VARIABLE RESPONSE TO INHALED NITRIC OXIDE IN POSTOPERATIVE PATIENTS OF MITRAL STENOSIS WITH PULMONARY HYPERTENSION

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Background: This study was carried out to determine the vasodilator response of inhaled nitric oxide in patients with pulmonary hypertension (PH) after valve replacement surgery for mitral valve disease. **Method:** This Quesi experimental study was carried out at the intensive care unit of Armed Forces Institute of Cardiology (AFIC) in collaboration with Department of Physiology, Army Medical College, Rawalpindi from March 2004 to February 2006. Thirty patients with systolic Pulmonary Artery Pressure (PAP) >50 mmHg on pre-operative echocardiography were inducted. Swan Ganz catheter was inserted to record baseline pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP), while cardiac output (CO) was recorded through lithium dilution method. Pulmonary Vascular Resistance (PVR) was calculated with the help of a formula. Inhaled nitric oxide (iNO) was administered after the surgery and the same parameters were recorded again after one hour. **Results:** The majority of patients were females (73%), while males were only 27%. Out of 30, 21 had isolated mitral stenosis and 9 had mixed mitral and aortic valve disease. 22 patients responded significantly to iNO therapy with ≥40.0% reduction in their baseline PVR while 8 patients showed insignificant improvement in their PVR (663±233 dynes.sec.cm^{-5} to 605±222 dynes.sec.cm^{-5}). **Conclusion:** Significant improvement in pulmonary vascular resistance in the responders and maintenance of high pressures despite iNO therapy in non-responders indicate that apart from some abnormality in nitric oxide pathway, some other factors may be a contributing in the causation of PH secondary to mitral stenosis in adults, which warrant further studies.

Keywords: Nitric Oxide, mitral stenosis, pulmonary hypertension, pulmonary artery pressure, pulmonary vascular resistance

INTRODUCTION

Pulmonary hypertension is defined as mean pulmonary artery pressure >25 mm Hg at rest or >30 mmHg after exercise on catheterization.[1] It is seen in an assortment of disorders including chronic obstructive lung disease, acute respiratory distress syndrome, congenital systemic-to-pulmonary shunts, mitral stenosis, persistent pulmonary hypertension of the newborn and human immunodeficiency virus (HIV) infection.[2]

In long standing mitral stenosis, fibrosis and calcification of the valve apparatus makes the blood flow turbulent. This results in obliterative changes in pulmonary arteries which ultimately lead to thickening of the tunica media of small arteries and obliteration of their lumen. As a consequence of this obliteration, there develops an increased retrograde pulmonary venous pressure and arteriolar vasoconstriction called as reactive vasoconstriction.[3]

In severe mitral stenosis, elevated pulmonary vascular resistance has been demonstrated to be an independent risk factor for early morbidity and mortality in patients undergoing corrective valvular surgery by compromising cardiac output. Cardiopulmonary bypass may exacerbate pulmonary hypertension resulting in acute right ventricular failure.[4]

Nitric oxide (NO) is a reactive, colourless gas that has been utilized since 1991 for the treatment of pulmonary hypertension as a selective pulmonary vasodilator.[5] When given through the inhalation route, NO causes relaxation of vascular smooth muscles in the pulmonary circulation, but as soon as it reaches into the vascular lumen it binds with the haemoglobin and is rapidly converted into nitrites and nitrates, and is thus rendered unavailable to systemic circulation.[6]

Inhaled nitric oxide is used in ICUs for the treatment of pulmonary hypertension after cardiac surgeries since 1993.[7] Its role in lowering raised pulmonary artery pressure in children with congenital heart diseases and adults undergoing heart transplantation has been the objective of several studies[8,9], but its role in the treatment of pulmonary hypertension after corrective surgery for left sided valvular heart diseases has been evaluated in very few studies, so the data on this subject is little and fragmentary. In view of this, the present study was carried out to evaluate the effect of inhaled nitric oxide on the pulmonary vascular indices in patients with mitral valve disease after corrective surgery.

MATERIAL AND METHODS

This was a collaborative study, between Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD) Rawalpindi and Department of Physiology, Army Medical College, Rawalpindi. It was carried out from March 2004 to February 2006. Thirty patients of mitral or mixed mitral and aortic valve disease admitted to various wards of AFIC for planned mitral valve replacement were enrolled in the study. Enrolment criteria was pulmonary hypertension with a systolic pulmonary artery pressure >50% of the systolic systemic arterial pressure measured during pre-operative echocardiography by a cardiologist. Patients were of either sex and their ages ranged between 20 and 60 years. Written and informed consent was taken from all the patients after explaining the procedure that would be performed on them.

Patients with right ventricular failure, ischemic heart disease, chronic obstructive pulmonary disease, collagen vascular disease, and primary pulmonary hypertension were excluded from the study.

One day before their scheduled corrective surgery, every patient was admitted to the Intensive Care Unit (ICU), where arterial cannulation, central venous catheterization and Swan Ganz catheterization was performed. Arterial cannula was attached with the Lithium Dilution Cardiac Output (LiDCO) monitor for the recording of heart rate, systemic arterial pressure, systemic vascular resistance, and cardiac output.

The LiDCO monitor[10] was calibrated by administrating lithium chloride through a central venous catheter (Arrow 7.5 French), which was introduced in right or left subclavian vein. After that, the arterial blood was passed through a lithium sensor attached to an arterial cannula introduced in the radial artery. This gave a graph after calculating the amount of lithium reaching the sensor in the peripheral artery. Three readings were taken for the recording of cardiac output and the mean value was finally calculated.

The Swan Ganz catheter[11] (Arrow 7.5 French) was introduced via another central venous line and threaded through a sterile sheath to ensure sterility of the Swan Ganz catheter after insertion. During its passage through various heart chambers central venous pressure, right ventricular pressure, pulmonary artery pressure and pulmonary capillary wedge pressure were recorded through a pressure transducer connected to the Swan Ganz catheter. At the end of the procedure, a chest x-ray postero-anterior (P/A) view was recorded to check the position of the Swan Ganz catheter.

Pulmonary vascular resistance was calculated in dynes.sec.cm^{-5} by using the following formula:

$$\frac{\text{Mean pulmonary artery pressure - Mean left atrial pressure}}{\text{Cardiac out put}} \times 80$$

Here left atrial pressure (LAP) was substituted by pulmonary capillary wedge pressure (PCWP).

Nitric oxide administration

On the next day, the patient underwent corrective surgery, i.e., valve implantation using standard surgical technique. When he was brought back into the ITC he was administered inhaled nitric oxide in a dose of 20 ppm through inspiratory limb of a Servo-300 (Siemens-Elema AB, Electromedical Systems Division) ventilator for one hour. The concentration of inhaled nitric oxide was continuously monitored by chemiluminescence. Likewise, the exhalation limb of breathing circuit was continuously monitored for NO_2 by chemiluminescence. Ventilator was set on SIMV (synchronized intermittent minute ventilation) pressure support. Tidal volume was set on 10 ml/Kg and fraction of inhaled oxygen (FiO_2) was kept at 50%. Plateau airway pressure was kept at 25–30 mmHg and positive end expiratory pressure (PEEP) at 5 mmHg. After 60 minutes of inhaled nitric oxide administration, all the study parameters were again recorded.

Response criteria

- >40% reduction in pulmonary vascular resistance = good response
- <40% reduction in pulmonary vascular resistance = poor response

Statistical analysis

The data was analysed using SPSS version 10. The baseline pulmonary artery pressure and pulmonary vascular resistance were compared with post inhaled nitric oxide administration pulmonary artery pressure and pulmonary vascular resistance by applying student's *t*-test. The *p*-value of <0.05 was taken as significant.

RESULTS

A total of 30 subjects, comprising 21 females and 9 males were studied. Out of these 30 patients, 21 (70.0%) had isolated mitral stenosis and 9 (30.0%) had mitral stenosis combined with aortic valve disease. Basic demographic data of subjects is shown in Table-1. Response to iNO provided two categories of subjects: Responders (22, 73.3%) and non-responders (8, 26.7%).

Table-2 shows the demographics of responders and non-responders; there were no significant differences in demographic variables between these two groups.

Table-3 shows the haemodynamic variables of responders and non-responders. The post iNO mean pulmonary artery pressures and pulmonary vascular resistance showed significant differences between the two groups (p<0.001). The pulmonary vascular resistance dropped significantly with iNO therapy in responders (910±344 dynes.sec.cm^{-5} to 256±109 dynes.sec.cm^{-5}) whereas it showed a very small decrease from 663±233 dynes.sec.cm^{-5} to 605±222 dynes.sec.cm^{-5} in non-responders; this difference in the post iNO values was highly significant (p<0.001). The mean pulmonary artery pressure also dropped significantly in responders whereas the non-responders showed a much smaller change; hitherto difference in the post iNO values was highly significant (p<0.001). Both groups showed a very significant improvement in cardiac output from 2.9±0.5 L/m to 4.1±1.14 L/m despite a varied effect on pulmonary vascular indices.

Table-1: Demographics of subjects (n=30)

Variables	Mean±SD
Age (years)	30.43±8.94
Weight (Kg)	50.60±7.35
Height (meters)	1.58±8.70

Table-2: Comparison of demographics of responders and non-responders

(Mean±SD)

Variables	Responders (n=22)	Non-responders (n=8)
Age (years)	31.82±9.28	26.63±7.07
Weight (Kg)	50.50±7.85	50.88±6.22
Height (meters)	1.56±8.12	1.62±9.59

Table 3: Comparison of Haemodynamic Parameters before and after the administration of inhaled Nitric Oxide in responders and non-responders

(Mean±SD)

Variables	Responders (n=22)		Non responders (n=8)	
	Pre iNO	Post iNO	Pre iNO	Post iNO
Cardiac output (l/min)	2.9±0.5	4.1±1.14	2.9±0.5	4.3±1.1
Mean pulmonary artery pressure (mmHg)	65.73±14.87	28.09±6.93	59.88±17.24	51.25±13.74*
Pulmonary vascular resistance (dynes.sec.cm-5)	910±344	256±109	663±233	605±222*

p<0.001 for the differences in post iNO values between responders and non-responders, iNO=inhaled nitric oxide.

DISCUSSION

The present study was undertaken to assess the role of inhaled Nitric Oxide (iNO) in relieving increased pulmonary vascular resistance.

Although different studies have shown significant role of inhaled nitric oxide in relieving pulmonary hypertension secondary to congenital heart disease[12,13], very little work was done to establish the response of pulmonary vessels to inhaled nitric oxide in patients with mitral valve disease. Moreover, most of the studies had very small sample size which didn't enable us to draw inference from their data regarding the efficacy of iNO.[14,15] We took a sample size of 30 which was large enough to draw statistically significant conclusions regarding use of inhaled nitric oxide in the critical postoperative period after corrective surgery. Patients undergoing valve replacement provided a homogenous group of subjects. Surgical access allowed accurate measurement of pulmonary venous pressures for calculation of PVR and ICU setting provided the opportunity to take advantage of the state of the art LiDCO monitor for measurement of cardiac output.

The main treatment directed against mitral stenosis complicated by pulmonary hypertension is corrective surgery but studies have shown that cardiopulmonary bypass (CPB) increases mean PAP and PVR.[16] This increased PVR and pulmonary hypertension often complicates the perioperative management of patients undergoing operation for mitral valve disease who already have pulmonary hypertension. That's why raised PVR and PH have been reported as independent risk factors for decreased survival in this population.[17,18]

In PH secondary to MS, increased PVR may be due to a combination of 3 problems (1) passive hydrostatic pressure, (2) anatomic remodelling of pulmonary vasculature leading to decreased compliance, and (3) altered endothelium dependent vascular tone. After surgical correction of mitral valve obstruction, the element of increased resistance due to passive hydrostatic pressure is relieved, so a still raised PVR suggests that this increased resistance is a minor contributor. Many studies point to the major contribution of anatomic remodelling to the raised PVR in patients with severe MS. However, when we administered iNO in these patients, PVR was acutely reduced in two thirds of the patients, suggesting that physiologic regulation of vascular endothelium dependent tone plays a critical role in the pathophysiology of elevated PVR in patients with MS.

In present study we evaluated the vasodilator response by measuring PAP and PVR. The PVR was determined by the formula:

MPAP-LAP/CO × 80

We replaced left atrial pressure with pulmonary capillary wedge pressure as a study by Krishnamoorthy *et al*[19] in patients with rheumatic mitral stenosis before and after balloon mitral valvuloplasty showed a good correlation between PCWP and left atrial pressure (LAP).

We administered iNO in a dose of 20 ppm which is proved to be an effective dose for patients undergoing cardiac surgery.[20,21]

In present study there was a significant increase in the cardiac output from the baseline level of 2.98±0.56 L/min to 4.21±1.12 L/min (p<0.001). Whereas some investigators found an increase in cardiac output with iNO therapy[22] others failed to demonstrate an improvement in systemic perfusion. [23] This improvement in cardiac output seen in our study can be attributed more to correction of mitral stenosis that was obstructing the left outflow tract. This finding is supported by the study carried out by Rawczynska-Englert I *et al*[24] in which the pulmonary cardiac index was increased after MVR.

Reports about an inconsistent response to inhaled nitric oxide have been published before.[25,26] Fullerton *et al* in two studies published in 1996[27] and 1997[28] documented the poor response to inhaled nitric oxide in post operative patients of mitral valve disease and pulmonary hypertension. The present study was carried out keeping in view the possibility of the variable response and thus laid out a strict response criterion to find non-responders. Our results revealed a total lack of response in one subset with a minimal improvement of 59.88±17.24 mmHg to 51.25±13.74 mmHg in PVR, while the other group comprised of responders, manifested significant improvement in PVR with iNO therapy.

Girard *et al*[23] investigated the vasodilator effects of inhaled NO in patients with mild PH after MVR. They showed statistically significant (p<0.05) decrease in MPAP and PVR after iNO administration.

Fattouch *et al*[29] carried out a prospective, double blind study to compare the hemodynamic effects of inhaled prostacyclin, nitric oxide and nitroprusside in 58 patients with mitral stenosis and elevated PVR (>200 dynes.sec/cm^{-5}) after mitral valve surgery. They administered inhaled nitric oxide in a dose of 20 ppm to 22 patients and showed a 45% reduction in PVR with iNO therapy (from 722±115 dynes.sec.cm-5 to 427±69 dynes.sec.cm-5). Like our study they also documented a significant improvement in cardiac output (from 3.8±0.3 L/min to 4.8±0.5 L/min).

CONCLUSION

We conclude that inhaled nitric oxide has a definitive role in lowering pulmonary hypertension after corrective surgeries for mitral valve disease as majority of our patients responded to iNO inhalation with a prompt reduction in pulmonary vascular resistance. the reasons for maintenance of high resistance values in the subset of non responders is not totally clear; and indicates that apart from NO pathway abnormalities, certain other factors like hypersecretion of locally derived vasoconstrictors is also playing a role in the causation of pulmonary hypertension in patients with mitral stenosis.

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