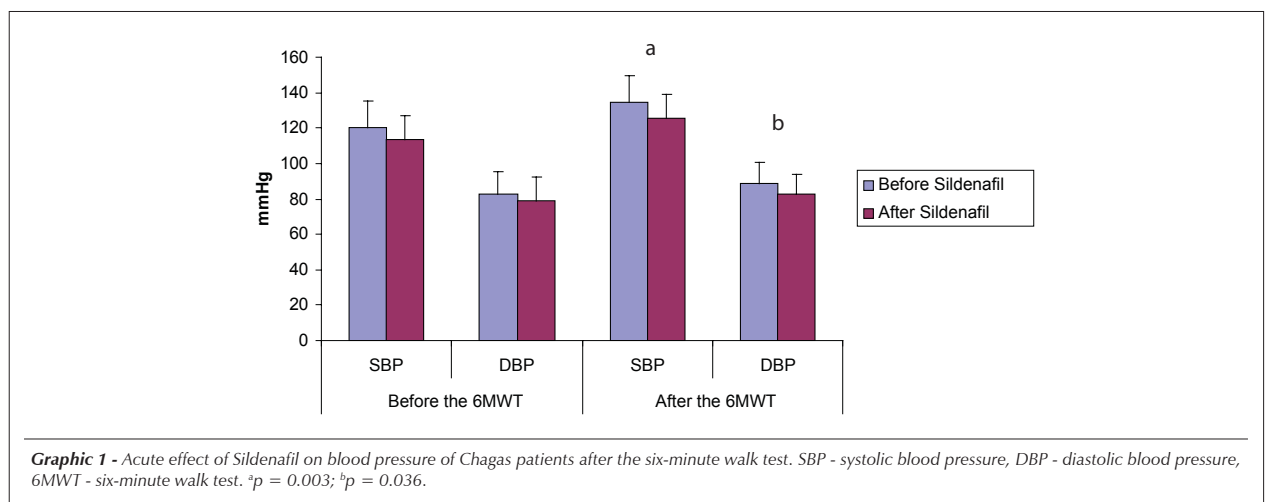
Mean systolic blood pressure before the 6MWT and the administration of Sildenafil (S1) was 120.5 ± 14.59mmHg. There was a statistically significant increase in systolic blood pressure after the six-minute walk test (S2), $134.2 \pm 15.17 – p = 0.002$. Statistically significant increases were also found for diastolic blood pressure before (S1) and after (S2) the 6MWT, even before the administration of Sildenafil (82.6 ± 12.59 versus 88.4 ± 12.41mmHg – $p = 0.009$). The same blood pressure increments were found after the administration of Sildenafil. Before the six-minute walk test but after the administration of Sildenafil (S3) systolic and diastolic blood pressures were 113.6 ± 13.37 and 78.5 ± 13.94 mmHg, respectively. After the 6MWT and drug administration (S4), the values were 125.5 ± 14.09 and 83.0 ± 10.87mmHg. The "p" value for systolic blood pressure was equal to 0.0004 and for diastolic 0.04.

Heart rate also presented a significant increase after exercise. The values before taking the medication were 75.5 ± 8.79 and 96.8 ± 10.36 bpm ($p = 0.00005$) and after 77.1 ± 9.81 and 96.1 ± 12.97 bpm ($p = 0.0003$).

Nevertheless, the increment increase (Δ) before and after Sildenafil administration did not reveal any difference ($p > 0.05$) for systolic or diastolic blood pressure or heart rate.

Comparison of the blood pressure and heart rate values in relation to the influence of Sildenafil on these parameters during the six-minute walktest are shown in Table 1. Significant statistical differences were only found for the systolic and diastolic blood pressure drop after the use of Sildenafil and the 6MWT (S2 and S4).

No patient reported symptoms during the study, presenting good tolerance to the 6MWT both before and after the administration of Sildenafil.

Graphic 1 - *Acute effect of Sildenafil on blood pressure of Chagas patients after the six-minute walk test. SBP - systolic blood pressure, DBP - diastolic blood pressure, 6MWT - six-minute walk test.* $^a p = 0.003$; $^b p = 0.036$.

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	S1	S2	S3	S4
Systolic blood pressure (mmHg)	120.5 ± 14.59	134.2 ± 15.17a	113.6 ± 13.37	125.2 ± 14.09a
Diastolic blood pressure (mmHg)	82.5 ± 12.59	88.4 ± 12.21b	78.5 ± 13.94	83.0 ± 10.87b
Heart rate (bpm)	75.5 ± 8.79	96.8 ± 10.36	77.1 ± 9.81	96.1 ± 12.97

Table 1 - Acute effect of Sildenafil on blood pressure and heart rate of Chagas patients after the six-minute walk test

S1 - before the 6MWT and administration of Sildenafil, S2 - after the 6MWT but before the administration of Sildenafil; S3 - before the 6MWT but after the administration of Sildenafil; S4 - after the 6MWT and the administration of Sildenafil. $^a p = 0.003$; $^b p = 0.036$.

Discussion

Erectile dysfunction is not a life-threatening pathology. Nevertheless, various studies show that sexual function is an important part of everyday life, a factor of quality of life, a marker of psychic and individual status and function, a factor of self-esteem and an early and significant marker for a series of other pathologies. Based on this, ED treatment is one way to improve the individual's quality of life and can even stimulate the treatment of the main disease[4].

Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE5) that is concentrated in male and female genitals. Even though PDE5 is dispersed throughout the circulatory system other phosphodiesterases appear to have a more significant effect on GMPc metabolism and therefore on systemic blood pressure. Sildenafil has an affinity close to 100 times greater than the types 1, 2, 3, and 4 phosphodiesterases. This relationship is important, since PDE3 is involved in cardiac contractibility. Sildenafil produces a slight and transient reduction in systolic and diastolic blood pressures. However, it could have catastrophic effects when associated with other types of blood pressure drugs such as nitrates, after which the production of GMPc increases drastically, causing severe hypotension[5].

In our study, Sildenafil reduced systemic blood pressure both before and after the six-minute walk test, however a statistically significant drop was only observed after physical exertion. Nevertheless, this alteration was not accompanied with symptomatology. Heart rate was not altered by the type 5 phosphodiesterase inhibitor. Energy expenditure during the sexual act has been demonstrated in various studies and is compared to a physical activity involving moderate to intense exertion. Even though sexual activity includes other aspects in addition to the physical element, such as emotional issues, the six-minute test is a viable method to simulate the patient's physical exertion during sexual relations.

According to Cheitlin et al[6], Sildenafil produces a slight and transient reduction in systolic (8 to 10 mmHg) and diastolic (5 to 6 mmHg) blood pressures with no noticeable effects on heart rate. The hypotensive effects are not dependent on dosages and rarely cause an orthostatic effect. In normal volunteers, no significant alterations in the cardiac index were observed in a 12 hour timeframe after taking an oral dose of Sildenafil (100 to 200 mg).

Bochi et al[7] conducted a double-blind, placebo controlled, randomized study with 24 class II, III and IV (NYHA) congestive heart failure (CHF) patients, submitted to a six-minute walk roughly 1 hour after taking Sildenafil or placebo. Their results revealed reduced resting heart rates and blood pressures, which normalized during exercise. They concluded that hypotension during sexual activity is an unlikely adverse effect of Sildenafil.

In another study, involving 35 patients with CHF and ED, an asymptomatic blood pressure reduction of 6 ± 3 mmHg was observed in the patients who took Sildenafil with no occurrences of symptomatic hypotension or other adverse effects[8]. In the study conducted by Katz et al[9], 60% (36/60) of the CHF patients that took Sildenafil and 48% (35/72) of the patients that took placebo, developed adverse effects including transient headache, facial flushing and weakness. Nevertheless the incidence of events related to cardiovascular effects was low[9].

The significance of the study is to prove that the effects and magnitude of Sildenafil on blood pressure and heart rate is comparable to that of other populations with heart failure[10]. In these studies, the majority of the patients had hypertension and coronary artery disease. Owing to the high prevalence of individuals with heart failure related to the Chagasic cardiomyopathy in Brazil, confirmation of these data is mandatory for patient safety. In this study, a significant BP reduction was observed after physical activity while using Sildenafil. However, during the six-minute walk test the patients did not report any symptoms, indicating that this effect seems to be insufficient to cause clinical manifestations in CMC and HF patients. Further studies are required to prove the actual safety of Sildenafil in patients with Chagasic cardiomyopathy.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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