Impact of Sublingual Sildenafil on Pulmonary Hypertension in Patients with Heart Failure

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Summary

Background: Pulmonary hypertension (PH) is a factor of poor prognosis in the postoperative period of heart transplant (HT) and thus, the study of the degree of reversibility to vasodilators is mandatory during the preoperative assessment.

Objective: To evaluate the pulmonary and systemic hemodynamic effects of sildenafil as a vasodilator during the PH reversibility test in patients that are candidates to HT.

Methods: Patients awaiting HT were submitted to the measurement of systemic and pulmonary hemodynamic variables before and after the administration of a single sublingual dose of 100 mg of sildenafil during right heart catheterization.

Results: Fourteen patients (age: 47±12 years, 71.4% men) with advanced heart failure Ejection Fraction (EF) 25 ± 7%, Functional Class (FC - NYHA) FC III - 6 and FC IV - 8, were evaluated in this study. The acute administration of sildenafil showed to be effective in decreasing the systolic (62.4 ± 12.1 *vs* 51.5 ± 9.6 mmHg, CI=95%, p<0.05) and mean (40.7 ± 7.3 *vs* 33.8 ± 7.6 mmHg, CI=95%, p <0.05) pressures of the pulmonary artery. There was also a significant decrease in the pulmonary (4.2 ± 3 *vs* 2.0 ± 0.9 uWood, CI=95%, p<0.05) and systemic vascular resistance (22.9 ± 6.8 *vs* 18.6 ± 4.1 Wood, CI=95%, p<0.05), associated to an increase in the cardiac output (3.28 ± 0.79 *vs* 4.12 ±1.12 uWood, CI=95%, p<0.05) without, however, significantly interfering in the systemic arterial pressure (87.8 ± 8.2 *vs* 83.6 ± 9.1 mmHg, CI=95%, p=0.3).

Conclusion: The sublingual administration of sildenafil is an effective and safe alternative as a vasodilator during the PH reversibility test in patients with heart failure and awaiting a HT. (Arq Bras Cardiol 2009;92(2):116-120)

Key Words: Vasodilatator agents; hypertension, pulmonary; heart failure.

Introduction

Pulmonary hypertension (PH) is known to be a poor prognostic factor in patients with Chronic Heart Failure (CHF)[1-5], increasing the mortality in the early postoperative period of heart transplant (HT) due to right ventricular dysfunction of the transplanted graft[3-9]. Thus, all patients in the preoperative assessment for HT are routinely submitted to the hemodynamic study of the degree of PH, in order to stratify the risk of this subgroup.

Depending on the degree of PH diagnosed during the right cardiac catheterization, some patients are submitted to the Vascular Reactivity Test, which evaluates the reversibility of the PH to vasodilators, as the post-HT prognosis of patients with reversible PH is similar to those with no evidence of preoperative pulmonary hypertension[4-9].

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Traditionally, the most frequently used vasodilator is sodium nitroprussiate, a fast-acting, low-cost and easy-to-manage arterial vasodilator, but which has important limitation due to the arterial hypotension it causes[8,10]. This limitation is particularly relevant in these patients, as the systemic systolic arterial pressure of patients with advanced heart failure (HF) is around 90 to 100 mmHg, which, is several situations, limits the applicability of the drug or even carrying out the pulmonary vascular reactivity test.

Sildenafil is a selective phosphodiesterase-5 (PDE-5) inhibitor, routinely used in the treatment of erectile dysfunction. In the last decade, several studies have demonstrated benefits of sildenafil use in the therapeutic management of idiopathic PH or PH associated to conjunctive tissue diseases without, however, resulting in adverse systemic effects[11,12]. Some studies have demonstrated the benefits of the chronic use of sildenafil in patients with HF, in the reduction of the pulmonary hypertension as well as in the improvement of the physical capacity[1,13-16].

In this study, we will evaluate the pulmonary and systemic vascular responsiveness to the acute administration of sildenafil in patients with heart failure and pulmonary hypertension awaiting a HT.

Methods

The present study was previously approved by the Ethics Committee on Research of *Hospital das Clínicas* of the School of Medicine of the University of Sao Paulo (HC-FMUSP) and all selected patients that accepted to participate in the study signed the Free and Informed Consent Form.

Patients

The patients of the present study were allocated in sequence from the Heart Failure and Transplant Outpatient Clinic of *Instituto do Coracao* (The Heart Institute) – InCor – in Sao Paulo. All patients had advanced-stage heart failure and a formal indication for HT according to the recommendations of the International Society of Heart and Lung Transplant[4] (ISHLT) and the I Directive of the Brazilian Society of Cardiology for Heart Transplant[17], in spite of the optimized standard therapy for chronic HF.

Exclusion criteria

Patients with decompensated HF, hemodynamic instability (systolic arterial pressure < 90 mmHg or using vasoactive IV drugs), dilated cardiomyopathy associated to arteriovenous shunt, chronic pulmonary obstructive disease and pulmonary thromboembolism, atrial fibrillation and those with a prior history of sildenafil use, fenfluramine and nitrates in the previous 24 hours, were excluded from the study.

Hemodynamic vsariables

At the test of pulmonary vascular reactivity, during the right cardiac catheterization, the following hemodynamic variables were assessed: pulmonary artery systolic pressure (PASP) and mean pulmonary artery pressure (MPAP), mean pulmonary capillary pressure (MPCP), mean transpulmonary gradient (MTPG), cardiac output (CO), pulmonary and systemic vascular resistance (PVR and SVR) and mean systemic blood pressure (MBP).

Study design

The patients selected for the study were submitted to right cardiac catheterization with measurement of the pulmonary and systemic variables. Subsequently, sildenafil was administered to all patients, at a single dose of 100 mg, sublingual, and after 60 minutes, a new measurement of the hemodynamic variables was carried out.

The 60-minute interval is equivalent to the highest bioavailability time of the drug and thus, it was considered as the optimal time to evaluate its effect[18].

Statistical analysis

The hemodynamic data ere compared at two times, before and after the drug administration. The statistical analysis of the data was carried out by Student's *t* test, with a 95% confidence interval (95%CI).

Results

The sample consisted of 14 patients with a mean age of 47 ± 12 years and the majority (71.4%) was of the male sex. All of them had previous history of advanced-stage heart failure for more than 12 months (EF: 25 ± 7%, FC III - 6 and FC IV - 8, NYHA), in addition to pulmonary hypertension (mean PASP: 62.4 ± 12.1mmHg). The etiologies of the cardiomyopathies were: ischemic (4), chagasic (3), idiopathic (3), hypertensive (2) or peripartum (2). None of the patients presented cardiac decompensation or used vasoactive intravenous drugs, nitrates, fenfluramine or PDE-5 inhibitors. The basal characteristics of the studied population are shown in Table 1.

The acute administration of sildenafil showed to be effective in decreasing the systolic (62.4 ± 12.1 *vs*. 51.5 ± 9.6 mmHg, CI=95%, p<0.05) and mean (40.7 ± 7.3 *vs*. 33.8 ± 7.6 mmHg, CI=95%, p <0.05) pulmonary artery pressures (Figure 1). This hemodynamic effect, however, was not observed for the mean pulmonary capillary pressure (27 ± 6.9 *vs*. 25.6 ± 8.2 mmHg, CI=95%, p=0.3).

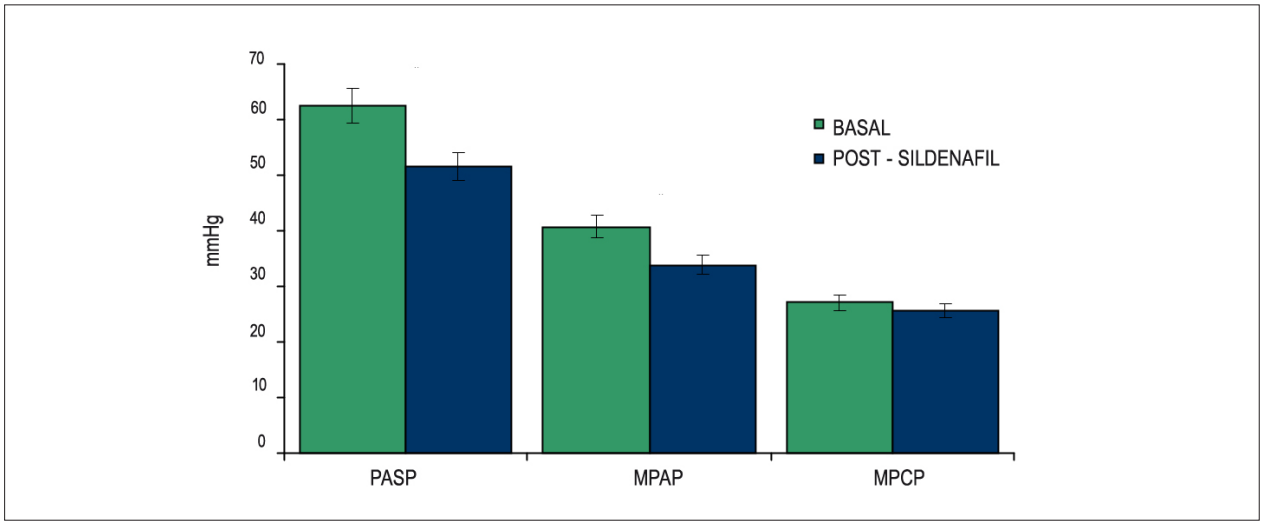

*Figure 1 - Hemodynamic effect of sildenafil on PASP, MPAP and MPCP; * p <0.05.*

Table 1 – Basal characteristics of the studied population

Variables	
Patients (n)	14
Mean age (yrs)	47 ± 12
Sex (M / F)	10 / 4
Functional Class (NYHA)	
III	6
V	8
Ejection fraction (%)	25 ± 7
PASP (mmHg)	62.4 ± 12.1
MPAP (mmHg)	40.7 ± 7.3
PVR (uWood)	4.2 ± 3
SVR (uWood)	22.9 ± 6.8
MPCP(mmHg)	27 ± 6.9
MCO (L/min.m^2)	3.28 ± 0.79
MBP	87.8 ± 8.2

PASP - Pulmonary Artery Systolic Pressure; MPAP - Mean Pulmonary Artery Pressure; PVR - Pulmonary Vascular Resistance; SVR - systemic vascular resistance; MPCP - Mean Pulmonary Capillary Pressure; MCO - Mean Cardiac Output; MBP - mean blood pressure.

Another finding was the influence of sildenafil in the significant decrease in the pulmonary (4.2 ± 3 *vs*. 2.0 ± 0.9 uWood, CI=95%, p<0.05) and systemic (22.9 ± 6.8 *vs*. 18.6 ± 4.1 Wood, CI=95%, p<0.05) vascular resistance (Figure 2) without, however, significantly interfering in the systemic blood pressure (SBP) (87.8 ± 8.2 *vs*. 83.6 ± 9.1 mmHg, CI=95%, p=0.3) (Figure 3).

In addition to the effects on the pulmonary circulation and minimal impact on the systemic blood pressure, we also observed a significant increase in cardiac output (3.28 ± 0.79 *vs*. 4.12 ±1.12 uWood, CI=95%, p<0.05) (Figure 4), probably caused by the decrease in the systemic vascular resistance.

Discussion

The choice of the vasodilator during the test of pulmonary vascular reactivity is essential for the pre-cardiac transplant risk stratification. Sodium nitroprussiate has been the drug of choice in several specialized centers, due to its easy availability and short half-life as well as for its intravenous administration route. However, the systemic arterial hypotension has become an important limiting factor of its broader applicability. This adverse effect is especially relevant in patients with advanced-stage heart failure, whose optimized therapeutic resources maintain a systolic blood pressure of around 90 to 100 mmHg.

Therefore, the use of elevated doses of sodium nitroprussiate in order to attain a pulmonary pressure level that is acceptable for the HT is prevented by the risk of cardiac decompensation. In our experience, approximately 18% of the patients with PH and in the preoperative period of HT are not submitted to the vascular reactivity test with sodium nitroprussiate, due to borderline blood pressure.

In this aspect, the applicability of sildenafil in the therapeutic management of PH, based on the specific vasodilation of the pulmonary circulation, could be an effective alternative for the vascular reactivity test, without, however, causing undesirable systemic effects.

In spite of a small sample size and the absence of a control group, this study established the efficacy of the acute administration of sildenafil in decreasing PH in patients with heart failure. Parallel to the benefits to pulmonary circulation, we also observed positive systemic effects, such as the increase in cardiac output without significant interferences on blood pressure.

At the start, we were uncertain regarding the administration of sildenafil by oral route due to the possibility of significant adverse effects, without, however, the means to reverse the picture.

In this context, the usefulness of the sodium nitroprussiate would be more beneficial; however, that was not what we observed. None of the 14 patients that received 100 mg of sildenafil presented arterial hypotension or other significant adverse effects, demonstrating the safety of the administration

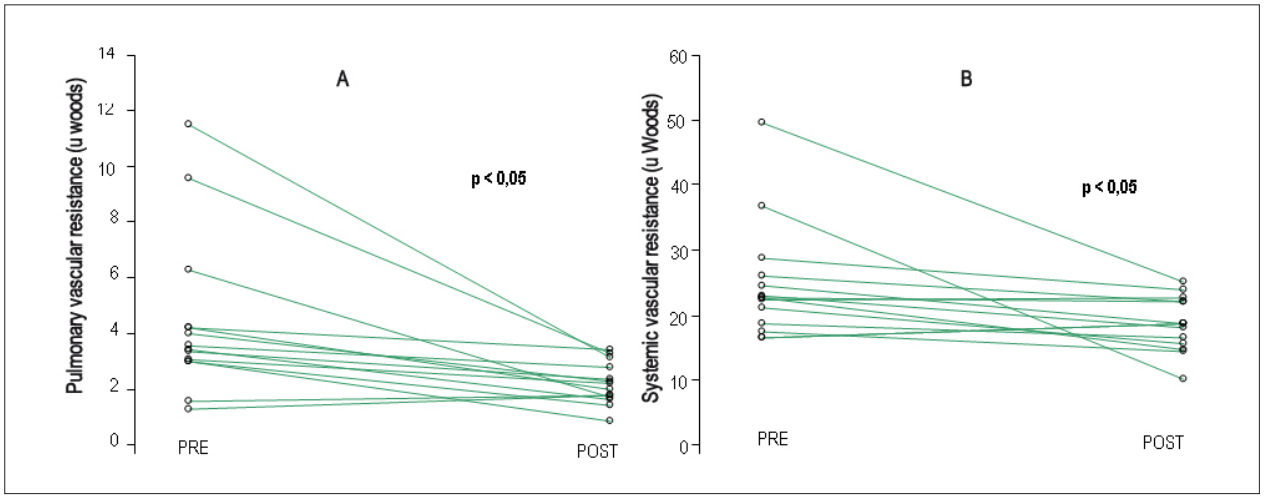

Figure 2 - *Decrease in Pulmonary Vascular Resistance (PVR) (A) and Systemic Vascular Resistance (SVR) (B) in 14 patients with chronic heart failure before and after sildenafil.*

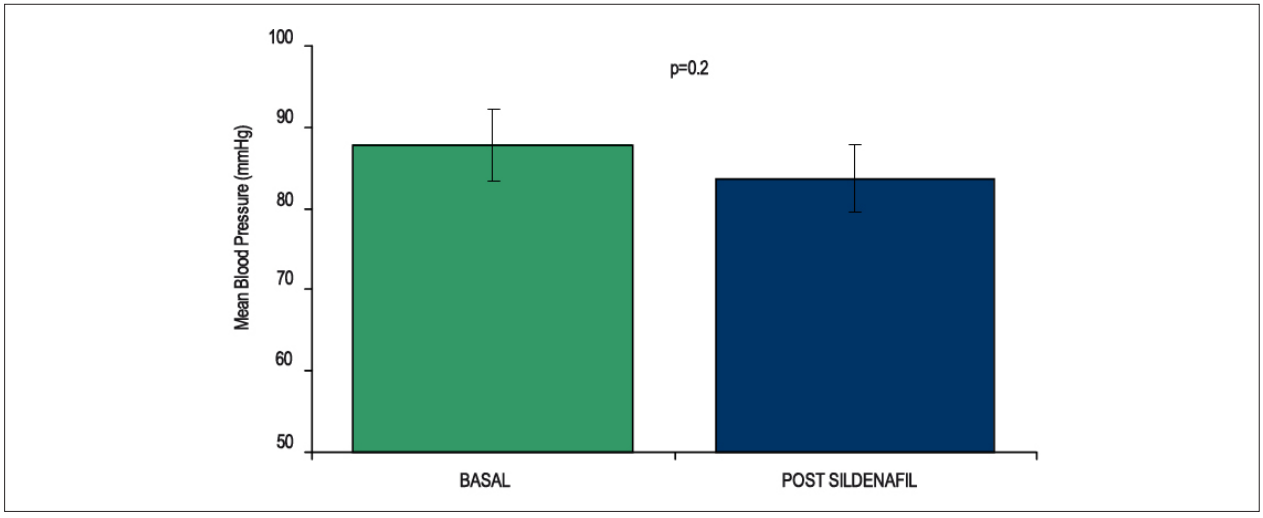

Figure 3 - Mean blood pressure before and after sildenafil administration.

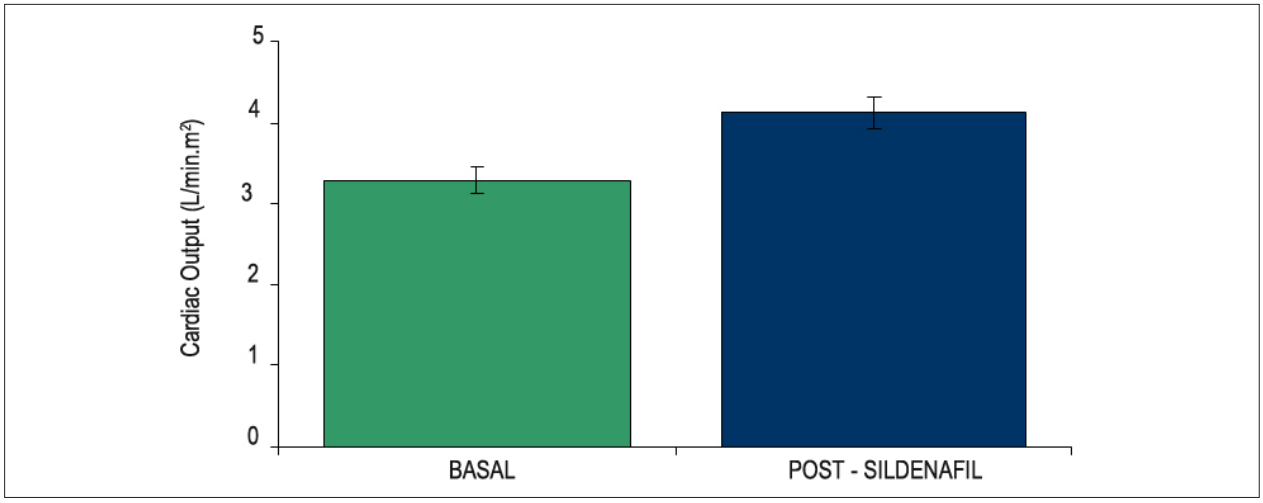

Figure 4 - Increase in cardiac output after acute administration of sildenafil ($p < 0.05$).

of the drug by oral route, as well as a higher pulmonary and systemic hemodynamic efficiency.

These findings can contribute to the use of sildenafil in the decrease of PH during the preoperative assessment of HT as well as in the management of PH and right ventricular dysfunction of the transplanted graft. It can be observed that its hemodynamic benefits and the safety of its administration are relevant findings, considering our reality.

Conclusion

Sildenafil is an effective and safe alternative in the acute management of pulmonary hypertension of patients with heart failure during the pulmonary vascular reactivity test. Their pulmonary hemodynamic benefits were obtained with no significant systemic consequences, such as arterial hypotension. These findings might contribute to the use of sildenafil in the PH control in the postoperative period of heart transplant, but further studies are necessary to define its applicability.

Potencial Conflict of Interest

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

Sources of Funding

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Study Association

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