

Effect of Nitroglycerin Inhalation on Patients with Pulmonary Hypertension Undergoing Mitral Valve Replacement Surgery

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Background: The aim of this study was to investigate the postoperative hemodynamic effects of nitroglycerin inhalation on patients with pulmonary hypertension undergoing mitral valve replacement surgery.

Methods: Twenty patients who underwent mitral valve replacement surgery were included in the study. In the surgical intensive care unit, at T_0 (before the inhalation of nitroglycerin), basal systemic and pulmonary hemodynamics were recorded. Then, $2.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ nitroglycerin liquid nebulized by a 2-l gas flow of 40% oxygen and air mixture was administered to the patients who were diagnosed as having pulmonary hypertension (mean pulmonary arterial pressures > 25 mmHg). The same parameters were measured at the first (T_1), third (T_2), and fifth (T_3) hours after the beginning of this treatment and 1 h after the end of nitroglycerin inhalation (T_4).

Results: There were no statistically significant differences at T_0 , T_1 , T_2 , T_3 , or T_4 with respect to heart rate, mean arterial pressure, systemic vascular resistance, cardiac index, mixed venous oxygen saturation, arteriovenous oxygen content difference, or arterial carbon dioxide tension. However, mean pulmonary artery pressure, pulmonary vascular resistance, and intrapulmonary shunt fraction were significantly lower, and the arterial oxygen tension/fraction of inspired oxygen ratio was higher at T_1 , T_2 , and T_3 when compared to that of T_0 and T_4 .

Conclusion: The results suggest that nitroglycerin inhalation produces a significant reduction in both mean pulmonary artery pressure and pulmonary vascular resistance in patients after mitral valve operations without reducing mean arterial pressure and systemic vascular resistance. Therefore, it might be a safe and useful therapeutic intervention during the postoperative course.

IN patients with mitral valve disease, the presence of pulmonary hypertension (PHT) is important because it affects prognosis. After cardiac surgery, it may be necessary to treat right ventricular failure caused by PHT.¹

Recent literature documents the use of inhaled nitric oxide²⁻⁴ in the treatment of PHT; however, it requires a complicated and expensive apparatus.⁵ PHT is usually treated with intravenous vasodilators, but their use is limited because of their systemic effects. Although it is well known that intravenous nitroglycerin decreases systemic blood pressure and pulmonary arterial pres-

ures,^{2,6-8} little is known about the effects of inhaled nitroglycerin on PHT.

This study was undertaken to determine whether inhaled nitroglycerin lowers pulmonary vascular resistance in patients with PHT after mitral valve replacement.

Materials and Methods

After obtaining ethics committee approval (Istanbul, Turkey), 20 patients with PHT (12 female and 8 male) were enrolled in this study, and informed consent was taken from all patients. Their ages were between 19-46 yr. All patients had undergone mitral valve replacement (70% for mitral stenosis, 30% for mitral regurgitation). Left ventricle ejection fractions were over 40% in all patients, and their mean pulmonary arterial pressures were higher than 25 mmHg during both the preoperative and postoperative periods.

Anesthesia was induced with intravenous fentanyl (20 $\mu\text{g}/\text{kg}$) and propofol (2 mg/kg). Muscle relaxation was provided with pancuronium (0.1 mg/kg). Anesthetic maintenance was ensured with fentanyl infusion (0.3-1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), isoflurane (0.4-1.0%), and propofol (1 mg/kg). During the first 8 postoperative hours, patients were sedated with 2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ fentanyl, and the study was continued at this time. The patients were ventilated with 40% oxygen. Tidal volume was set at 10 ml/kg. Respiratory rate was adjusted to establish an arterial carbon dioxide tension and arterial pH of approximately 35 mmHg and 7.40, respectively.

The measured hemodynamic parameters were heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, and pulmonary capillary wedge pressure. Cardiac output determinations were made in triplicate at the end of expiration by a thermodilution technique using 10 ml iced dextrose, 5%, in water, each time using a cardiac output computer (Baxter Healthcare Corporation, Cardiovascular Group Edwards Critical Care Vigilance, Irvine, CA). The mean of the three readings was taken as the cardiac output for each time. Cardiac index, systemic vascular resistance, and pulmonary vascular resistance were derived from the measured hemodynamic variables using standard formulae.

Before the inhalation of nitroglycerin (at T_0), basal heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac index, pulmonary vascular

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Fig. 1. The device used for nitroglycerin administration.

resistance, and systemic vascular resistance were measured.

Then, 2.5 $\mu\text{g}/\text{kg}$ nitroglycerin, nebulized by a 2-l/min air jet device shown in figure 1 (Ref. 41883, MICRO MIST Small Volume Nebulizer; Hudson Respiratory Care Inc., Temecula, CA) was inhaled by the patient from the inspiratory limb of the ventilator. The previous measurements were again performed at the first (T_1), third (T_2), and fifth (T_3) hours after the beginning of this treatment and 1 h after the end of nitroglycerin inhalation (T_4).

Arterial and mixed venous blood samples were drawn during each assessment point and immediately analyzed by the Stat Profile-M (Nova Biomedical, Boston, MA). Besides the evaluation of arterial carbon dioxide tension (PaCO_2 ; mmHg) and mixed venous oxygen saturation (SvO_2), arteriovenous oxygen content difference (AvDO_2), pulmonary shunt fraction (Qs/Qt), and arterial oxygen tension/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio were calculated by standard formulas.

Statistical Analysis

Statistical procedures were performed using SPSS 10.0 (Statistical Package for the Social Sciences; SPSS Inc.,

Chicago, IL). Data are expressed as mean \pm SD and compared at T_0 , T_1 , T_2 , T_3 , and T_4 . The variables were analyzed with repeated-measures one-way analysis of variance. *Post hoc* comparisons were performed using the Student-Newman-Keuls test. *P* value of less than 0.05 was considered to indicate statistical significance.

Results

The hemodynamic parameters are shown in table 1. There were no statistically significant differences at T_0 , T_1 , T_2 , T_3 , and T_4 with respect to heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance ($P > 0.05$). Inhaled nitroglycerin produced significant reduction in mean pulmonary artery pressure and pulmonary vascular resistance. Mean pulmonary artery pressure and pulmonary vascular resistance returned to prenitroglycerin values 1 h after withdrawal of inhaled nitroglycerin. We did not observe any rebound PHT during this period. Mean pulmonary artery pressure and pulmonary vascular resistance were significantly lower at T_1 , T_2 , and T_3 compared to T_0 and T_4 ($P < 0.001$). There were no statistically differences between T_0 and T_4 with respect to all parameters obtained.

Gas exchange data are shown in table 2. Inhaled nitroglycerin increased the $\text{PaO}_2/\text{FiO}_2$ ratio at T_1 , T_2 , and T_3 when compared to T_0 and T_4 . In addition, it also decreased the Qs/Qt ratio during the same periods ($P < 0.05$). Gas exchange values were similar at T_0 and T_4 . There were no statistically significant differences at T_0 , T_1 , T_2 , T_3 , and T_4 with respect to PaCO_2 tension, SvO_2 , and AvDO_2 ($P > 0.05$).

Discussion

Although the mechanism changes according to the primary pathology, PHT is usually the endpoint of mitral valve disease.^{9,10} At least three pathophysiologic mechanisms contribute to the PHT seen in longstanding val-

Table 1. Hemodynamic Data

	Preoperative Values	T_0	T_1	T_2	T_3	T_4
HR, beats/min	82 \pm 16.2	87.1 \pm 19.6	83.8 \pm 15.9	87.7 \pm 17.9	86.3 \pm 16.8	84.2 \pm 15.4
MAP, mmHg	60 \pm 8.3	76.1 \pm 9.8	75.6 \pm 9.3	74.9 \pm 7.7	75.1 \pm 6.5	76.2 \pm 7.6
MPAP, mmHg	39 \pm 3.9	29.7 \pm 3.5	23.4 \pm 4.6*†	22.8 \pm 3.7*†	21.7 \pm 3.3*†	27.8 \pm 4.1
PVR, $\text{dyn} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$	613 \pm 104	463 \pm 128	328 \pm 88*†	335 \pm 94*†	329 \pm 82††	402 \pm 86
SVR, $\text{dyn} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$	2,200 \pm 326	2,176 \pm 314	2,242 \pm 324	2,194 \pm 345	2,221 \pm 338	2,235 \pm 327
CVP, mmHg	12.3 \pm 3.2	7.1 \pm 3.5	8.2 \pm 3.8	7.5 \pm 3.4	6.9 \pm 3.8	7.1 \pm 2.9
PCWP, mmHg	21.3 \pm 2.8	10.2 \pm 2.6	9.7 \pm 2.7	9.6 \pm 2.8	10.7 \pm 2.7	10.5 \pm 2.6
CI, l/min	3.2 \pm 0.7	3.8 \pm 0.58	3.7 \pm 0.54	3.6 \pm 0.67	3.8 \pm 0.52	3.7 \pm 0.69

Data are expressed as mean \pm SD.

* Intragroup comparisons with baseline. † Intragroup comparisons with T_4 period. *† $P < 0.001$.

CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance. T_0 = before nitroglycerin inhalation; T_1 = 1 h after the beginning of nitroglycerin inhalation; T_2 = 3 h after the beginning of nitroglycerin inhalation; T_3 = 5 h after the beginning of nitroglycerin inhalation; T_4 = after the withdrawal of nitroglycerin inhalation.

Table 2. Gas Exchange Data

	T ₀	T ₁	T ₂	T ₃	T ₄
Paco ₂ , mmHg	34.4 ± 4.6	36.2 ± 4.8	35.7 ± 4.3	36.9 ± 4.5	35.3 ± 4.3
PaO ₂ /Fio ₂ , mmHg	180.7 ± 116.5	240.6 ± 122.2*†	238.5 ± 118.3*†	242.2 ± 121.8*†	194.4 ± 116.3
Qs/Qt, %	25.2 ± 9.3	19.1 ± 9.8*†	18.5 ± 9.7*†	19.4 ± 9.7*†	23.8 ± 9.4
Av \dot{V} O ₂ , ml · min ⁻¹ · m ⁻²	5.1 ± 0.6	4.9 ± 0.8	4.8 ± 0.6	4.9 ± 0.6	5 ± 0.7
Svo ₂ , %	61.3 ± 3.7	63.1 ± 3.7	63.4 ± 3.2	64.1 ± 3.7	62.3 ± 3.8

Data are expressed as mean ± SD.

* Intragroup comparisons with baseline. † Intragroup comparisons with T₄ period, *P* < 0.05.

Av \dot{V} O₂ = arteriovenous oxygen content difference; Paco₂ = arterial carbon dioxide tension; PaO₂/Fio₂ = arterial oxygen tension/inspired oxygen fraction; Qs/Qt = intrapulmonary shunt fraction; Svo₂ = mixed venous oxygen saturation; T₀ = before nitroglycerin inhalation; T₁ = 1 h after the beginning of nitroglycerin inhalation; T₂ = 3 h after the beginning of nitroglycerin inhalation; T₃ = 5 h after the beginning of nitroglycerin inhalation; T₄ = after the withdrawal of nitroglycerin inhalation.

vular disease. These are increased left atrial pressure transmitted retrograde into the pulmonary circulation, vascular remodelling 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 in origin during the immediate postoperative period. However, in time, other morphologic changes take place.^{11,12}

The treatment of mitral valvular disease is usually mechanical. In addition to original pathology, cardiopulmonary bypass itself might contribute to the increased mean pulmonary arterial pressure in this group of patients. Several days or even weeks might be required for the increased pulmonary vascular resistance to return to normal after valve replacement. Unfortunately, control of pulmonary vascular resistance in such patients may be a problem. Thus, patients undergoing valve surgery most often require pulmonary vasodilator therapy during the immediate postoperative period.¹³

However, PHT is not always associated with increased pulmonary vascular resistance. Congestive heart failure induces a postcapillary PHT characterized by pulmonary vasodilatation and normal pulmonary vascular resistance. Selective vasodilators, such as nitroglycerin, do not induce any further dilation. Therefore, in planning a therapy regimen in patients with PHT, the primary etiologic factor is important.^{11,12}

Vasodilator agents are one of the therapeutic options in PHT. Recently, inhalation of nitric oxide has become a popular treatment modality in experimental models of PHT.^{2,3} However, nitric oxide inhalation may have toxic adverse reactions, and the application requires expensive and complicated systems.⁵

On the other hand, nitroglycerin is metabolized to nitric oxide, which is a potent vascular smooth muscle relaxant in the vascular endothelial cells.³ In addition, administration of nitroglycerin is easier compared to nitric oxide. Although inhalation of high concentrations of nitric oxide can be lethal because of severe acute pulmonary edema and methemoglobinemia,¹⁴ there is little evidence of toxicity when the concentration is

below 50 ppm.¹⁵ There is no study showing toxicity of nitroglycerin inhalation in the literature. This is most probably because of the use of doses of nitroglycerin lower than the intravenous doses that are reported to be toxic. Nitroglycerin doses of 5 mg kg⁻¹ day⁻¹ and over should be avoided to prevent significant methemoglobinemia.¹⁶ Intravenous infusion of nitroglycerin is used commonly to treat PHT; however, it not only decreases pulmonary artery pressure but also systemic blood pressure. Recently, it has been shown that nitroglycerin inhalation is free of this side effect.^{5,17} Therefore, in this study, we used nitroglycerin inhalation to reduce pulmonary artery pressure in patients with PHT. Our results demonstrate that inhaled nitroglycerin, after mitral valve replacement surgery, produces significant reductions in mean pulmonary artery pressure and pulmonary vascular resistance without affecting mean arterial pressure, systemic vascular resistance, or cardiac index. The decline in mean pulmonary artery pressure and pulmonary vascular resistance was found to be statistically significant (*P* < 0.001). These results are similar to those of Gong *et al.*⁵ that in dogs with experimentally induced PHT, inhalation of nebulized nitroglycerin decreases mean pulmonary artery pressure, diastolic pulmonary artery pressure, and systolic pulmonary artery pressure without affecting systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, systemic vascular resistance, or cardiac output.

Bando *et al.*¹⁷ compared nitroglycerin infusion and inhalation in doses of 1 and 2.5 μg · kg⁻¹ · min⁻¹, respectively, in dogs with hypoxic pulmonary vasoconstriction and reported that nitroglycerin inhalation in doses of 2.5 μg · kg⁻¹ · min⁻¹ decreased mean arterial pressure, mean pulmonary artery pressure, and pulmonary vascular resistance but did not affect cardiac output. The same doses of nitroglycerin infusion did not decrease mean pulmonary artery pressure but decreased mean arterial pressure. They concluded that inhalation of nitroglycerin is more effective in pulmonary circulation when compared to nitroglycerin infusion.

Omar *et al.*¹⁸ investigated the effects of nitroglycerin inhalation in PHT resulting from congenital cardiac de-

fects and reported decreases in systolic pulmonary artery pressure and mean pulmonary artery pressure as a result of nitroglycerin administration; however, heart rate, systolic arterial pressure, and mean arterial pressure were not affected. Therefore, the literature supports the theory that nitroglycerin inhalation can be a less expensive, easy, and effective alternative for PHT therapy when compared with nitric oxide inhalation.

Inhaled nitroglycerin produces vasodilatation of pulmonary vasculature adjacent to well-ventilated alveoli, increases blood flow to these areas, and preferentially shunts blood away from poorly ventilated regions; thus, it matches ventilation/perfusion and reduces intrapulmonary shunt. This results in improved oxygenation and reduced pulmonary vascular resistance and right ventricular afterload.

In conclusion, nitroglycerin inhalation decreases mean pulmonary artery pressure, pulmonary vascular resistance, and Qs/Qt ratio without affecting heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, or cardiac output after mitral valve replacement surgery. In addition, inhalation of nitroglycerin increases the PaO₂/FiO₂ ratio. Thus, it can be used as alternative mode of therapy in patients with PHT associated with mitral valve diseases.

It is known that at low doses, nitroglycerin acts as a venodilator, whereas at high doses it becomes an arteriodilator. Because mean arterial pressure was not affected by the doses used in this study, we assume that nitroglycerin acts as a venodilator at this dose, but in this study design, it is not possible to predict the exact dose reaching the distal lung. This can be regarded as a drawback of our study. Therefore, further randomized trials are needed.

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