Inhaled NO and Sildenafil Combination in Cardiac Surgery Patients with Out-of-Proportion Pulmonary Hypertension: Acute Effects on Post-Operative Gas Exchange and Hemodynamics

Matamis et al: iNO and Sildenafil in Cardiac Surgery Patients

Dimitrios Matamis¹ MD PhD
Smaro Pampori¹ MD,
Athanasios Paphathanasiou² MD PhD
Panagiota Papakonstantinou¹ MD
Mathew Tsagourias¹ MD PhD
Eftichia Galiatsou² MD PhD
Vasilios Koulouras² MD PhD
George Nakos² MD PhD DTM FCCP

¹Intensive Care Unit, Papageorgiou General Hospital, Thessalonica, Greece,
²Intensive Care Unit, University Hospital of Ioannina, Ioannina, Greece

Address for Correspondence
Professor G Nakos MD PhD DTM FCCP
Intensive Care Unit
University Hospital of Ioannina
45500 Ioannina, Greece
Tel: +302651099279
Fax: +302651099343
E-mail: gnakos@cc.uoi.gr

Journal Subject Code: [18] Pulmonary circulation and disease
Abstract

Background—To examine the effects of co-administration 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 randomized postoperatively into two groups: group A received 10ppm of iNO followed by sildenafil (100mg) pos 30 min later, and group B received initially sildenafil (100mg) orally followed by 10ppm of iNO 60 min later. Hemodynamic and gas exchange data were obtained at baseline, after administration of either iNO or sildenafil alone and at 90 min from baseline. In group A, iNO resulted in a significant reduction in MPAP and PVRI (by 9.6% and 20.8% respectively). In group B, sildenafil administration also resulted in a significant decrease in MAP, MPAP, PAOP, PVRI, SVRI but also in PO2/FiO2 ratio (by 18.7%, 22.0%, 15.7%, 31.6% 21.3% and 14% respectively). In both groups the co-administration of the two drugs resulted in a significant further reduction of MAP, MPAP, PAOP, SVRI, PVRI, while CI and SvO2 remained unchanged. The hypoxemia after sildenafil administration in group B improved after the co-administration of iNO and thus PO2/FiO2 returned to values towards baseline.

Conclusions—In this study, the postoperative co-administration of iNO and oral sildenafil in patients with out-of-proportion pulmonary hypertension undergoing cardiac surgery is safe and results in an additive favourable effect on pulmonary arterial pressure and pulmonary vascular resistance, without systemic hypotension and ventilation/perfusion mismatch.

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. In left heart disease, pulmonary hypertension 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. In some cases the elevation of pulmonary artery pressure is greater than that expected by the elevation of left atrial pressure (transpulmonary gradient>12mmHg), possibly because of intrinsic changes in the pulmonary circulation leading to so-called reactive or ‘out-of-proportion’ pulmonary hypertension.

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). Administration of inhaled nitric oxide (iNO) dilates pulmonary vessels, thereby decreasing pulmonary vascular resistance, pulmonary arterial pressure and right ventricular afterload. Conversely, in left ventricular failure, inhalation of NO may cause a decrease in PVR associated with increased increased pulmonary artery wedge pressure without affecting pulmonary arterial pressure. The use of iNO is limited due to technical difficulties and its delivery and monitoring remain complex and cumbersome. In addition, abrupt discontinuation of iNO therapy can lead to acute rebound pulmonary hypertension and hypoxemia.

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 PDE5 is abundantly expressed in pulmonary vascular smooth muscle cells, it is a logical therapeutic target in PH. Oral sildenafil, a phosphodiesterase type 5 (PDE-5) inhibitor, that prevents the degradation of cGMP and enhances NO signalling, has been shown to be
as effective as iNO in the setting of primary pulmonary hypertension.\textsuperscript{10} Recently there are substantial data concerning the efficacy and safety of sildenafil administration in patients with PH due to with congestive heart failure.\textsuperscript{10-12} In addition, its beneficial effects regarding myocardial remodelling further support its potential use in patients undergoing cardiac surgery.\textsuperscript{1, 13-15} Furthermore, administration of sildenafil does not require a special delivery system and does not induce rebound pulmonary hypertension. 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.\textsuperscript{2-3} 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 inhaled nitric oxide 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 that underwent valve replacement surgery.

**Methods**

Study population

This was a prospective randomized study that took place in the ICU of two hospitals in Greece during a two-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 pulmonary hypertension due to left heart valvular disease (category 2) as defined by the 3\textsuperscript{rd} World Symposium on Pulmonary Hypertension and applied during the study period.\textsuperscript{16} Since then, the classification of PH has been modified, and
pulmonary hypertension due to left heart valvular disease was defined as pulmonary artery systolic pressure more than 25mmHg and pulmonary wedge pressure more than 15mmHg and was further categorized as postcapillary out-of-proportion pulmonary hypertension if transpulmonary gradient (mean pulmonary artery pressure minus pulmonary wedge pressure) more than 12mmHg, and passive postcapillary pulmonary hypertension if transpulmonary gradient was less than 12mmHg. In order to comply with the recently published definitions of pulmonary hypertension 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 pulmonary hypertension were excluded from the further investigation.

From the 54 patients 34 were excluded postoperatively (Figure 1): 23 due to hemodynamic instability or low cardiac output syndrome necessitating high doses of inotropes and vasopressors postoperatively, 8 due to emergency re-operation for hemorrhage, and 3 due to cardiac tamponade.

Finally the study protocol 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 ICU and remained under mechanical ventilation.

Postoperative medication for all patients included sedation (midazolam 0.1mg/Kg body weight, fentanyl 10 mg/kg body weight) muscle relaxant (vecuronium) heparin, diuretics, and low dose of dobutamine (≤5mcg/kg/min).

Just after ICU admission, a transesophageal echocardiographic examination (TEE) 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 trans-gastric short axis view at the level of the papillary muscles. The mean value of three subsequent measurements was taken into account. Right ventricular dysfunction was defined as dilatation and/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 6-8 ml/Kg, rate 12-18 breaths/min, inspiration to expiration ratio of 1:2, adequate inspired fraction of oxygen (FiO₂) to achieve saturation of oxygen in arterial blood (SaO₂) >90%, and positive end expiratory pressure (PEEP) 3-7 cm H₂O. Ventilator settings were kept constant during the study protocol.

After hemodynamic stabilization patients were randomized into two groups. In the group A (n=10) patients received continuously iNO for 90 min and 30 min after iNO initiation, 100 mg sildenafil was administered orally. In group B (n=10) patients received initially 100mg of sildenafil orally and 60 min later iNO was added for 30 min (Figure 2). Inhaled NO is a short acting agent reaching plateau effectiveness within 3-6 minutes of administration. ¹⁷ The study protocol was designed so that adequate time is allowed for
sildenafil to reach its maximum effect, while iNO remains 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 in order to decrease the contact time of NO with O₂. The concentrations of NO and its toxic metabolite nitric dioxide (NO2) were measured in the common limb of the respiratory circuit, using a fast response apparatus (DelNO Sensor Medics Crit. Care®). iNO was delivered from a 900 ppm NO in N2 gas tank.

Hemodynamic and gas exchange data were obtained i) at baseline, ii) before the administration of the second medication (at 30 minutes for group A and 60 minutes for group B) and iii) 90 min from baseline measurements. Mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP) and central venous pressure (CVP) were continuously displayed and obtained from a monitor. Pulmonary artery occlusive pressure (PAOP) was recorded at the end of expiration. Cardiac output (CO), cardiac index (CI) and mixed venous oxygen saturation (SvO₂) were continuously recorded using a CCO-SvO₂ - PAC (Edwards Lab®). The transducers were zeroed at mid-axillary level. At each time point an arterial blood sample was obtained and partial pressure (PaO₂) and SaO₂ were recorded. Arterial and mixed venous blood samples were collected and analyzed using blood gas analyzer (ABL 70® Radiometer Kopenhagen). Systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were calculated according to standard formulas, i.e. PVRI = (MPAP-PAOP) / CI and SVRI = (MAP-CVP) / CI.
Statistical analysis

Continuous variables in each group of patients were expressed as mean values ± standard deviation (SD). The PaO₂/FiO₂ ratio was expressed as an absolute value. The normality for each variable was assessed by Kolmogorov-Smirnov test. Differences within and between groups were evaluated by repeated measures analysis of variances (ANOVA), or by Friedman's test (the non-parametric equivalent) as appropriate. This was followed by the Bonferroni's correction for the multiple comparisons procedure. Baseline characteristics between the two study groups were compared using t-test or Mann Whitney test when appropriate. In all cases a p value of less than 0.05 was considered significant as determined with SPSS® 11.0 Software (SPSS, Inc; Chicago, Ill) statistics.

Results

A total of 20 patients (11 males, 9 females, mean age 65±6 years) were included in the study. Demographic data between group 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 two study groups (Table).

Mean left ventricular ejection fraction, based on initial TEE (before baseline measurements) was similar between the two 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 and/or hypokinesia, was detected in any patients.

Hemodynamics and oxygenation during the 90 min treatment period in group A and B are shown in the Table. Individual data for MPAP - PVRI and MAP - SVRI are shown in Figures 3 and 4 respectively. Inhaled NO 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 vasodilation 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 towards baseline values resulting in a difference that was no longer statistically significant (Table).

In both groups of patients, levels of CI and SvO2 remained unchanged compared to baseline during the study protocol (Table).

**Discussion**

According to our pilot study, in patients with out-of-proportion pulmonary hypertension 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. Inhaled NO improved the PaO2/FiO2 ratio and maintained both CI and SvO2. Furthermore, sildenafil administration was effective in decreasing MAP, MPAP, PAOP, PVRI, but also resulted in a significant decrease in SVRI. Sildenafil also improved PAOP without reducing SvO2...
or CI, while resulted in a significant reduction in the \( \text{PaO}_2/\text{FiO}_2 \) ratio. The co-administration of iNO and oral sildenafil maintains the beneficial effects of each respective substance in pulmonary and systematic circulation, without significantly deteriorating the \( \text{PaO}_2/\text{FiO}_2 \) ratio. Moreover, in these patients, the co-administration 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 \( \text{PaO}_2/\text{FiO}_2 \) 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 two drugs acting on the NO-cGMP signalling pathway. The downstream effects of this pathway, that 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. Since spatial distribution and signalling of cGMP appears heterogeneous, such a combination could have a sound physiological basis: drugs that modulate the cGMP pathway may have differential and/or synergistic effects depending on which pools of cGMP they act on.

In patients with left ventricular dysfunction, especially those undergoing cardiac surgery, pulmonary hypertension (PH) adversely affects postoperative morbidity and mortality. In these patients treatment of postoperative pulmonary hypertension improves hemodynamic status and may influence the outcome. Even though PH importance is sufficiently outlined, its management can be challenging.

Inhaled NO administration in patients with pulmonary hypertension decreases pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular afterload. Inhaled NO has also been used in patients with severe pulmonary hypertension, attributable to left
ventricular dysfunction, undergoing cardiac transplantation as part of their preoperative assessment or treatment.\textsuperscript{7,8} 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, due to non systemic absorption.\textsuperscript{5,22}

Previous studies have shown that, in patients with left ventricular failure, the administration of 80ppm iNO resulted in a decrease of PVR along with an increase in left atrial end-diastolic pressure.\textsuperscript{6} As showed by Loh et al,\textsuperscript{6} 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 LV filling pressure was due to a small increase in LV volume that occurred secondary to an increase in pulmonary venous return to the failing LV in patients with “decompensated heart failure” (PAOP more than 18mmHg and CI less that 2.1 L/[min · m\(^{-2}\)]).\textsuperscript{6} In our study the administration of iNO did not affect PAOP and no patient experienced signs of pulmonary edema. This could be explained by the fact that our patients were in a “compensated” state of heart failure with PAOP less than 18mmHg and CI more than 2.1 L/[min · m\(^{-2}\)]. Additionally, the dose of iNO used in our study was only 10ppm compared to 80ppm used by Loh et al.\textsuperscript{6}

Oral sildenafil represents a useful adjunctive treatment for PH in patients with systolic heart failure that are either heart transplant candidates\textsuperscript{23} or have received left ventricular assist devices.\textsuperscript{10} Jae Kwang Shim et al\textsuperscript{24} showed that in patients with PH undergoing valve replacement surgery the administration of oral sildenafil before the introduction of anaesthesia resulted in a significant pulmonary vasodilator effect with predominant selectivity of sildenafil to pulmonary vasculature. In addition, its beneficial effects in regards to myocardial remodelling further advocate its potential use in cardiac surgery patients.\textsuperscript{13-15} 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 remodelling.

In our study the reduction in SVRI and MAP observed by the administration of sildenafil was statistically significant compared to 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 PDE-5 receptors in pulmonary vasculature offers the possibility of relatively selective pulmonary vasodilation with slight systemic hypotension.24-25

Sildenafil alone reduced the PaO$_2$/FiO$_2$ ratio, a phenomenon that was not evident in the administration of either iNO alone or in the combined administration. It is known that vasodilators administered systemically cause non-specific vasodilation in the lungs and thus can redistribute pulmonary blood flow to poorly ventilated lung areas, inducing ventilation/perfusion mismatch and thus hypoxemia.22 On the other hand, administration of inhaled vasodilators, such as iNO, selectively dilates pulmonary capillaries in alveoli that are well-ventilated, thus reducing PAP while improving oxygenation.22 Co-administration of both a systematic vasodilator (sildenafil) and a selective inhaled pulmonary vasodilator (iNO) in our study resulted in both pulmonary and systemic vasodilation, with the iNO compensating the effect of sildenafil in ventilation/perfusion mismatch, maintaining PaO$_2$/FiO$_2$ ratio to baseline values.

The combination of these drugs was synergistic in decreasing the PVRI and MPAP without any significant reduction in both SvO$_2$ and CI. Preston et al.26 showed that in patients with acute and chronic pulmonary hypertension, the addition of iNO potentiates the pulmonary vasodilator effects of sildenafil lowering PVR more than each agent alone.26 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 more
effective when the two were combined. These additive effects induced by the combination of the two 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, i.e. 90 minutes. Since the aim of this study was the evaluation of short-term effects of these two drugs on post-operative gas exchange and hemodynamics rather than an evaluation on outcome, the short duration of the protocol has been chosen in order to ensure steady state conditions, because the specific patients are susceptible to several confounding factors that may influence hemodynamic stability postoperatively. In order to examine any longer-term effects and/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, due to the strict inclusion criteria and the rarity of the specific disorder, the number of patients finally included in the study during the two-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 100mg sildenafil is approximately 25 Euros while the cost for iNO administration at 10 ppm for 30 or 90 minutes did not exceed 60-90 Euros. Thus the expected improvement in outcome seems to be cost-effective, given that the cost of co-administration is not very high as compared to 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 co-administration of iNO and oral sildenafil in patients with out-of-proportion pulmonary hypertension 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, while 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 post-operatively. 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


22. Siobal MS. Pulmonary vasodilators. Respir Care. 2007;52:885-899


Table. Hemodynamic and oxygenation parameters of the two study groups

<table>
<thead>
<tr>
<th></th>
<th>GROUP A (n=10 patients)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BASELINE</td>
<td>Administration of iNO (30 min)</td>
<td>p-value vs baseline</td>
<td>Administration of iNO plus SILDENAFIL (90 min)</td>
<td>p-value vs baseline</td>
<td>p-value vs NO alone</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>--------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>MAP (mmHg)</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 (mmHg)</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 (mmHg)</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 (mmHg)</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 (dyne · sec · 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 (dyne · sec · 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>

<table>
<thead>
<tr>
<th></th>
<th>GROUP B (n=10 patients)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BASELINE</td>
<td>Administration of SILDENAFIL (60 min)</td>
<td>p-value vs baseline</td>
<td>Administration of SILDENAFIL plus iNO (90 min)</td>
<td>p-value vs baseline</td>
<td>p-value vs NO alone</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>--------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>MAP (mmHg)</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 (mmHg)</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(mmHg)</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 (mmHg)</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 (dyne · sec · 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 (dyne · sec · 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></td>
<td>Mean ± SD</td>
<td>p-value</td>
<td>Mean ± SD</td>
<td>p-value</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>59.2 ± 8.6</td>
<td>0.438</td>
<td>60.3 ± 9.7</td>
<td>0.921</td>
<td>0.338</td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>327.7 ± 63.4</td>
<td>0.006</td>
<td>298.5 ± 83.3</td>
<td>0.094</td>
<td>0.046</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusive pressure; CVP, central venous pressure; CI, cardiac index; SvO₂, mixed venous oxygen saturation; PaO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; NS, not statistical.
Figure Legends

**Figure 1.** Flow chart showing inclusion and exclusion criteria of patients enrolled in the study (* patients with sPH according to the classification by the 3rd World Symposium on Pulmonary Hypertension, ** patients out-of-proportion PH due to heart disease according to classification by the 4th World Symposium on Pulmonary Hypertension, *** patients with sPH criteria of the recently published classification).(PH, pulmonary hypertension, sPH, secondary pulmonary hypertension).

**Figure 2.** Flow chart of the study protocol. iNO: inhaled nitric oxide

**Figure 3.** Individual data showing alterations in (A) MPAP and (B) PVRI during the study protocol.

**Figure 4.** Individual data showing alterations in (A) MAP and (B) SVRI during the study protocol.
Screened
n = 654

Patients with sPH
Initially included
n = 62 *

excluded
n = 8 ***

Patients with out-of proportion PH
finally included
n = 54 **

Included (n=20)
AV replacement (n=6)
MV replacement (n=4)
MV & AV replacement (n=2)
MV replacement and CABG (n=4)
AV replacement and CABG (n=4)

Excluded (n=34):
- hemodynamic instability or low cardiac output syndrome necessitating high doses of inotropes and vasopressors (n=23)
- Emergency re-operation for hemorrhage (n=8)
- Tamponade (n=3)

Randomization

GROUP A (n=10)  GROUP B (n=10)
Inhaled NO and Sildenafil Combination in Cardiac Surgery Patients with Out-of-Proportion Pulmonary Hypertension: Acute Effects on Post-Operative Gas Exchange and Hemodynamics
Dimitrios Matamis, Smaro Pampori, Athanasios Papathanasiou, Panagiota Papakonstantinou, Mathew Tsagourias, Eftichia Galiatsou, Vasilios Koulouras and George Nakos

Circ Heart Fail. published online November 4, 2011;
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/early/2011/11/04/CIRCHEARTFAILURE.111.963314

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/