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ORIGINAL ARTICLE

# Intravenous sildenafil in right ventricular dysfunction with pulmonary hypertension following a heart transplant

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## ABSTRACT

The objective of the present work is to describe the experience with intravenous (IV) sildenafil in heart transplant (HT) patients with reactive pulmonary hypertension (PH) who developed right ventricular dysfunction (RVD) in the immediate postoperative period. The first 5 patients who received IV sildenafil followinga HT are presented. The HTs took place between March 2011 and September 2012 in patients aged 37 to 64 years; all patients were male. Prior to the HT, mean pulmonary artery pressure (mPAP) was 32-56 mmHg. In all cases, the hemodynamic study demonstrated PH reactivity (positive vasodilator test with nitric oxide). All 5 patients developed RVD with hemodynamic instability immediately after the HT, despite the administration of nitric oxide from the time of intubation prior to the implant, optimal medical treatment in all cases, and a ventricular assist in 2 cases. In all patients, IV sildenafil was initiated at 10 mg/8 h for 48 h and was subsequently increased to 20 mg/8 h. in its oral formulation until discharge from the hospital. The change in pulmonary pressure was assessed using a Swan-Ganz catheter. Ventricular function was assessed using echocardiography. Length of stay in the Resuscitation Unit and mid-term survival were also assessed.

Average time of extracorporeal circulation was 200 ± 110 min and organ ischemic time was 210 ± 95 min. All of the patients demonstrated pulmonary and systemic hemodynamic improvement, as well as recovery of right ventricular function after completing the treatment with IV sildenafil. The stay in the Resuscitation Unit lasted 3-25 days. All the patients were discharged from hospital with no mortality to date. Intravenous sildenafil improves right ventricle hemodynamics associated with pulmonary hypertension post-HT. Prophylactic prevention with this drug could be indicated for patients with reactive PH who are about to receive a transplant.

**Keywords:** Cardiac transplant, PDE-5 inhibitor, Intravenous sildenafil, Pulmonary hypertension, Right ventricular dysfunction.

## Introduction

Right ventricular dysfunction (RVD) in the immediate post-operative period of heart surgery in general, and followingheart transplant (HT) in particular, is one of the most feared complications due to its high morbidity-mortality (1). Pulmonary hypertension (PH) is one risk factor associated with this complication and, in the post-operative period, it may be exacerbated by dysfunction in the pulmonary endothelium due to extra corporeal circulation and ischemia-reperfusion injury.

Sildenafil is a selective phosphodiesterase type 5 inhibitor responsible for the degradation of cGMP at a vascular level, thus producing vasodilation (2). It is most widely used in erectile dysfunction (3), in patients with Dana Point classification group I PH (4), and in cases of hypoxia related to pulmonary vasoconstriction (5).

For several years, sildenafil has also been used for the study of PH reversibility in patients being assessed for HT (6, 7). In these cases, oral sublingual administration is adopted. It reduces mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) in patients with PH caused by left ventricular systolic dysfunction and a high transpulmonary gradient.

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**TABLE I -** Preoperative patients' characteristics

| Patient | Diagnosis | Age, years | SaO2 | Prior surgeries | Code |
|---|---|---|---|---|---|
| 1 | Idiopathic DCM | 59 | 99 | No | Elective |
| 2 | Idiopathic DCM | 37 | 92 | No | Emergency |
| 3 | Ischemic cardiomyopathy | 57 | 99 | No | Elective |
| 4 | Congenital cardiomyopathy | 55 | 98 | Yes | Elective |
| 5 | Ischemic cardiomyopathy | 64 | 99 | No | Elective |

DCM = dilated cardiomyopathy; SaO2 = oxygen saturation.

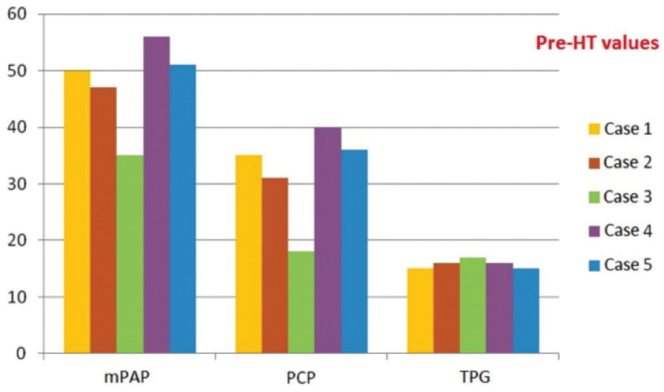


**Fig. 1 -** Values prior to the heart transplant. mPAP = mean pulmonary artery pressure; PCP = pulmonary capillary pressure; TPG = trans-pulmonary gradient; HT = heart transplant.

**TABLE II -** Need for vasoactive drugs, pulmonary vasodilator, mechanical assistance in the perioperative phase and time of stay in the Intensive Care Unit

| Patient | Noradrenaline mcg/kg/min | Dobutamine mcg/kg/min | Levosimendane mcg/kg/min | Adrenaline mcg/kg/min | NO | ECMO | IAB | Days ICU |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 20 | - | - | Y | N | N | 20 |
| 2 | 1.5 | 22 | 0.2 | 0.06 | Y | Y | Y | 25 |
| 3 | 0.8 | 10 | - | - | N | N | N | 6 |
| 4 | 1 | 12 | 0.4 | 0.04 | Y | N | Y | 14 |
| 5 | 0.8 | 15 | - | - | Y | N | N | 7 |

NO = nitric oxide; ECMO = extracorporeal membrane oxygenator; IAB = intra-aortic balloon; Y = yes; N = no; min = minutes; ICU = Intensive Care Unit.

Some authors have published good results for the combination of oral sildenafil and inhaled nitric oxide (iNO) in heart surgery and in post-HT patients with PHand RVD (8).

The treatment of acute dysfunction of heart grafts and the use of intravenous sildenafil is the subject of frequent debate in scientific sessions. It is for this reason that the objective of this document is to describe our experience with intravenous sildenafil in 5 patients who have undergone a HT and demonstrated RVD with PH in the immediate postoperative period, and who also were non-responsive to conventional optimal treatment (9).

## Materials and Methods

This is a retrospective study including 5 male patients (age 37-64 years) who underwenta HT from March 2011 to September 2012 (Tab. I). In the pre-transplant assessment, patients had a mean PAP of between 32 and 56 mm Hg. After performing a vasodilator test with iNO, reactive PH was confirmed (Fig. 1).

After the appearance of RVD and compromised hemodynamics, optimal medical treatment was established with vasoactive drugs, iNO and ventricular assistance when necessary (Tab. II). If, in spite of this, RVD persisted, treatment with IV sildenafil was started with slow bolus 10 mg/8 h for 48 hand subsequently replaced by the oral formulation at a dose of 20 mg/8 h. During the entire treatment, the patient was monitored using a Swan-Ganz catheter and echocardiograms were performed in order to assess ventricular function.

## Results

Extracorporeal circulation time was 200 ± 110 min and organ ischemic time was of 210 ± 95 min (Fig. 2). Two patients required ventricular assistance in addition to vasoactive drugs. One of these patients, prior to HT, required mechanical assistancein the form of extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon (IAB) with counter pulsation for 9 days, which was maintained postoperatively for 4 days due to severe RV dysfunction. Another patient required IAB.

All patients demonstrated favorable progress from the time that intravenous sildenafil was first administered and after switching to oral sildenafil. Improvement of the pulmonary and systemic hemodynamic parameters and right ventricular function was observed (Figs. 3 and 4). The stay in the Resuscitation Unit lasted from 3 to 25 days. All patients were able to be discharged from hospital and no patient has died during the follow-up period.

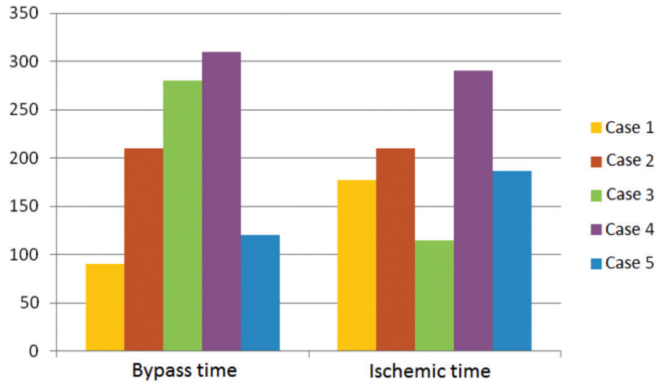


**Fig. 2 -** Time of extracorporeal circulation and organ ischemic time.

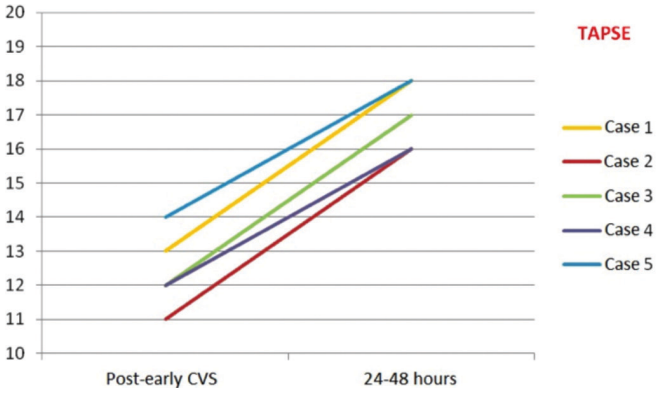


**Fig. 3 -** Postoperative TAPSE values after intravenous sildenafil. CVS = cardiovascular surgery; TAPSE = tricuspid annular plane systolic excursion.

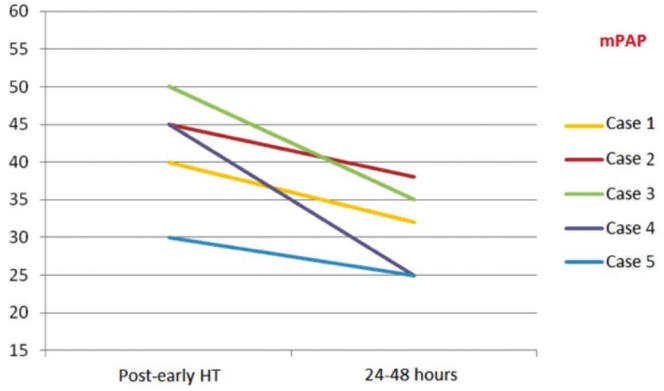


**Fig. 4 -** Mean pulmonary artery pressure after intravenous sildenafil. mPAP = mean pulmonary artery pressure; HT = heart transplant.

## Discussion and Conclusions

According to data from the International Society for Heart and Lung Transplantation, heart graft dysfunction represents the main cause of mortality in the subsequent postoperative period, making up approximately 37% of early deaths (10). Cardiac dysfunction, following a HT, takes place more frequently in the right ventricle than in the left ventricle. Therefore, pre-HT PH and its post-HT progress play a key role. One of the objectives of the treatment of this complication is basedon the reduction of pulmonary vascular resistance (PVR) and maintaining systemic arterial pressures and coronary perfusion. Nowadays, iNO is the pulmonary vasodilator most used, since it is a selective pulmonary vasodilator with no effects on a systemic level. However, its administration requires the patient to be intubated and to have mechanical ventilation, as well as be monitored to determine toxic metabolites. Therefore, new formulas are being sought to allow the administration of pulmonary vasodilator drugs that are easier to administer in patients with spontaneous breathing.

Sildenafil is a selective phosphodiesterase type 5 inhibitor responsible for cGMP degradation. Certain studies indicate that sildenafil reduces pressure in the pulmonary artery with an increase in the cardiac index and an improvement in right ventricular contractility.

There are few papers describing the oral use of sildenafil in heart transplant patients and even fewer describing its intravenous administration. Some authors report their initial experiences with oral sildenafil with good results overall (11, 12). In other articles, its use is even recommended in the perioperative period for the prevention of RVD, since its use improves prognosis as well as short- and long-term outcomes (13).

Even though the oral route is that most frequently used, the intravenous formulation may be indicated in the early postoperative period in which the oral route cannot be used. Thus, we find certain very interesting documents comparing intravenous sildenafil with milrinone in patients with heart failure, obtaining similar PVR and systemic reductions, as well as improvements in the cardiac index (14).

In the present work, we have attempted to demonstrate that intravenous sildenafil is an efficient tool in patients who have undergone a HT with RVD and PH. Apart from the overall good progress of patients, an improvement in pulmonary pressure and right ventricular function was observed in all cases. Another aspect that also supports our paper is the sequence used; in this way, no clinical worsening was observed upon switching from IV sildenafil to its oral formulation.

There is no doubt that one of the questions to bear in mind in HT patients is its potential interference with immuno suppressive drugs. Therefore, it is necessary to maintain strict control of immuno suppression levels.

This descriptive study has limitations due to the low number of patients and its retrospective nature. Therefore, echocardiographic studies were not regulated. Likewise, not all of the hemodynamic parameters were available in all cases, which could have helped to better profile the patients' clinical condition. However, intravenous sildenafil is a drug that has been recently included in the medical pharmacopeia. There arelittle data on experience available and no long series have been published. This work will help widen our knowledge about this drug and its uses.

Therefore, in patients with disproportionate but reversible PH of a cardiac cause, who undergo a HT and have RVD associated with PHT, the early administration of intravenous

sildenafil, whether associated with iNO or not, helps to reduce pulmonary pressure, improve right ventricular function and clinically stabilize patients.

## Disclosures

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Conflict of interests: The authors declare no potential conflict of interests.

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