

# Farmacologic test pre-implants in hypertension pulmonary elevated and still in candidates to heterotopic transplantation

*Teste farmacológico pré-implante na hipertensão pulmonar elevada e fixa em candidatos a transplante heterotópico*

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## Abstract

**Background:** Evaluation of pulmonary artery pressure just before transplanting with sodium nitroprusside may allow conversion to orthotopic technique.

**Methods:** Between 1992 and 2007, 228 transplants were performed systematically and this was used in seven patients with preoperative hemodynamic evaluation: Pre NP (mmHg) Post NP (mmHg) Systolic systemic blood pressure (PSAS) 108-78 (101.7 ± 10.9) 90-74 (79.5 ± 15.2) pulmonary arterial systolic pressure (PASP) 88-51 (69.8 ± 13.2) 70-40 (57.8 ± 9.9) Gradient transpulmonary (GTP) 16-11 (14.2 ± 1.7) 14-11 (12.4 ± 1.2) pulmonary vascular resistance (PVR/w) 7.9 to 4.8 (6.2 ± 1.0) 5.9-4.1 (5.0 ± 0.8).

**Results:** The intraoperative findings were: Pre NP (mmHg) e Post NP (mmHg), respectively, PSAS 91-78 (8.5 ± 5.2) and 65-59 (4.2 ± 63.8) ( $P = 0.017$ ), decrease 19.9%, decrease 29.3%; PSAP 71-52 (61.8 ± 6.1) and 43-32 (37.5 ± 3.3) ( $P = 0.018$ ), decrease 28%, decrease 41%. In light of these data, patients were transplanted by orthotopic technique not being observed mortality in the short and long-term evolution from 5 months to 6 years.

**Conclusion:** This methodology allowed the conversion of the technique for heterotopic orthotopically, with good early and late outcomes.

**Descriptors:** Hypertension, pulmonary. Heart transplantation. Pulmonary artery.

## Resumo

**Objetivos:** Avaliar a pressão da artéria pulmonar, nos momentos que precedem ao transplante, e verificar se o nitroprussiato de sódio pode possibilitar a conversão para técnica ortotópica.

**Métodos:** Entre 1992 e 2007, foram realizados 228 transplantes e esta sistemática foi empregada em sete pacientes que apresentavam na avaliação hemodinâmica pré-operatória: Pré NP (mmHg) Pós NP (mmHg) Pressão Sistólica Arterial Sistêmica (PSAS) 108 - 78 (101,7 ± 10,9) 90 - 74 (79,5 ± 15,2) Pressão Sistólica Arterial Pulmonar (PSAP) 88 - 51 (69,8 ± 13,2) 70 - 40 (57,8 ± 9,9) Gradiente Transpulmonar (GTP) 16 - 11 (14,2 ± 1,7) 14 - 11 (12,4 ± 1,2) Resistência Vascular Pulmonar (RVP/w) 7,9 - 4,8 (6,2 ± 1,0) 5,9 - 4,1 (5,0 ± 0,8).

**Resultados:** Os achados intra-operatórios foram: Pré NP (mmHg) e Pós NP (mmHg), respectivamente, PSAS 91-78 (8,5 ± 5,2) e 65-59 (4,2 ± 63,8) ( $P = 0,017$ ), queda 19,9%, queda 29,3%; PSAP 71-52 (61,8 ± 6,1) e 43-32 (37,5 ± 3,3) ( $P = 0,018$ ), queda 28%, queda 41%. Diante destes dados, os pacientes foram transplantados pela técnica ortotópica, não sendo constatada mortalidade a curto e a longo prazo em evolução de 5 meses a 6 anos.

**Conclusão:** A aplicação desta metodologia permitiu a conversão da técnica heterotópica para ortotópica, com bons resultados imediatos e tardios.

**Descritores:** Hipertensão pulmonar. Transplante de coração. Artéria pulmonar.

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## INTRODUCTION

Many patients with advanced degrees of heart failure (HF) have elevated pulmonary artery pressure, and pulmonary hypertension (PH) is considered a serious contraindication to orthotopic transplantation due to the risk of acute or chronic failure of the right ventricle by the inability to adapt to high pressures within the lung after its implantation in the recipient [1,2].

However, some patients with moderate to severe PH are successfully transplanted. In those patients, the assessments are made in the preoperative hemodynamic selection which shows a decrease of pulmonary artery pressure, thus illustrating the reversibility of PH [3-5]. Hemodynamic tests of the potential reversibility of PH by the administration of FIO<sub>2</sub> at 100%, nitroglycerin or sodium nitroprusside is often used in evaluating candidates for heart transplantation (HT) [6,7].

Unquestionably, HT is the treatment of choice for patients in the final stages of heart failure. The increased pulmonary vascular resistance (PVR) may determine the high-risks in the short- and long-term, making it difficult to select candidates [8]. Thus, patients with fixed, unresponsive, high PVR to vasodilator therapy are often contraindicated for heart transplant [9,10].

The degree of PH and its reversibility on pulmonary vasodilation has an important impact on the post-transplantation outcome. PH levels above which mortality rate increases are varied in the literature [11,12]. Many techniques have been described to reduce it before and after surgery [13,14]. Since the initial studies reporting the relationship between elevated PVR and increased mortality rate after orthotopic heart transplant, different conclusions have been observed [15].

The use of orthotopic technique is indicated for patients with PVR < 5 Wood units. Patients with PVR ranging from 5 units and 8 units would be considered candidates to heterotopic transplantation [16]. The advantages are as follows [17]:

1. The heart of the recipient functions as a device of assisted circulation and can maintain the circulation:

1. after reversible or irreversible loss of the heart function by acute or chronic rejection;
2. during the adjustment period; a little size heart for the size of the recipient;
2. It allows the recovery of the native heart in acute disorders;
3. It can be performed even in the presence of elevated PVR.

The disadvantages are as follows:

1. Risk of systemic embolism due to the recipient's heart;
2. Need for permanent anticoagulation;

3. Persistence of angina in patients with ischemic cardiomyopathy;

4. Risk of infection or thrombus in patients with prosthetic heart valves;

5. Arrhythmias requiring treatment with drugs that may impair the prosthesis function.

The guideline on Cardiac Transplantation of the Brazilian Society of Cardiology [18] recommends carrying out a hemodynamic study with or without vasodilators (sodium nitroprusside, nitric oxide, prostaglandins). It considers the findings of PVR < 4 units as a good prognosis; PVR > 4 units and Gradient transpulmonary (GTP) > 15 mmHg as higher risk. The orthotopic technique is contraindicated if PVR ≥ 6 units (less responsive or unresponsive to vasodilators), being recommended the heterotopic technique.

Costard-Jackle et al. [19] understand that a PVR > 2.5 units without a test with a hypotensor, and a PVR ≤ 2.5 units after or without reduction lower than or equal to the systemic systolic arterial pressure, the mortality rate 3 months after surgery are high. Mehra et al. (International Society for Heart and Lung Transplant Guidelines) direct the attention to a pulmonary artery pressure (PAP) ≥ 50 mmHg, or GTP ≥ 15 mmHg, or PVR > 3 units with systemic systolic arterial pressure > 85 mmHg with an indication for responsiveness to vasodilator testing (Class I, evidence level C). When a response to a vasodilator does not occur, the indication is for mechanical circulatory assistance due to an irreversible PH (Class II b, evidence level C). The orthotopic heart transplant in this case is contraindicated [20].

## METHODS

In the period between 1992 to 2007, the Transplant Medical Facility at the Institute Dante Pazzanese de Cardiologia/São Paulo carried out 228 heart transplant using the following techniques: classical (21–9.2%), bicaval unipulmonar (8–3.5%), bicaval bipulmonar (197–86.4%), and heterotopic (2–0.8%). From this series, we have selected seven patients with elevated PVR and GTP, less responsive or unresponsive to vasodilator therapy with sodium nitroprusside (SN) intravenous applied during the hemodynamic study performed during the evaluation and selection of recipients.

The majority of the patients (6) were male, age ranging from 29 to 64 years (46.2 ± 12.7 years) with dilated (4), chagasic (2), and ischemic (1) cardiomyopathy.

In view of these data, these patients were accepted as candidates for heterotopic heart transplant and were enrolled in the Single List of the Center of Notification, Collection, and Distribution of Organs (CNCDO) from the Health Secretariat of São Paulo State. At this time, it was

adopted the strategy of requiring the equivalence of weight and body surface donor/recipient in the likeness of the candidates for orthotopic heart transplants.

With the recipient in the operating room with continuous control of MAP, ECG, CVP, temperature and diuresis, under general anesthesia with mechanical ventilation and the heart exposed by median thoracotomy, in the moments that precede the initiation of implantation of the donor's organ, Jelco [14] had the pulmonary artery catheterized and SASP (mmHg) PSAS (mmHg) evaluated continuously and simultaneously, initially with FIO<sub>2</sub> concentrations ranging up to 100% and after the infusion of SN.

Donor's age ranged from 18 to 49 years (30.3 ± 11.3) and the causes of brain coma were head injury (3), hemorrhagic stroke (2), cerebral anoxia (1) and brain tumor (1). The origin of these donors was HC OPO/SP (3), IDPC OPO/SP (3), and EPM OPO/SP (1).

When the graft arrived at the operating room, the recipient was placed on cardiopulmonary bypass (CPB) support by cannulation of the ascending aorta and selective of superior e inferior vena cava. After CBP was started, the temperature was lowered to around 25°C. The native organ was completely removed, leaving only stumps of the right and left pulmonary veins, the inferior and superior vena cava, the pulmonary artery, and the aorta.

The myocardial protection of the graft was performed with an infusion of 1000 ml of crystalloid cardioplegia at 4°C (KCl, 19.1%, 6 ml; NaHCO<sub>2</sub>, 2 ml) at the aortic root. At the time after removal from the donor's body, the organ was then preserved into a sterile container containing saline solution at 4°C in sterile plastic bags. The container was placed in an isothermal box with ice for transplantation. Before the beginning of the procedure, at the operation room, the recipient was administered another infusion

(500ml) of cold crystalloid cardioplegia at 4°C in the aortic root, repeated approximately at every 40 minutes during the implantation.

The anastomoses were initiated by the right and left pulmonary veins, inferior and superior vena cava, pulmonary artery, and aorta using the technique of bicaval orthotopic heart transplant lung ventilation [21].

After the anastomoses were concluded and after temperature comes to normal, heart beats were resumed, and the CPB support was withdrawn. After the neutralization of the heparin with protamine sulfate, the hemostasis was reviewed and the synthesis of the thorax was made in planes.

## RESULTS

The pressure findings found during the hemodynamic study in the preoperative evaluation of lung transplant candidates are shown in Table 1.

The pressure findings found at the moments prior to the implantation of the donated organ, with and without the use of SN, allow us to verify the impact of vasodilators on the systemic and pulmonary circulations (Table 2, Figures 1 and 2).

On account of these results, all patients were considered eligible to receive the implant orthotopically, once the allocated organs are adequate to the relation donor/recipient weight/body surface.

The ischemia time ranged from 110 to 182 minutes (139.2 ± 25.6 min) and implantation time ranged from 72 to 118 minutes (95 ± 14.3 min).

The in-hospital course was uneventfully. All the patients were discharged from 10 to 21 days after surgery. The survival of the patients ranges from three months to six years; all of them evolving stable as expected.

Table 1. Findings of pressure of the preoperative hemodynamic study in the selection of recipients, pre- and post-application of sodium nitroprusside.

	Before SN (mmHg)	After SN (mmHg)
Systolic systemic blood pressure (PSAS)	108 - 78 (101.7 ± 10.9)	90 - 74 (79.5 ± 15.2)
Pulmonary Artery Systolic Pressure (PASP)	88 - 51 (69.8 ± 13.2)	70 - 40 (57.8 ± 9.9)
Transpulmonary Gradient (GTP)	16 - 11 (14.2 ± 1.7)	14 - 11 (12.4 ± 1.2)
Pulmonary Vascular Resistance (PVR/W)	7.9 - 4.8 (6.2 ± 1.0)	5.9 - 4.1 (5.0 ± 08)

\* Endovenous sodium nitroprussite 20 to 50 mg/min

Tabela 2. Findings of pressure at the moments prior to the implantation of the donated organ, with and without the use of sodium nitroprusside.

	Before SN (mmHg)	After SN (mmHg)	P	Fall	Fall
PSAS	91 - 78 (8.5 ± 5.2)	65 - 59 (63.8 ± 4.2)	0.017	19.9%	29.3%
PASP	71 - 52 (61.8 ± 6.1)	43 - 32 (37.5 ± 3.3)	0.018	28%	41%

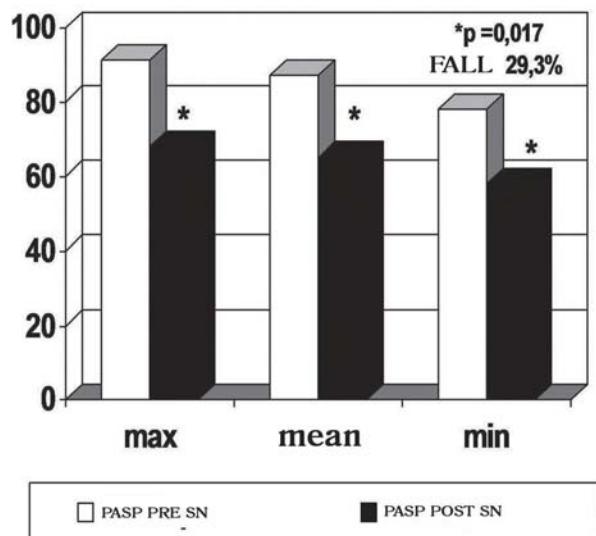


Fig.1 – Intraoperative systemic arterial pressures before and after the use of sodium nitroprusside

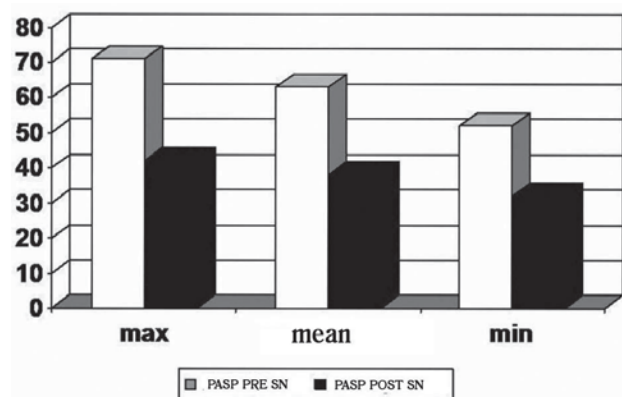


Fig. 2 – Intraoperative pulmonary arterial pressures before and after the use of sodium nitroprusside

## DISCUSSION

The high incidence of PH is considered a risk factor for mortality in the short- and long-term after heart transplant. It was demonstrated the correlation of PVR with mortality in a linear fashion. The importance of the vasodilator therapy in the pre-transplant has been reported in patients with elevated PH. It can be observed conflicting opinions about the degree of PH associated with a poor prognosis [8,19].

However, a decrease in PVR immediately to as well as long after the transplantation has been described in patients with high levels of PH. Despite the convincing data that PH is an independent risk factor for death, multicenter studies need to identify the specific levels of PVR and GTP

above which the risk of death is substantial. The literature addressing a consistent definition for PVR, the various methods of reversibility test, the non-standardization in the periods analyzed after heart transplant has not reached a consensus yet [22,23].

Thus, Chen et al. [8] described a low mortality rate in the first 30 days after heart transplant in patients with PVR > 3 Wood units. In a series of patients with GTP > 12 mmHg and PVR > 2.5 units, with or without response to vasodilator, Delgado et al. found a significant mortality rate in patients with low PH and PVR. Other authors [23] have found differences in early mortality rate and late complications in patients with PVR > 3 units and GTP > 12 mmHg. On the other hand, Klotz et al. [11] showed no difference in survival after heart transplant in patients with high and low PH.

In a recent study, Chang et al. [15] described a significant correlation between PVR with mild to moderate PH prior to heart transplant during the first 6 months of postoperative course. The same did not occur in greater postoperative courses. In cases of high PH, the mortality rate was higher with no impact on the long-term.

On the other hand, it is important to know that in many heart transplant programs, patients with these characteristics are referred to the heterotopic technique or even to the heart/lung technique, using the strategy of accepting donors with greater weight and body surface area for patients with reversible or partially reversible elevated PH using the orthotopic technique [24].

The PVR reduction usually occurs immediately after transplantation, and it is due to its reversible component [22]. However, there are reports of irreversibility in evolution up to five years in patients with elevated PH, as well as in cases of elevated but yet reversible PVR, a continuous time-dependent reduction occurs [23]. The complications and mortality rates are independent of PVR prior to transplantation and increased cardiac output and fall of the GTP are not the only factors that determine the PVR reduction. Chang et al. [15] concluded that the decrease in PVR was associated with an increased cardiac output without changes in GTP. A reduction in PVR (< 3 units) in 83% of cases with mild to moderate PH and in 80% of the cases with severe PH was found [24]. These patients had better and longer survival when compared with those with HP e' 3 w in the first year of HT; PVR in the first 30 days was similar to that found after the first 12 months, usually in normal or near normal values, leading us to assume that the vast majority of patients with elevated PH has a component of reversibility.

The decrease of PVR and GTP, in face of the increase in the cardiac output generated by the transplanted organ, supports the theory of slow reaction time-dependent components of PVR after heart transplant, making it possible

to conclude that mild, moderate, or severe reversible PVR does not have a negative influence in the short- and long-term post-transplantation when donors of larger hearts are used orthotopically, and residual PH is associated with a long-term survival reduction [25].

The assessment of HP reversibility moments before the implantation of a donor heart has peculiar characteristics, which do not occur in the pressure test carried out during the candidates' selection phase, where these procedures are performed in a hemodynamic laboratory with the patient conscious, breathing spontaneously with lower FIO<sub>2</sub>. In the operating room, patients are under the effects of anesthetic agents, with mechanical ventilation and higher FIO<sub>2</sub>. These differences may be responsible for the findings obtained in this study, which were quite different from those of the pre-operative phase.

The PH generated by the excessive blood flow in congenital heart disease that led to steady and high levels of blood pressure (Eisenmenger syndrome) is well-known and stratified. The same does not occur with a PH originated from CI deeper degrees, whose spectrum is very varied, and its pathophysiology is poorly understood. On the other hand, the technique for orthotopic heart transplant is appropriate because the donor organ replaces the native organ and fully recovers the body weakened and depleted, restoring hope and the quality of life. The applicability of the heterotopic technique with its many drawbacks are exceptional, and it is restricted to patients with an unresponsive PH.

In face of the evidence found in the literature and those obtained in this study, when the accuracy of hemodynamic data of less or none PH irreversibility obtained at the preoperative cardiac catheterization is compared to the assessment obtained in the operating room in the moments prior to the implantation many doubts arise. The pharmacological impact was so conclusive, that all patients who had an indication for the heterotopic technique were orthotopically transplanted. All of them presented consistent results in the short- and long-term.

Another important aspect of this study is the strategy to establish the linearity of the donor-recipient weight/body surface of the donated organ, thus enabling the application of either surgical technique depending on the pressure profile of each case.

## CONCLUSION

The hemodynamic evaluation with SN at the moments prior to the implantation of donor heart showed resoluteness, allowing us to wait for a chance to use the appropriate surgical methodology/approach with the patients presenting elevated and unresponsive PH, the simplicity and originality being some of its main features.

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