

# A Comparison of the Acute Hemodynamic Effects of Inhaled Nitroglycerin and Iloprost in Patients with Pulmonary Hypertension Undergoing Mitral Valve Surgery

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**Background:** Since the presence of pulmonary hypertension (PHT) affects the prognosis of the patients, it is important to manage and evaluate PHT. The aim of this study was to compare the hemodynamic effects of inhaled nitroglycerin and iloprost during early postoperative period, in patients with PHT undergoing mitral valve replacement surgery.

**Materials and Methods:** One hundred patients with PHT (mean pulmonary artery pressure (MPAP) >25 mmHg at rest), were randomized to receive either inhalation of nitroglycerin (group I; n=50) or iloprost (group II; n=50) in the postoperative period. In both groups, baseline hemodynamic parameters were recorded before the treatment (T<sub>0</sub>). Then, patients in group I received 20 µg.kg<sup>-1</sup> nitroglycerin and those in group II received 2.5 µg.kg<sup>-1</sup> iloprost. The same parameters were recorded immediately after the end of the treatment (T<sub>1</sub>).

**Results:** In both study groups MPAP and pulmonary vascular resistance (PVR) were found to be significantly lower at T<sub>1</sub> when compared to that of T<sub>0</sub> period ( $p<0.05$ ). MPAP and PVR were significantly lower and mean arterial pressure (MAP) was significantly higher in group II when compared to group I at T<sub>1</sub> period ( $p<0.05$ ). In addition to decreases in PVR and MPAP, iloprost also increased cardiac output (CO)(4.9±1.3 vs 5.1±0.9,  $p<0.05$ ) and stroke volume (SV)(48±13 vs 56±13,  $p<0.05$ ).

**Conclusion:** Inhaled iloprost and nitroglycerin, both effectively reduce MPAP and PVR without affecting MAP, systemic vascular resistance (SVR) and CO. However, iloprost seems to be a more powerful pulmonary vasodilator, therefore we suggest iloprost inhalation in patients with severe PHT. (Ann Thorac Cardiovasc Surg 2006; 12: 319–23)

**Key words:** pulmonary hypertension, iloprost, nitroglycerin

## Introduction

Pulmonary hypertension (PHT) is a clinical entity, that is

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frequently seen in patients with mitral valve disease. Unfortunately, elevated pulmonary artery pressure (PAP) might persist after mitral valve replacement in the early postoperative period.<sup>1)</sup>

Elevated PAP and/or pulmonary vascular resistance (PVR), increases the risk of development of acute right heart failure. Thus, strict control of PAP is an essential part of the postoperative care of this subset of patients.<sup>2–4)</sup> Although parenteral vasodilators are theoretically beneficial, they have been used with limited clinical results because of the lack of pulmonary selectivity. Therefore, in

recent years inhaled nitric oxide, nitroglycerin and prostacyclin (PGI<sub>2</sub>) analogues become popular.<sup>2,5,6</sup> In our previous study we have shown that inhaled nitroglycerin decreases PAP and PVR without affecting systemic arterial pressure in patients with PHT undergoing mitral valve replacement surgery.<sup>7</sup> The present study aims to compare the effects of inhaled iloprost, a synthetic prostacyclin analogue, and inhaled nitroglycerin again in this subset of patients.

## Materials and Methods

After obtaining ethic committee approval and informed consent, 100 patients with PHT (having mean PAP (MPAP) >25 mmHg) were randomized to receive either inhalation of nitroglycerin (group I; n=50) or iloprost (group II; n=50) in the postoperative period. Exclusion criteria were a history of chronic obstructive pulmonary disease and left ventricular ejection fraction <40%.

Anesthesia was induced with intravenous fentanyl (20 µg.kg<sup>-1</sup>) and propofol (2 mg.kg<sup>-1</sup>). Muscle relaxation was provided with pancuronium (0.1 mg.kg<sup>-1</sup>). Anesthetic maintenance was ensured with fentanyl infusion 0.3–1.0 µg.kg<sup>-1</sup>.min<sup>-1</sup>, propofol (1 mg.kg<sup>-1</sup>), and isoflurane (0.4–1.0%). During the first 8 postoperative hours patients were sedated with fentanyl 2 µg.kg<sup>-1</sup>.h<sup>-1</sup> and the study was continued. They were ventilated with 40% oxygen. Tidal volume was set at 10 ml.kg<sup>-1</sup>, respiratory rate was adjusted to establish an arterial carbon dioxide tension and arterial pH approximately 35 mmHg and 7.40, respectively.

The measured hemodynamic parameters were heart rate (HR), mean arterial pressure (MAP), MPAP, central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). Parameters derived by standard formulas include cardiac output (CO), pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). CO was measured using a 7-F thermodilution pulmonary artery catheter during expiration. In both groups, baseline hemodynamic parameters were recorded before the treatment (T<sub>0</sub>), upon arrival to the surgical intensive care unit (SICU). Then, patients in group I and group II, inhaled 20 µg.kg<sup>-1</sup> nitroglycerin, and 2.5 µg.kg<sup>-1</sup> iloprost liquid, nebulised by 2 L.min<sup>-1</sup> air jet, from the inspiratory limb of the ventilator. The previous measurements were repeated at the end of the treatment (T<sub>1</sub>).

## Statistical Analysis

Statistical procedures were done by using statistical software package (STATISTICA™ 6.0, StatSoft Inc., USA). Statistical power analysis using  $\alpha=0.05$  and  $\beta=0.2$  indicated that a total of 50 observations would be needed to detect a difference between groups with an assumed standard deviation (SD) of 10 with the power of 80%. Data are expressed as mean±SD. The variables were analysed with Student-t test.  $P<0.05$  was considered to indicate statistical significance.

## Results

Between January 2004 and November 2005, 100 patients with PHT undergoing mitral valve replacement surgery were prospectively enrolled. Patient characteristics are presented in Table 1. There were no statistically significant differences between the study groups. All patients tolerated iloprost and nitroglycerin inhalation without side effects.

The hemodynamic parameters are illustrated in Table 2. There were no significant differences between the study groups with respect to baseline hemodynamic characteristics (T<sub>0</sub>). In both study groups MPAP and PVR significantly decreased after treatment (T<sub>1</sub>) as compared with baseline (T<sub>0</sub>)( $p<0.05$ ). Whereas, MPAP, PVR and CVP were significantly lower in group II when compared to group I at T<sub>1</sub> period ( $p<0.05$ ). Iloprost inhalation reduced PVR (289±136 vs 124±57 dyn.sec<sup>-1</sup>.cm<sup>-5</sup>,  $p<0.05$ ), MPAP (36±6 vs 19.5±4 mmHg,  $p<0.05$ ) and CVP (10±3 vs 8±3 mmHg,  $p<0.05$ ) (Figs. 1 and 2). In addition to decreases in PVR and MPAP, iloprost also increased CO (4.9±1.3 vs 5.1±0.9,  $p<0.05$ ) and stroke volume (SV) (48±13 vs 56±13,  $p<0.05$ ).

## Discussion

Although the quantity of blood flowing through the lungs is essentially equal to that flowing through the systemic circulation, the pressures in the pulmonary circulation are significantly low compared to the systemic circulation. Thus, pulmonary circuit is a low-resistance system. The smooth muscle cells in the pulmonary vessel walls, by reacting the substances released from the endothelium, not only keep the pulmonary vascular tree compliant, but also diverge the blood flow to those segments of the lungs where the alveoli are best oxygenated. Vascular endothelium contributes this regulation by releasing a number of

**Table 1. Patient characteristics**

Parameters	Nitroglycerin	Iloprost	<i>p</i> value
Age (years)	49.2±9.7	53.8±11.7	ns
Sex (M/F)	22/28	21/29	ns
Weight (kg)	63.3±10.7	70.7±12.4	ns
Height (mt)	1.61±5.9	1.65±6.07	ns

M, male; F, female; ns, not significant.

**Table 2. Hemodynamic parameters**

Variables	Nitroglycerin		Iloprost	
	T <sub>0</sub>	T <sub>1</sub>	T <sub>0</sub>	T <sub>1</sub>
HR (min <sup>-1</sup> )	98±11	95±13	96±11	98±12
CO (L.min <sup>-1</sup> )	5.0±1.3	4.9±0.9	4.9±1.3	5.1±0.9*†
SVR (dyn.sec <sup>-1</sup> .cm <sup>-5</sup> )	1,468±377	1,294±345	1,340±496	1,145±374
PVR (dyn.sec <sup>-1</sup> .cm <sup>-5</sup> )	286±192	162±59.6*	289±136	124±57*†
SV (ml.beat <sup>-1</sup> )	49±14	50±11	48±13	56±13*†
MAP (mmHg)	72±8	66±9	70±12	68±11
MPAP (mmHg)	37±10	24.5±4*	36±6	19.5±4*†
CVP (mmHg)	9±5	8±4	10±3	8±3*†
PCWP (mmHg)	19±7	15±9	20±5	16±8

Effects of inhaled nitroglycerin and iloprost in heart rate.

Data are expressed as mean±SD.

\*, *p*<0.05 versus baseline; †, *p*<0.05 versus nitroglycerin group.

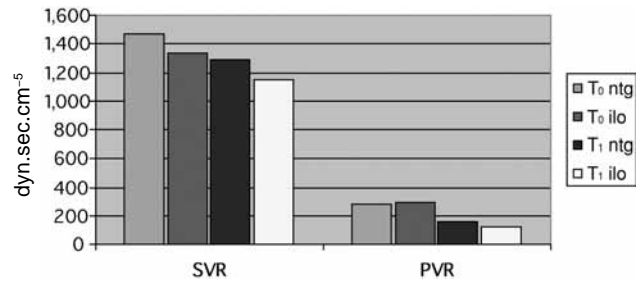
HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SV, stroke volume; MAP, mean arterial blood pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

vasoactive substances.<sup>8)</sup>

PHT is a pathophysiologic state that can be primary or associated with many other clinical conditions. It is common in patients with long-standing cardiac valvular pathology. At least three pathophysiologic mechanisms contribute to the PHT seen in this subgroup of patients. These include; increased left atrial pressure transmitted retrograde into the pulmonary circulation. Vascular remodeling of the pulmonary vasculature in response to chronic obstruction to pulmonary venous drainage (fix component) and pulmonary arterial vasoconstriction (reactive component). PHT is usually a reflex originating during the immediate period. However, over time other morphologic changes take place. In these cases the treatment of PHT is represented by the treatment of the underlying pathology.<sup>9)</sup>

The treatment of mitral valvular disease is usually mechanical and necessitates the use of extracorporeal circulation. In addition, cardiopulmonary bypass (CPB) might contribute to the increased MPAP and therefore increase the work-load of the right ventricle in this group of pa-

tients. Several days even weeks might be required for the increased PVR to return to normal after the valve replacement.<sup>10,11)</sup> During this critical period it is important to keep PVR within the limits against which the right ventricle can work. Thus, patients undergoing valve surgery might require pulmonary vasodilator therapy during the immediate postoperative period.<sup>12)</sup> The main limitation of systemic vasodilator therapy is accompanying systemic hypotension. The long-term use of calcium-channel blockers decreases the PAP and PVR. Approximately 25% of patients can tolerate this treatment.<sup>13,14)</sup> Intravenous administration of nitroglycerin and PGI<sub>2</sub> was shown to improve hemodynamic variables. However, the lack of pulmonary selectivity and the occurrence of tolerance limits the usefulness of these vasodilators.<sup>8,15)</sup> These shortcomings necessitate the search for the new agents and techniques to decrease adverse effects. During the last decade research has been directed towards inhaled nitric oxide (INO). INO was shown to be effective in the treatment of PHT, but it is expensive and toxic side effects limit its use.<sup>16)</sup> On the other hand, nitroglycerin is metabolized to



**Fig. 1.** SVR and PVR changes.

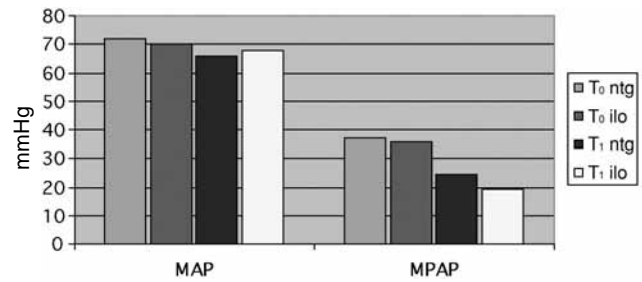
SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; ntg, nitroglycerin; ilo, iloprost.

nitric oxide which is a potent vascular smooth muscle relaxant in the vascular endothelial cells.<sup>1)</sup> We recently showed that inhalation of nitroglycerin decreases PAP without affecting systemic blood pressure in the early postoperative period in patients who underwent mitral valve replacement surgery. Our results were consistent with previous findings published by Gong et al.,<sup>17)</sup> in dogs with experimentally induced PHT and Omar et al.<sup>18)</sup> in patients with PHT resulting from congenital cardiac defects. In this study we extended these findings to compare the effects of two agents; nitroglycerin and iloprost, the stable analogue of PGI<sub>2</sub>.

This study corroborates our previous findings that inhaled nitroglycerin reduces MPAP and PVR without affecting MAP, SVR, and CO.<sup>7)</sup> However, inhalation of aerosolized iloprost seems to be a more effective approach considering the results of the two groups; MPAP and PVR were significantly lower and MAP, SV and CO were significantly higher in group II when compared to group I at the T<sub>1</sub> period. In addition, although not statistically significant, iloprost caused a decrease in PCWP. These findings suggest that inhaled iloprost selectively targets the pulmonary vasculature.

Theodoraki et al. reported that a selective pulmonary vasorelaxation was achieved by iloprost in cardiac surgery patients who presented with severe RV dysfunction following discontinuation of CPB.<sup>2)</sup> After iloprost inhalation, MPAP and PVR decreased with no change in MAP and SVR.<sup>2)</sup> Their results compare favorably with our findings.

Sablutzki et al. studied the effects of inhaled aerosolized iloprost in patients with PHT due to chronic cardiac failure.<sup>19)</sup> They found that iloprost caused a significant reduction in MPAP and PVR with no effects on SVR and arterial blood pressure. In comparison to the results of



**Fig. 2.** MAP and MPAP changes.

MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; ntg, nitroglycerin; ilo, iloprost.

Sablutzki et al. we found similar effects of iloprost both on pulmonary and systemic circulation.<sup>19)</sup>

Inhaled PGI<sub>2</sub> was shown to be a more potent pulmonary vasodilator than INO in several studies.<sup>20,21)</sup> Olschewski et al. tested the short-term effects of INO, PGI<sub>2</sub>, and iloprost and found that INO-evoked decrease in PVR was less than that seen in response to inhaled iloprost and PGI<sub>2</sub>.<sup>12)</sup> Hoeper et al. reported more potent effects of inhaled iloprost on the pulmonary vascular bed as compared to INO in patients with primary PHT.<sup>22)</sup> Our results are parallel to that of Hoeper et al.<sup>22)</sup> and Olschewski et al.,<sup>21)</sup> the decrease in MPAP and PVR was more pronounced in iloprost group and associated with an increase in CI, SV and MAP.

In our study, inhaled iloprost was well tolerated. The side effects, such as, jaw pain, syncope and flushing were seen in no patients.

Overall, our data support the conclusion that aerosolized iloprost caused marked pulmonary vasodilatation and increase in CI and MAP. Thus, it appeared to be an effective and safe treatment in patients with PHT after mitral valve replacement.

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