Inhaled NO and Sildenafil Combination in Cardiac Surgery Patients With Out-of-Proportion Pulmonary Hypertension
Acute Effects on Postoperative Gas Exchange and Hemodynamics

Dimitrios Matamis, MD, PhD; Smaro Pampori, MD; Athanasios Papathanasiou, MD, PhD; Panagiota Papakonstantinou, MD; Mathew Tsagourias, MD, PhD; Eftichia Galiatsou, MD, PhD; Vasilios Koulouras, MD, PhD; George Nakos, MD, PhD, DTM, FCCP

Background—The goal of this study was to examine the effects of coadministration of sildenafil and inhaled nitric oxide (iNO) in patients with out-of-proportion pulmonary hypertension who underwent cardiac valve replacement surgery.

Methods and Results—Twenty consecutive cardiac surgery patients with out-of-proportion pulmonary hypertension were randomly assigned postoperatively into 2 groups: group A received 10 ppm of iNO followed by sildenafil (100 mg) orally 30 minutes later, and group B initially received sildenafil (100 mg) orally followed by 10 ppm of iNO 60 minutes later. Hemodynamic and gas exchange data were obtained at baseline, after administration of either iNO or sildenafil alone, and at 90 minutes from baseline. In group A, iNO resulted in a significant reduction in mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance index (PVRI) (by 9.6% and 20.8%, respectively). In group B, sildenafil administration also resulted in a significant decrease in mean arterial pressure, MPAP, pulmonary artery occlusive pressure, PVRI, and systemic vascular resistance index but also in the PaO2/inspired fraction of oxygen ratio (by 18.7%, 22.0%, 15.7%, 31.6%, 21.3%, and 14%, respectively). In both groups, the coadministration of the 2 drugs resulted in a significant further reduction of mean arterial pressure, MPAP, pulmonary artery occlusive pressure, systemic vascular resistance index, and PVRI, whereas cardiac index and mixed venous oxygen saturation remained unchanged. The hypoxemia after sildenafil administration in group B improved after the coadministration of iNO, and thus PaO2/inspired fraction of oxygen returned to values near baseline.

Conclusion—In this study, the postoperative coadministration of iNO and oral sildenafil in patients with out-of-proportion pulmonary hypertension undergoing cardiac surgery is safe and results in an additive favorable effect on pulmonary arterial pressure and pulmonary vascular resistance, without systemic hypotension and ventilation/perfusion mismatch. (Circ Heart Fail. 2012;5:47-53.)

Key Words: pulmonary hypertension ■ sildenafil ■ nitric oxide ■ cardiac surgery ■ heart failure

In patients with left ventricular dysfunction undergoing cardiac surgery, the presence of pulmonary hypertension (PH) may adversely affect the outcome.1 In left heart disease, PH is initially due to passive backward transmission of the elevated filling pressures of the left ventricle (pulmonary venous hypertension), but over time, an increase in pulmonary artery resistance may develop, in part as a protective mechanism against pulmonary edema.2 In some cases the elevation of pulmonary artery pressure is greater than that expected by the elevation of left atrial pressure (transpulmonary gradient >12 mm Hg), possibly because of intrinsic changes in the pulmonary circulation leading to so-called reactive or “out-of-proportion” PH.3

Clinical Perspective on p 53

Treatment of out-of-proportion PH in such patients may be challenging. It has been proposed that reduced levels of endogenous nitric oxide (NO) may play an important role in the pathogenesis of pulmonary arterial hypertension (PH).4 Administration of inhaled nitric oxide (iNO) dilates pulmonary vessels, thereby decreasing pulmonary vascular resistance (PVR), pulmonary arterial pressure, and right ventricular afterload.5 Conversely, in left ventricular failure, inhalation of NO may cause a decrease in PVR associated with increased pulmonary artery wedge pressure without affecting pulmonary arterial pressure.6 The use of iNO is limited because of technical difficulties, and its delivery and monitoring remain complex and cumbersome.7 In addition, abrupt discontinuation of iNO therapy can lead to acute rebound PH and hypoxemia.8

The intracellular second messenger of NO, cyclic guanosine monophosphate (cGMP), plays an important role in pulmonary vascular disease. cGMP is inactivated by phosphodiesterases (PDEs), especially the isoenzymes PDE1 and PDE5. Because

Received May 31, 2011; accepted October 31, 2011.
From the Intensive Care Unit, Papageorgiou General Hospital, Thessalonica, Greece (1); Intensive Care Unit, University Hospital of Ioannina, Ioannina, Greece (A.P., E.G., V.K., G.N.).
Correspondence to George Nakos, MD, PhD, DTM, FCCP, Intensive Care Unit, University Hospital of Ioannina, 45500 Ioannina, Greece. E-mail gnakos@cc.uoi.gr
© 2011 American Heart Association, Inc.

Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.111.963314
PDE5 is abundantly expressed in pulmonary vascular smooth muscle cells, it is a logical therapeutic target in PH. Oral sildenafil, a PDE5 inhibitor that prevents the degradation of cGMP and enhances NO signaling, has shown to be as effective as iNO in the setting of primary PH. Recently, substantial data have been reported concerning the efficacy and safety of sildenafil administration in patients with PH due to with congestive heart failure. In addition, its beneficial effects regarding myocardial remodeling further support its potential use in patients undergoing cardiac surgery. Furthermore, administration of sildenafil does not require a special delivery system and does not induce rebound PH.

Although left heart disease is the most common cause of PH, very few data on the pathophysiology and treatment of out-of-proportion PH due to left heart disease are available. Several previous studies have focused on either iNO or oral sildenafil administration in patients with PH; nevertheless, the combined use of these agents in patients with out-of-proportion PH due to left heart disease is not well documented.

The aim of our study was to evaluate the effects of oral sildenafil and iNO on hemodynamic and gas exchange when administered immediately postoperatively either alone or in combination in postoperative patients with out-of-proportion PH due to left valvular heart disease who underwent valve replacement surgery.

**Methods**

**Study Population**

This was a prospective randomized study that took place in the intensive care units of 2 hospitals in Greece during a 2-year period (from March 2005 to February 2007). All 654 consecutive patients who were candidates for valve replacement surgery underwent right heart catheterization at the time of the routine preoperative coronary angiography and were screened for PH due to left heart valvular disease (category 2) as defined by the Third World Symposium on Pulmonary Hypertension and applied during the study period. Since then, the classification of PH has been modified, and PH due to left heart valvular disease was defined as pulmonary artery systolic pressure more than 25 mm Hg and pulmonary wedge pressure more than 15 mm Hg. It was further categorized as postcapillary out-of-proportion PH if transpulmonary gradient (mean pulmonary artery pressure minus pulmonary wedge pressure) was more than 12 mm Hg and as passive postcapillary PH if transpulmonary gradient was less than 12 mm Hg. To comply with the recently published definitions of PH, only 54 out of the 62 initially included patients with out-of-proportion PH, based on the right heart catheterization, were included in the analysis. Patients with passive postcapillary PH were excluded from the further investigation.

Of the 54 patients, 34 were excluded postoperatively (Figure 1): 23 because of hemodynamic instability or low cardiac output syndrome necessitating high doses of inotropes and vasopressors postoperatively, 8 because of emergency reoperation for hemorrhage, and 3 because of cardiac tamponade.

Finally, the study protocol was applied in the remaining 20 patients. These patients underwent the following procedures: aortic valve replacement (6 patients), mitral valve replacement (4 patients), aortic valve replacement and coronary artery bypass grafting (4 patients), mitral valve replacement and coronary artery bypass grafting (4 patients), and aortic valve replacement and mitral valve replacement (2 patients).

The hospitals’ ethics committees approved the study protocol, and informed consent was obtained from all participants before surgery.

**Study Protocol**

A Swan Ganz catheter was advanced into the pulmonary artery through the right jugular vein under fluoroscopy in all patients perioperatively. At the end of the surgical procedure, the patients were admitted to the intensive care unit and remained under mechanical ventilation. Postoperative medication for all patients included sedation (midazolam, 0.1 mg/kg body weight; fentanil, 10 mg/kg body weight), muscle relaxant (vecuronium), heparin, diuretics, and low dose of dobutamine (≤5 μg/kg/minute).

Just after intensive care unit admission, a transesophageal echocardiographic examination was performed to assess right and left ventricular function postoperatively and to exclude any common postoperative complications, such as prosthetic valve dysfunction, hypovolemia, and tamponade. Left ventricular function was estimated by visual assessment taking into account all possible views. Ejection fraction was calculated using the end-diastolic and end-systolic diameter of the left ventricle in the transgastric short axis view at the level of the papillary muscles. The mean value of 3 subsequent measurements was taken into account. Right ventricular dysfunction was defined as dilatation or hypokinesia of the right ventricle free wall by visual estimation.

The settings on mechanical ventilation were as follows: volume control (constant inspiratory flow), tidal volume 6 to 8 mL/kg, rate 12 to 18 breaths/minute, inspiration to expiration ratio of 1:2, adequate inspired fraction of oxygen (FiO₂) to achieve saturation of oxygen in arterial blood >90%, and positive end expiratory pressure 3 to 7 cm H₂O. Ventilator settings were kept constant during the study protocol.

After hemodynamic stabilization patients were randomly assigned into 2 groups. In group A (n=10), patients received continuously iNO for 90 minutes, and 30 minutes after iNO initiation, 100 mg of sildenafil was administered orally. In group B (n=10), patients initially received 100 mg of sildenafil orally, and 60 minutes later, iNO was added for 30 minutes (Figure 2). iNO is a short-acting agent reaching plateau effectiveness within 3 to 6 minutes of administra-
The study protocol was designed so that adequate time was allowed for sildenafil to reach its maximum effect and iNO remained in maximum plateau effect during the study protocol.

In all patients the maximum vasodilatory response to iNO was observed with doses between 8 and 12 parts per million (ppm), with a mean dose of 10 ppm for both study groups. Sildenafil was administered via the nasogastric tube diluted in 50 mL of water. iNO was administered continuously, during the entire respiratory cycle, in the y piece of the respiratory circuit of the ventilator to decrease the contact time of NO with O2. The concentrations of NO and its toxic metabolite nitric oxide (NO2) were measured in the common limb of the respiratory circuit, using a fast response apparatus (DelNO Sensor Medics Critical Care). iNO was delivered from a 900 ppm NO in N2 gas tank.

Hemodynamic and gas exchange data were obtained (1) at baseline, (2) before the administration of the second medication (at 30 minutes for group A and 60 minutes for group B), and (3) 90 minutes after baseline measurements. Mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and central venous pressure were continuously displayed and obtained from a monitor. Pulmonary artery occlusive pressure (PAOP) was recorded at the end of expiration. Cardiac output, cardiac index, and mixed venous oxygen saturation (SvO2) were continuously recorded using a CCO-SvO2-PAC (Edwards Laboratory). The transducers were zeroed at midaxillary level. At each time point, an arterial blood sample was obtained, and partial pressure (PaO2) and saturation of oxygen in arterial blood were recorded. Arterial and mixed venous blood samples were collected and analyzed using blood gas analyzer (ABL 70 Radiometer Copenhagen). Systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were calculated according to standard formulas, ie, PVRI=(MPAP-PAOP)/cardiac index and SVRI=(MAP-central venous pressure)/cardiac index.

Statistical Analysis
Continuous variables in each group of patients were expressed as mean values±SD. The PaO2/FiO2 ratio was expressed as an absolute value. The normality for each variable was assessed by the Kolmogorov-Smirnov test. Differences within and between groups were evaluated by repeated-measures ANOVA or by Friedman’s test (the nonparametric equivalent) as appropriate. This was followed by the Bonferroni correction for the multiple comparisons procedure. Baseline characteristics between the 2 study groups were similar. Group A patients had a mean age of 65.8±7.8 years (5 females), and group B patients had a mean age of 63.7±8.4 years (4 females). No statistically significant differences were observed in baseline characteristics between the 2 study groups (Tables 1 and 2).

Results
A total of 20 patients (11 males and 9 females, mean age 65±6 years) were included in the study. Demographic data between groups A and B were similar. Group A patients had a mean age of 65.8±7.8 years (5 females), and group B patients had a mean age of 63.7±8.4 years (4 females). No statistically significant differences were observed in baseline characteristics between the 2 study groups (Tables 1 and 2).

Mean left ventricular ejection fraction, based on initial transesophageal echocardiographic examination (before baseline measurements), was similar between the 2 study groups (34.2±6.3% and 35.1±8.1% in group A and group B patients, respectively; P=0.672). No right ventricular dysfunction, defined as dilatation or hypokinesia, was detected in any patient.

Hemodynamics and oxygenation during the 90 minutes treatment period in groups A and B are shown in Tables 1 and 2. Individual data for MPAP−PVRI and MAP−SVRI are shown in Figures 3 and 4, respectively. iNO alone in group A patients significantly decreased MPAP and PVRI (P=0.0001 and P=0.002, respectively) without any effect on systemic pressure or resistance (P=0.876 and P=0.464, respectively). In contrast, the administration of sildenafil alone in group B patients decreased both systemic and pulmonary vascular pressures and resistances (MPAP and PVRI, P=0.0001 and P=0.002, respectively; MAP and SVRI, P=0.0001 and P=0.004, respectively). Consistent with the impact of sildenafil on MAP and SVRI, the addition of sildenafil to iNO significantly decreased the MAP and SVRI (group A, P=0.004 and P=0.023, respectively). In contrast, the addition of iNO to sildenafil did not further alter MAP and SVRI (group B, P=0.818 and P=0.167, respectively). In both groups, the combination of sildenafil and iNO produced significantly larger pulmonary vasodilatation than either drug alone. Sildenafil alone decreased the PaO2/FiO2 ratio (P=0.006), but iNO alone was associated with no significant change (P=0.118). When iNO was added to the sildenafil (group B), the ratio returned to near-baseline values, resulting in a difference that was no longer statistically significant (Tables 1 and 2).

In both groups of patients, levels of cardiac index and SvO2 remained unchanged compared with baseline during the study protocol (Tables 1 and 2).

Discussion
According to our pilot study, in patients with out-of-proportion PH due to left ventricular dysfunction undergoing cardiac valve replacement surgery, the immediate postoperative administration of iNO resulted in the improvement of pulmonary circulation parameters with no effect on the systemic circulation and PAOP. iNO improved the PaO2/FiO2 ratio and maintained both cardiac index and SvO2. Furthermore, sildenafil administration was effective in decreasing MAP, MPAP, PAOP, and PVRI, but it also resulted in a
significant decrease in SVRI. Sildenafil also improved PAOP without reducing SvO₂ or cardiac index and resulted in a significant reduction in the PaO₂/FiO₂ ratio. The coadministration of iNO and oral sildenafil maintained the beneficial effects of each respective substance in pulmonary and systemic circulation without significantly deteriorating the PaO₂/FiO₂ ratio. Moreover, in these patients, the coadministration of both iNO and oral sildenafil seemed to be safe and also had an additive effect in decreasing both pressure and resistance in the pulmonary circulation without affecting cardiac output and the PaO₂/FiO₂ ratio.

Recent evidence indicates that heart failure with increased PVR is associated with raised systemic and pulmonary arterial stiffness and decreased sensitivity of pulmonary vessels to endogenous vasodilators, which responds to sildenafil. In this study, we have used a combination of 2 drugs acting on the NO-cGMP signaling pathway. The downstream effects of this pathway, which is possibly downregulated both in the myocardium and the pulmonary vasculature of subjects with group II PH, include reduction of vascular tone and attenuation of cellular proliferation. Because spatial distribution and signaling of cGMP appear heterogeneous, such a combination could have a sound physiological basis: drugs that modulate the cGMP pathway may have differential or synergistic effects depending on which pools of cGMP they act on.

In patients with left ventricular dysfunction, especially those undergoing cardiac surgery, PH adversely affects postoperative morbidity and mortality. In these patients, treatment of postoperative PH improves hemodynamic status and may influence the outcome. Even though PH importance is sufficiently outlined, its management can be challenging. iNO administration in patients with PH decreases PVR, pulmonary arterial pressure, and right ventricular afterload. iNO has also been used in patients with severe PH, attributable to left ventricular dysfunction, undergoing cardiac transplantation as part of their preoperative assessment or treatment. The findings of these studies are in accordance with our data, in which iNO reduced both MPAP and PVRI. iNO administration alone did not alter systemic hemodynamic parameters as expected by its selective pulmonary vasodilatory effects, because of nonsystemic absorption.

Previous studies have shown that in patients with left ventricular failure, the administration of 80 ppm iNO resulted in only a minor improvement in systemic hemodynamics, and pulmonary vascular resistance returned to baseline levels. The present study shows that the combination of sildenafil and iNO has resulted in a greater improvement in systemic and pulmonary hemodynamics. These results suggest that the combination of sildenafil and iNO may be more effective than either drug alone in the treatment of PH.

### Table 1. Hemodynamic and Oxygenation Parameters of Study Group A (n=10 Patients)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Administration of iNO (30 min)</th>
<th>P Value vs Baseline</th>
<th>Administration of Sildenafil Plus iNO (90 min)</th>
<th>P Value vs Baseline</th>
<th>P Value vs NO Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>78.4±13.2</td>
<td>79.1±14.7</td>
<td>0.876</td>
<td>69.4±12.0</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>31.3±3.9</td>
<td>28.3±3.6</td>
<td>0.0001</td>
<td>26.0±4.3</td>
<td>0.0001</td>
<td>0.005</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>13.9±2.6</td>
<td>13.6±3.0</td>
<td>0.678</td>
<td>12.5±3.0</td>
<td>0.004</td>
<td>0.103</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>11.6±3</td>
<td>11.3</td>
<td>0.849</td>
<td>11.5±3</td>
<td>0.924</td>
<td>0.878</td>
</tr>
<tr>
<td>CI, L/(min×m⁻²)</td>
<td>2.8±0.4</td>
<td>2.9±0.4</td>
<td>0.943</td>
<td>2.9±0.4</td>
<td>0.753</td>
<td>0.849</td>
</tr>
<tr>
<td>SVRI, dynes×s×cm⁻⁵×m⁻²</td>
<td>1907.1±440.6</td>
<td>1875.5±516.0</td>
<td>0.464</td>
<td>1595.7±401.2</td>
<td>0.008</td>
<td>0.023</td>
</tr>
<tr>
<td>PVRi, dynes×s×cm⁻⁵×m⁻²</td>
<td>504.4±135.7</td>
<td>399.3±111.0</td>
<td>0.002</td>
<td>367.5±105.8</td>
<td>0.001</td>
<td>0.034</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>63.7±11.3</td>
<td>66.7±9.6</td>
<td>0.127</td>
<td>65.3±10.9</td>
<td>0.283</td>
<td>0.465</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>305.7±126.2</td>
<td>318.9±118.6</td>
<td>0.118</td>
<td>283.5±126.2</td>
<td>0.055</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data are expressed as means±SD.

iNO indicates inhaled nitric oxide; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusive pressure; CVP, central venous pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; SvO₂, mixed venous oxygen saturation; PaO₂/FiO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen.

### Table 2. Hemodynamic and Oxygenation Parameters of Study Group B (n=10 Patients)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Administration of Sildenafil (60 min)</th>
<th>P Value vs Baseline</th>
<th>Administration of Sildenafil Plus iNO (90 min)</th>
<th>P Value vs Baseline</th>
<th>P Value vs NO Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>85.6±11.3</td>
<td>69.6±8.9</td>
<td>0.0001</td>
<td>70.1±10.6</td>
<td>0.0001</td>
<td>0.818</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>32.7±5.5</td>
<td>25.5±4.0</td>
<td>0.0001</td>
<td>23.5±4.0</td>
<td>0.0001</td>
<td>0.032</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>14.0±4.2</td>
<td>11.8±3.4</td>
<td>0.005</td>
<td>11.7±3.8</td>
<td>0.001</td>
<td>0.737</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>9.5±4</td>
<td>7.5±3</td>
<td>0.05</td>
<td>14±4</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>CI, L/(min×m⁻²)</td>
<td>2.6±0.7</td>
<td>2.7±0.6</td>
<td>0.614</td>
<td>2.6±0.6</td>
<td>0.654</td>
<td>0.723</td>
</tr>
<tr>
<td>SVRI, dynes×s×cm⁻⁵×m⁻²</td>
<td>2339.2±673.8</td>
<td>1848.4±491.5</td>
<td>0.004</td>
<td>1725.5±489.5</td>
<td>0.001</td>
<td>0.167</td>
</tr>
<tr>
<td>PVRi, dynes×s×cm⁻⁵×m⁻²</td>
<td>600.0±171.4</td>
<td>410.5±115.4</td>
<td>0.002</td>
<td>356.8±77.8</td>
<td>0.001</td>
<td>0.016</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>59.2±8.6</td>
<td>60.4±10.1</td>
<td>0.438</td>
<td>60.3±9.7</td>
<td>0.921</td>
<td>0.338</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>327.7±63.4</td>
<td>283.4±81.6</td>
<td>0.006</td>
<td>298.5±83.3</td>
<td>0.094</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Data are expressed as means±SD.

iNO indicates inhaled nitric oxide; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusive pressure; CVP, central venous pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; SvO₂, mixed venous oxygen saturation; PaO₂/FiO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen.
in a decrease of PVR along with an increase in left atrial end-diastolic pressure. As showed by Loh et al, the specific increase of left atrial filling pressure was evident in patients with “decompensated heart failure.” The authors suggested that the NO-induced increase in left ventricle filling pressure was due to a small increase in left ventricle volume that occurred secondary to an increase in pulmonary venous return to the failing left ventricle in patients with decompensated heart failure (PAOP more than 18 mm Hg and cardiac index less that 2.1 L/minute×m$^{-2}$)). In our study, the administration of iNO did not affect PAOP, and no patient experienced signs of pulmonary edema. This could be ex-

![Figure 3](image1.png)

**Figure 3.** Individual data showing alterations in mean pulmonary artery pressure (MPAP) (A) and pulmonary vascular resistance index (PVRi) (B) during the study protocol.

![Figure 4](image2.png)

**Figure 4.** Individual data showing alterations in mean arterial pressure (MAP) (A) and systemic vascular resistance index (SVRI) (B) during the study protocol.
plained by the fact that our patients were in a “compensated” state of heart failure, with PAOP less than 18 mm Hg and cardiac index more than 2.1 L/(minute×m²). Additionally, the dose of iNO used in our study was only 10 ppm, compared with 80 ppm used by Loh et al.

Oral sildenafil represents a useful adjunctive treatment for PH in patients with systolic heart failure who either are heart transplant candidates or have received left ventricular assist devices. Shim et al. showed that in patients with PH undergoing valve replacement surgery, the administration of oral sildenafil before the introduction of anesthesia resulted in a significant pulmonary vasodilator effect with predominant selectivity of sildenafil to pulmonary vasculature. In addition, its beneficial effects in regard to myocardial remodeling further advocate its potential use in cardiac surgery patients. In our study, sildenafil administration reduced MPAP and PVRI but also reduced PAOP and SVRI, improving both left ventricular preload and afterload, factors that are known to influence myocardial remodeling.

In our study, the reduction in SVRI and MAP observed by the administration of sildenafil was statistically significant compared with baseline but not as profound as the respective reduction in PVRI and MPAP. These systemic effects of sildenafil are in accordance with previously published data that showed that the abundance of PDE5 receptors in pulmonary vasculature offers the possibility of relatively selective pulmonary vasodilation with slight systemic hypotension. Sildenafil alone reduced the PaO₂/FiO₂ ratio, a phenomenon that was not evident with the administration of either iNO alone or with the combined administration. It is known that vasodilators administered systemically cause nonspecific vasodilation in the lungs and thus can redistribute pulmonary blood flow to poorly ventilated lung areas, inducing ventilation/perfusion mismatch and thus hypoxemia. On the other hand, administration of inhaled vasodilators, such as iNO, selectively dilates pulmonary capillaries in alveoli that are well ventilated, thus reducing pulmonary artery pressure while improving oxygenation. Coadministration of both a systemic vasodilator (sildenafil) and a selective inhaled pulmonary vasodilator (iNO) in our study resulted in both pulmonary and systemic vasodilation, with the iNO compensating for the effect of sildenafil in ventilation/perfusion mismatch, maintaining the PaO₂/FiO₂ ratio at baseline values.

The combination of these drugs was synergistic in decreasing the PVRI and MPAP without any significant reduction in both SvO₂ and cardiac index. Preston et al. showed that in patients with acute and chronic PH, the addition of iNO potentates the pulmonary vasodilator effects of sildenafil lowering PVR more than each agent alone. In patients who are candidates for heart/lung transplantation, the pulmonary vasodilator effects of oral sildenafil were found to be as effective as iNO, but it was more effective when the 2 were combined. These additive effects induced by the combination of the 2 drugs may indicate a synergistic effect, providing pulmonary vascular smooth muscle relaxation due to mechanisms mediated by cGMP.

One potential limitation of our study is the rather short duration of the protocol, ie, 90 minutes. Because the aim of this study was the evaluation of short-term effects of these 2 drugs on postoperative gas exchange and hemodynamics rather than that an evaluation of outcome, the short duration of the protocol has been chosen to ensure steady-state conditions, because the specific patients are susceptible to several confounding factors that may influence hemodynamic stability postoperatively. To examine any longer term effects or any impact on outcome of oral sildenafil administration postoperatively in such patients, with and without iNO, larger prospective studies are required.

Another limitation was that, because of the strict inclusion criteria and the rarity of the specific disorder, the number of patients finally included in the study during the 2-year study period was small. Nevertheless, our findings reached strong statistical significance despite the small number of patients.

Regarding the cost of the combined treatment, the small number of subjects did not allow extensive cost-effectiveness evaluation. The cost of 100 mg of sildenafil is approximately 25 euros, whereas the cost for iNO administration at 10 ppm for 30 or 90 minutes did not exceed 60 to 90 euros. Thus, the expected improvement in outcome seems to be cost-effective, given that the cost of coadministration is not very high as compared with the administration of iNO alone, but no safe conclusions about the cost-effectiveness of the combined therapy could be drawn by our study.

In conclusion, the immediate postoperative coadministration of iNO and oral sildenafil in patients with out-of-proportion PH due to left ventricular failure undergoing cardiac valve replacement surgery is safe. The combination of sildenafil and iNO have an additive effect in decreasing pulmonary vascular pressure and resistance more than either alone. Further evidence of the salutary effect of this combination is that, in contrast to iNO alone, sildenafil unloaded the left ventricle, reducing both preload and afterload, whereas the iNO added to the sildenafil eliminated the decreased PaO₂/FiO₂ ratio induced by sildenafil alone. To our knowledge, this is the first study showing the effects of the combined administration of sildenafil and iNO in valve replacement cardiac surgery patients immediately postoperatively. This combination should be studied in a larger population for a longer period of time to further clearly establish the role of these regimens in such patients after cardiac valve operations.

Disclosures

None.

References


Matamis et al


**CLINICAL PERSPECTIVE**

In patients with left ventricular dysfunction undergoing cardiac surgery, the presence of pulmonary hypertension (PH) may adversely affect the outcome. Although left heart disease is the most common cause of PH, very few data on the pathophysiology and treatment of out-of-proportion PH due to left heart disease are available. Several previous studies have focused on either inhaled nitric oxide (iNO) or oral sildenafil administration in patients with PH. The combined use of these agents in patients with out-of-proportion PH due to left heart disease is well not documented. To our knowledge, this study is the first that evaluates the effects of oral sildenafil and iNO on hemodynamic and gas exchange when administered immediately postoperatively either alone or in combination in postoperative patients with out-of-proportion PH due to left valvular heart disease who underwent valve replacement surgery. The combination of sildenafil and iNO has an additive effect in decreasing pulmonary vascular pressure and resistance more than either alone. Further evidence of the salutary effect of this combination is that, in contrast to iNO alone, sildenafil unloaded the left ventricle, reducing both preload and afterload, whereas the iNO added to the sildenafil improved ventilation/perfusion mismatch (eliminated the decreased PaO2/FiO2 ratio) induced by sildenafil alone. The findings of our study may suggest improved outcome of these patients and thus a new therapeutic approach, an insight that has to be confirmed by larger studies.
Inhaled NO and Sildenafil Combination in Cardiac Surgery Patients With Out-of-Proportion Pulmonary Hypertension: Acute Effects on Postoperative Gas Exchange and Hemodynamics

Dimitrios Matamis, Smaro Pampori, Athanasios Papathanasiou, Panagiota Papakonstantinou, Mathew Tsagourias, Eftichia Galiatsou, Vasilios Koulouras and George Nakos

Circ Heart Fail. 2012;5:47-53; originally published online November 4, 2011; doi: 10.1161/CIRCHEARTFAILURE.111.963314

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/1/47

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/