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# Effects of inhaled nitric oxide on pulmonary hypertension in patients after mitral valve surgery

***Efeitos do óxido nítrico inalatório na hipertensão pulmonar de pacientes após cirurgia valvar mitral***

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***Abstract***

***Objective:*** **Cardiac surgery in patients with pulmonary hypertension may present severe postoperative complications. The study consists of verifying the effects of using inhaled nitric oxide (iNO) in patients during the postoperative period of mitral valve surgery.**

***Methods:*** **The effects of iNO were measured mainly by verifying changes in pulmonary artery pressure (PAP). Other measures performed included mean arterial pressure (MAP), mean central venous pressure (CVP), mean left atrial pressure (LAP), oxygen saturation by pulse oximetry, and static pulmonary compliance.**

***Results:*** **In the 20 patients studied, a median time of iNO use of 19.1 hours was obtained. The mean PAP was significantly reduced from 33.8 ± 6.17 mm Hg (pre-iNO) to 29.1 ± 6.46 mm Hg in the initial 30 min and to 28.4 ± 5.22 mm Hg considering the mean of all post-iNO measures ($p < 0.05$). No significant changes occurred in the other hemodynamic measures.**

***Conclusion:*** **The findings indicate that the use of iNO, in post-operative period of mitral valve operation associated with pulmonary hypertension, reduces PAP without systemic effects, demonstrating a selective vasodilator effect on the pulmonary vascular system.**

***Descriptors:*** **Nitric Oxide. Hypertension, pulmonary. Mitral valve, surgery.**

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***Resumo***

***Objetivo:*** **O estudo consiste em verificar os efeitos da utilização do óxido nítrico inalatório (NOi) em pacientes no pós-operatório de cirurgia valvar mitral.**

***Método:*** **Os efeitos do NOi foram medidos principalmente por meio da verificação de alterações na pressão arterial pulmonar (PAP). Outras medidas realizadas incluíram: pressão arterial média (PAM), pressão venosa central média (PVC), pressão média de átrio esquerdo (PAE), saturação de oxigênio por oximetria de pulso, complacência pulmonar estática e gradiente transpulmonar (GTP).**

***Resultados:*** **Nos 20 pacientes estudados, obteve-se tempo mediano de utilização do NOi de 19,1 horas. A PAP média reduziu significativamente de 33,8 ± 6,17 mmHg (pré-NOi) para 29,1 ± 6,46 mmHg, nos 30 minutos iniciais e para 28,4 ± 5,22 mmHg, considerando a média de todas as medidas pós-NOi (p< 0,05). O GTP também apresentou redução estatisticamente significativa. Não houve alterações significativas nas demais medidas hemodinâmicas.**

***Conclusão:*** **Os achados indicam que a utilização do NOi reduz a PAP sem efeitos sistêmicos, demonstrando efeito vasodilatador seletivo no sistema vascular pulmonar.**

***Descritores:*** **Óxido nítrico. Hipertensão pulmonar. Valva mitral, cirurgia.**

## INTRODUCTION

Pulmonary hypertension (PH) is a clinical and hemodynamic syndrome that results in vaso-occlusive alterations of the micro circulation system, aggravated by pathologic interactions between the vascular wall and circulating elements [1]. The disease constitutes a problem that can lead to substantial morbidity and mortality rates in the postoperative period of heart surgery [2,3].

Mitral valve lesions, such as stenosis and insufficiency, make the blood flow turbulent and may lead to progressive fibrosis and calcification of the valve apparatus, enlargement of the left atrium and calcification and obliterate changes of the pulmonary artery bed [4]. Consequently, there is an increase in the retrograde pulmonary venocappilary pressure and the appearance of reactive arteriolar vasoconstriction that causes anatomic restrictions of the pulmonary vascular bed due to thickening of the media layers of small arteries and arterioles, by peripheral extension of the smooth musculature of these vessels and partial or complete obliteration of their lumens [5].

In 1987, Palmer et al. [6] demonstrated that the endothelial-derived relaxation factor (EDRF) was a free radical: nitric oxide (NO). NO mediates several cellular phenomena including endothelium-dependent vasorelaxation, macrophage-mediated cytotoxicity, inhibition of the activation, adhesion and aggregation of platelets [7].

The idea that inhaled NO might cause selective pulmonary vasodilation motivated several studies in animals. From these studies, it was proved that vasodilation can be achieved with low concentrations of NO (5-80 ppm) without associated systemic effects. Since then, the utilization of inhaled NO (NOi) has been well defined, not only for pulmonary diseases, but also in association with heart disease [8,9]. Thus, this work aims at verifying the effects of the utilization of NOi in patients with pulmonary hypertension in the postoperative period of mitral valve surgery.

## METHOD

### Design and sampling

This research is a non-controlled clinical trial that followed a pre-established protocol for the used of inhaled NO in the Postoperative Unit of the Instituto de Cardiologia do Rio Grande do Sul / FUC. The individuals who participated in the study were patients in the immediate postoperative period of following mitral valve surgery (elective surgery) with or without the association of other heart lesions or atrial fibrillation, which were also corrected during the surgical procedure.

The patients were diagnosed with pulmonary hypertension secondary to the mitral valve lesion. Those with systolic pulmonary arterial pressure (SPAP) greater than 60 mmHg in the postoperative period estimated by echocardiography or catheterism were selected. In the postoperative period, the pre-selected patients were using mechanical respiratory support and have a SPAP greater than or equal to 40 mmHg or a mean pulmonary arterial pressure (MPAP) greater than or equal to 25 mmHg. The postoperative PAP measurements were achieved by a rigid percutaneous catheter fixed in the pulmonary artery during the surgical procedure.

### Technique of NOi supply

The technique to supply the NOi was using a specialized system with monitoring (Printer Nox of White Martins) with a cylinder containing NO in equilibrium with nitrogen. The distal inspiratory branch of the ventilation circuit is connected to the gas supply system. An electrochemical analyzer is maintained in contact with the proximal part of the inspiratory branch of the ventilator, enabling the system to continuously monitor the levels of NOi to the patient and the levels of nitrogen dioxide ($NO_2$) that may be being formed (NOi reacts with the oxygen present in the ventilatory circuit, making the formation of $NO_2$ which is slightly toxic possible).

The participating individuals received a fixed dose of 20

ppm of NO by the aforementioned system. The formation of $NO_2$ was tolerated up to 3 ppm, as above this level it may be toxic.

The utilization of NOi was established during the period in which the patients remained on mechanical respiratory support. For all the patients, fluctuation in the NO dose offered was prevented.

Weaning from the system was performed when the patient presented with hemodynamic stability (adequate pulmonary and system hemodynamic values), according to the clinical parameters. Weaning was achieved by reducing the supply by 5 ppm every 30 minutes until zero and then disconnecting. Progressive removal is necessary to avoid the possibility of a rebound effect on the PAP.

**Measurements**

The evaluations performed included periodic measurements of PAP (the main measurement), central venous pressure (CVP), mean left atrium pressure (LAP), mean arterial pressure (MAP) and oxygen saturation (Sat O2) by pulse oximetry. The measurements were first made on arrival of the patient in the postoperative unit (before using NOi), thirty minutes after installation of the NOi supply system and at six-hour intervals until the ventilatory system was disconnected. When taking the measurements, if necessary, the patients were sedated with midazolam, to prevent alterations of the pressures readings, which were performed using a multiparameter monitor configured for invasive pressure readings (Datascope 1). The choice of this medication was based on the fact that it does not affect the pulmonary circulation. As the time of NOi varies according to the necessities of each patient, the results of the aforementioned variables were considered for the pre-NOi, 30 minutes post-NOi and in respect to the mean of all the measurements taken after the installation of the NOi (mean post-NOi).

Static pulmonary complacency was also verified on arrival of the patient in the unit (prior to using NOi) and thirty minutes after the installation of the system, as at these times the patients were still under the effects of anesthesia (the correct measurement of static pulmonary complacency requires the patient to be under the effects of anesthesia). The formula utilized to calculate the complacency was: $C_{est} = \Delta v / Pplat - peep$, where $\Delta v$ = variation in volume; Pplat = plateau or alveolar pressure; and peep = positive end expiratory pressure [10].

Other parameters included the intubation time and the time of stay in the ICU (time in hours).

**Statistics**

Analysis of the data was achieved using the t test for matched samples and the Pearson Correlation considering a power of 99% and an alpha error of 0.05. The results were expressed as means ± standard deviation or medians.

**Ethics**

The work was approved by the Research Ethics Committee of the Instituto de Cardiologia do Rio Grande do Sul / FUC where the work was carried out. All the patients signed written consent forms.

RESULTS

In the period from November 2003 to January 2005, a total of 20 patients were enrolled in the study. The mean time of NOi was 19.16 hours (minimum 2 and maximum 62 hours). The level of $NO_2$ remained below 1 ppm for all patients.

Of the patients, 55% had associated lesions which were corrected in the same surgical procedure (tricuspid and aortic valve lesions and ischemic heart disease). Additionally, 30% of them had already been submitted to heart surgery.

Seventeen patients (85%) underwent mitral valve replacement (16 with biological prostheses and one with a metallic prosthesis) and three patients (15%) were submitted to mitral valvuloplasty.

The functional class (NYHA), gender, ethnicity, type of mitral valve lesion and the existence of other associated lesions were not associated with the results (p-value > 0.05).

Table 1 illustrates the demographic and clinical data of the patients. Of these data, only the ejection fraction was correlated with the results: the higher the percentage of the preoperative left ventricle ejection fraction (LVEF%) the greater the drop in the PAP (R = 0.43 and p-value = 0.05).

In respect to the EAP, CVP, MAP and Sat $O_2$ measurements, there were no significant alterations comparing the pre- and post-NOi values (Table 2).

The static pulmonary complacency presented an increase from 43.20 ± 10.17 mL/cm $H_2O$ pre-NOi to 45.08 ± 11.57 mL/cm $H_2O$ 30 minutes post-NOi without giving a statistically significant difference between the two readings.

The time of tracheal intubation varied from 11 to 167 hours with a median of 24 hours. The mean time in the intensive care unit was 139.22 ± 67.5 hours (minimum 70 and maximum 313 hours).

Fifteen patients (75%) used dopamine concomitant to the utilization of NO; three of these patients also received noradrenalin and two received dobutamine. Another two patients (10%) received dobutamine in isolation. The data were adjusted in respect to confounding factors which showed that the patients who used dopamine in association to noradrenaline had a lower drop in the mean PAP (p-value = 0.045). The isolated use of dopamine did not present a statistically significant correlation in respect to the results.

Table 1. Demographic and clinical data

| Patient | Age | Gender | NYHA | Rhythm | LVEF% | SPAP | Mitral Lesion | MV area | CPB | clamping |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 63 | F | III | AF | 73 | 70 | stenosis | 0.79 | 120 | 63 |
| 2 | 50 | M | IV | AF | 67 | 66 | insufficiency | 1.2 | 130 | 108 |
| 3 | 34 | F | IV | AF | 59 | 57 | stenosis | 2.3 | 135 | 62 |
| 4 | 37 | F | II | NR | 65 | 90 | DL | 1.4 | 136 | 114 |
| 5 | 50 | M | III | AF | 61 | 61 | DL | 1 | 95 | 63 |
| 6 | 59 | F | III | AF | 67 | 65 | stenosis | 0.67 | 75 | 43 |
| 7 | 70 | M | III | AF | 73 | 88 | insufficiency | - | 58 | 34 |
| 8 | 35 | M | IV | NR | 44 | 61 | stenosis | 3.9 | 104 | 78 |
| 9 | 64 | M | II | AF | 77 | 60 | insufficiency | 1 | 70 | 50 |
| 10 | 77 | F | IV | NR | 54 | 83 | insufficiency | - | 100 | 52 |
| 11 | 62 | F | IV | AF | 34,8 | 66 | insufficiency | 2.8 | 66 | - |
| 12 | 40 | F | III | NR | 68 | 104 | stenosis | 0.8 | 92 | 62 |
| 13 | 73 | M | IV | NR | 64 | 72 | DL | 1.4 | 137 | 100 |
| 14 | 61 | F | II | AF | 67 | 75 | stenosis | 1.9 | 123 | 88 |
| 15 | 48 | F | III | AF | 68 | 64 | DL | 1.05 | 139 | 72 |
| 16 | 50 | M | III | AF | 63 | 75 | insufficiency | 2.1 | 101 | 80 |
| 17 | 47 | F | II | NR | 51,3 | 100 | stenosis | 0.8 | 60 | 40 |
| 18 | 63 | F | III | AF | 77 | 80 | insufficiency | 3.5 | 100 | 82 |
| 19 | 32 | F | III | NR | 64 | 77 | DL | 0.9 | 73 | 61 |
| 20 | 61 | M | IV | NR | 20 | 68 | insufficiency | 4.7 | 80 | 54 |
| Mean ± SD | 53.8±13.4 | | | | 60.8±14.2 | 74.1±13.2 | | 1.3* | 99.7±27.6 | 68.7±22.4 |

*Age in years; F – feminine; M – male; NYHA – New York Heart Association (functional class); AF – Atrial fibrillation; NR – normal rhythm; LVEF% - Preoperative left ventricle ejection fraction; SPAP – preoperative systolic pulmonary artery pressure (mmHg); DL – double lesion; MV area – Mitral valve area (cm2); CPB – Cardiopulmonary bypass in minutes; clamping – time of clamping in minutes.*
** value expressed as a median*

Table 2. Results of secondary variables

| | Pre-NOi | 30 min Post-NOi | Mean Post-NOi |
|---|---|---|---|
| EAP | 15.75 ± 4.76 | 14.85 ± 5.18 | 14.48 ± 4.38 |
| CVP | 11.70 ± 4.23 | 10.80 ± 3.50 | 10.6 ± 3.34 |
| MAP | 73.95 ± 6.69 | 73.75 ± 9.02 | 76.18 ± 6.65 |
| Sat O2 % | 97.3 ± 2.43 | 97.3 ± 2.08 | 98.06 ± 1.23 |

*Values expressed in mean ± SD*
*EAP, CVP and MAP in mmHg; pre-NOi – prior to installation of inhaled nitric oxide; 30 min post-NOi – thirty minutes after installation of inhaled nitric oxide; Mean post-NOi – mean of all measurements after installation of inhaled nitric oxide*

The principle variable, PAP, demonstrated a significant drop of between 14% and 17% (Table 3).

The graph of Figure 1 shows the pre-NOi, 30 minutes post-NOi and the mean post-NOi of MPAP, SPAP and diastolic pulmonary artery pressure (DPAP).

The transpulmonary gradient (TPG = MPAP – EAP) presented a significant reduction from 18.05 ± 7.54 mmHg in the pre-NOi to 14.25 ± 7.48 mmHg at 30 minutes in the post-NOi and to 14.08 ± 5.03 mmHg in relation to the mean post-NOi (p-value < 0.001).

Table 3. Results of main variable

| PAP (mm Hg) | Pre-NOi | 30 min Post-NOi | Mean Post-NOi |
|---|---|---|---|
| Mean * | 33.80 ± 6.17 | 29.10 ± 6.46 | 28.40 ± 5.22 |
| Systolic * | 47.45 ± 9.17 | 39.85 ± 9.96 | 39.82 ± 8.86 |
| Diastolic ** | 24.55 ± 6.11 | 21.65 ± 5.40 | 20.90 ± 4.27 |

*Values expressed in mean ± SD*
*PAP – Pulmonary artery pressure; pre-NOi – prior to installation of inhaled nitric oxide; 30 min post-NOi – thirty minutes after installation of inhaled nitric oxide; Mean post-NOi – mean of all measurements after installation of inhaled nitric oxide. * p-value < 0.001; ** p-value < 0.05*

One patient presented with a rebound effect of the pulmonary pressures on two attempts of weaning from NOi. Only the third attempt of weaning was successful.

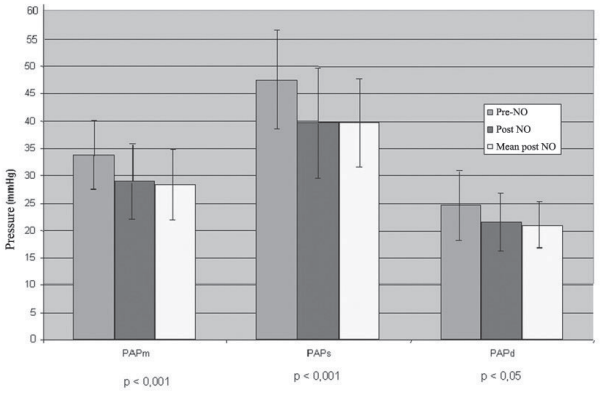


*Fig. 1 - General variation of PulmonarArtery Pressure (PAP)*

## DISCUSSION

Several articles have shown the effectiveness of inhaled NO in patients with pulmonary hypertension with different etiologies. Solina et al. [11] in 2000 and Schimid et al. [12] in 1999 demonstrated the selective pulmonary vasodilator effect of NOi in comparison with intravenous vasodilators, which also cause systemic vasodilation. The findings of the current study show this selective effect of NOi, as no significant alteration was seen in the MAP.

The significant reduction in the PAP, the main measurement of this study, shows that the NO is an efficacious resource in the management of pulmonary hypertension in the postoperative period of heart surgery, confirming the results of other studies.

In 2002, Maxey et al. [13] utilized doses of between 20 and 30 ppm of NOi in 17 patients with pulmonary hypertension in the postoperative period of heart surgery. The results demonstrated a significant reduction in the MPAP and right ventricular function and increases in the $PaO_2/FiO_2$ ratio without associated systemic alterations. Krasuski et al. [14] in 2000 considered a drop in the MPAP or pulmonary vascular resistance (PVR) greater than or equal to 20% as being a significant response to NOi. The data demonstrated that NO is a safe and effective agent for pulmonary vasoreactivity in both primary and secondary pulmonary hypertension. The study by Hayward et al. [9] in 1999 demonstrated selective pulmonary vasodilation as a rapid action caused by NOi. These data confirm our findings, which demonstrated a significant drop in the PAP within the first 30 minutes using the agent.

The objective of this research was also to evaluate the effects of NOi in a specific population: patients with pulmonary hypertension in the postoperative period of mitral valve surgery as the majority of works include more wide-ranging populations. It is well-known the patients with mitral valve disease can present with pulmonary hypertension even after surgical repair [15]. Moreover, according to Fullerton et al. [16] in 1997, pulmonary hypertension caused by valve disease can be refractory to NOi as his study did not demonstrate benefits using NOi in 10 adult patients after valve surgery.

The study by Timotoeo et al. [17] in 2003 analyzed a postoperative mitral valve stenosis case with hemodynamic instability and pulmonary hypertension. The use of NOi promotes a better control of pulmonary pressures and better ventilation. Girard et al. [15] in 1992 utilized NOi in six patients with chronic pulmonary hypertension after mitral valve replacement. The results showed pulmonary arterial vasodilation and hemodynamic improvement without changes in the systemic pressures. The improvement in the PVR was 22%. In 1993, Rich et al. [18] in a series of surgical patients predominantly with mitral valve disease, demonstrated a reduction of 35% in the PVR. Similarly, Snow et al. [19] in 1994 demonstrated a reduction of 42% in the PVR in nine patients in the postoperative period of mitral valve surgeries. Rawczynska-Englert et al. [20] in 1992 studied the utilization of NOi in 32 patients who underwent mitral valve replacement surgeries showing a significant difference in the right atrium, right ventricle and pulmonary capillary pressures and the PVR. According to Évora et al. [8] (2002) in the postoperative period of mitral valve surgeries, there was a reduction in the PVR of on average 20%, whilst the reduction in the PAP was 10%.

The PVR of our patients was not measured, but our results demonstrated a reduction in the pulmonary pressure of between 14% and 17%. We believe that the study of Fullerton et al. [16] in 1997 did not obtain satisfactory results due to the severity of the pulmonary hypertension of the patients involved.

The dose of 20 ppm of NOi utilized in this study is routinely utilized and is considered a safe dose. Experimental and clinical studies have not reported histological abnormalities in the pulmonary vascular system with the use of doses between 20 and 80 ppm of NOi [9]. We believe that the utilization of lower doses of between 10 and 20 ppm may have less toxic effects and the same benefits as higher doses [8,9,21].

Nitrogen dioxide formed in the reaction between NO and oxygen in the ventilation circuit, was continuously monitored in our patients. Although some guidelines accept maximum inspired concentrations of $NO_2$ of 3 ppm, the levels for the patients in this current study were less than 1 ppm.

The blood concentration of metahemoglobin was not measured in our patients, although this is common practice during the clinical administration of NOi. Despite of this, it is known that significant methaemoglobinaemia or formation of $NO_2$ is uncommon in patients who receive doses of NOi of up to 80 ppm [21].

The rebound effect that occurred in one patient, even though weaning was progressive, may be explained by the increases in the levels of endothelin in patients who utilize NO: a potential cause of pulmonary hypertension rebound [21,22].

Although our results were satisfactory, it is important to mention that the study had some limitations, which, perhaps, clearly masked the effects. Firstly, the absence of a control group which did not allow a comparison to assess the direct effect attributable exclusively to NO. However, it is known that when the obstructive lesion is removed (in our case surgery of the mitral valve) the hypertension and vascular lesions are reversed, although, a variable amount of time may be required for a relatively normal functional and morphological status to return [5]. Additionally, in our study we were able to observe alterations in the PAP soon after the installation of NOi, with significant reductions within the first 30 minutes of treatment. Another factor that should be mentioned is that the majority of our patients used dopamine. It is well known that this drug produces effects opposite to NO, although without proving to be statistically significant in our results. Secondly, our main measurement was PAP and it has been recognized that PVR is more dramatically affected by NOi. However, we were able to calculate the transpulmonary gradient, which was significantly reduced.

We should also take into account the severity of the disease of the participants in the study. Of all our patients, 55% had lesions associated with mitral valve lesions and 60% presented with chronic atrial fibrillation. Moreover, the severity of the pulmonary hypertension increases the surgical and postoperative risks of these patients.

For these reasons, we believe that the selection of patients to utilize NOi should be made with much caution. It is important to determine if reversible vasoreactivity is present. It is known that the only pulmonary arterial alterations with real possibilities of returning to near normal are hypertrophy and hyperplasia of the smooth muscle cells in the media layer. In responding patients, NOi gives beneficial vasodilation effects of the microvascular system, reducing the PAP and the PVR when there is established pulmonary hypertension. Additional to this, it has an antithrombotic action by inhibiting platelet aggregation, as well as improving the ventilation/perfusion ratio [8].

New possibilities are being presented by more recent studies which include the use of sildenafil. Leuchte et al. [23] in 2004 demonstrated the beneficial effects on the MPAP and PVR comparing sildenafil, NOi and iloprost. All caused significant responses. However, the studies of Lepore et al. [24] in 2002, Ghofrani et al. [25] in 2002 and Michelakis et al. [26] in 2002 showed that the combined therapy of NO and sildenafil presents more expressive results. Moreover, the association of the use of sildenafil may reduce the rebound effect after cessation of NOi, as it prolongs the vasodilation effect [21,24]. Although these results are promising, there are few data on the long-term treatment using sildenafil for pulmonary hypertension and the results were only from small series of patients. We believe that control studies are necessary to determine the efficacy, the size of the effect and the safety. Anyway, the combination of drugs with different mechanisms to maximize the clinical benefits is emerging as a good therapeutic action for pulmonary hypertension.

## CONCLUSION

The utilization of NOi demonstrates significant reductions in the PAP and PTG of patients with pulmonary hypertension in the postoperative period of mitral valve surgery. Moreover, its selective pulmonary effect can be proven as there are no significant changes in the MAP.

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