Comparison of the Effects of Nitric Oxide, Nitroprusside, and Nifedipine on Hemodynamics and Right Ventricular Contractility in Patients With Chronic Pulmonary Hypertension*

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Study objectives: The effects of inhaled nitric oxide (NO) on hemodynamics and right ventricular (RV) contractility were compared with those of nitroprusside and nifedipine in 14 patients with severe chronic pulmonary hypertension.

Study design: Micromanometer and balloon-tipped right heart catheterization were performed. Inhaled NO, IV nitroprusside, and sublingual nifedipine were administered sequentially while patients breathed > 90% oxygen.

Setting: Cardiac catheterization laboratory in a tertiary care teaching hospital.

Patients: Fourteen patients with severe pulmonary hypertension unrelated to left ventricular dysfunction.

Measurements and results: During NO inhalation, mean systemic arterial pressure (MAP) was unchanged, but pulmonary artery (PA) pressure ([mean ± SEM] 49 ± 2 mm Hg vs 44 ± 2 mm Hg; p < 0.01), pulmonary vascular resistance (PVR; 829 ± 68 vs 669 ± 64 dyne · s · cm⁻⁵; p < 0.01) and RV end-diastolic pressure (RVEDP; 12 ± 1 vs 10 ± 1 mm Hg; p < 0.01) decreased. Stroke volume index (SVI; 31 ± 2 vs 35 ± 3 mL/m²; p < 0.05) increased, and the first derivative of RV pressure at 15 mm Hg developed pressure (RV +dP/dt at DP15) was unchanged. During nitroprusside administration, MAP decreased (105 ± 5 vs 76 ± 5 mm Hg; p < 0.01), PA was unchanged (48 ± 2 vs 45 ± 3 mm Hg; p = not significant), and PVR decreased (791 ± 53 vs 665 ± 53 dyne · s · cm⁻⁵; p < 0.01). RV +dP/dt at DP15 increased (425 ± 22 vs 465 ± 29 mm Hg/s; p < 0.05), but SVI was unchanged. Nifedipine decreased MAP (103 ± 5 vs 94 ± 5 mm Hg; p < 0.01), PA and PVR were unchanged, RVEDP increased (12 ± 1 vs 14 ± 2 mm Hg; p < 0.01), and RV +dP/dt at DP15 decreased (432 ± 90 vs 389 ± 21 mm Hg/s; p < 0.05).

Conclusions: Inhaled NO is a selective pulmonary vasodilator in patients with chronic pulmonary hypertension that improves cardiac performance without altering RV contractility. Nitroprusside caused a similar degree of pulmonary vasodilation. In contrast to inhaled NO, nitroprusside caused systemic hypotension associated with an increase in RV contractility. Acute administration of nifedipine did not cause pulmonary vasodilation, but RVEDP increased and RV contractility decreased.

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Key words: inotropism; nifedipine; nitric oxide; nitroprusside; pulmonary hypertension

Abbreviations: LV = left ventricular; NO = nitric oxide; MAP = mean systemic arterial pressure; mPAP = mean pulmonary artery pressure; RV = right ventricle, ventricular; RV +dP/dt = rate of change in right ventricular pressure at 15 mm Hg developed pressure; RVEDP = right ventricular end-diastolic pressure; RV +dP/dt = right ventricular end-diastolic pressure

Nitric oxide (NO) is an effective, selective pulmonary vasodilator in a variety of conditions associated with increased pulmonary vascular tone including pulmonary hypertension of the newborn,1 ARDS,2,3 primary pulmonary hypertension,4 pulmonary hypertension secondary to left ventricular (LV) dysfunction,5 and mitral valve disease.6 Continuous administration of NO for days to weeks has been described in ARDS and in newborns with respiratory...
failure. Furthermore, long-term administration of NO has been investigated in patients with end-stage primary pulmonary hypertension who were refractory to other treatment.7,8

The effects of inhalation of NO on myocardial function are not well documented, but are of particular interest in light of observations that suggest that endogenous NO has negative inotropic effects and may be an intermediary in the cardiac dysfunction seen in sepsis.9,10 We and others have shown that LV filling pressures increase during NO inhalation in patients with severe heart failure,5 and this effect is associated with a deterioration in LV performance.11

Currently, the treatment of patients with isolated pulmonary hypertension remains problematic.12 The use of calcium-channel antagonists and epoprostenol are recent advances that have improved the outlook for patients primary pulmonary hypertension; however, both calcium-channel antagonists and epoprostenol are nonselective vasodilators, and their use may be limited by systemic vasodilation. IV epoprostenol improves survival in patients with primary pulmonary hypertension but requires continuous IV infusion, and catheter-related complications may occur in > 10% of patients.13 Calcium-channel antagonists are effective in a minority of patients and have negative inotropic effects, which may limit their use in patients with right ventricular (RV) dysfunction.14,15 Lung and heart-lung transplantation is an option for suitable candidates, but its application is limited because of a shortage of donors.

If long-term administration of NO is considered, any negative inotropic effect of NO would be particularly important in patients with isolated pulmonary hypertension. In 1991, a median survival of only 2.8 years after diagnosis was reported for patients with primary pulmonary hypertension, with RV failure the most significant predictor of mortality.16 In the current study, we examined the effects of inhaled NO on pulmonary hemodynamics and right heart function in patients with severe pulmonary artery hypertension unrelated to LV dysfunction. These effects were compared with the effects of IV nitroprusside and sublingual nifedipine. Patients were studied while breathing oxygen to assess the additional vasodilating properties of these agents beyond those caused by the reversal of hypoxic pulmonary vasoconstriction.17,18

### Materials and Methods

#### Patient Population

The baseline demographic and hemodynamic characteristics of 14 patients referred for evaluation of pulmonary hypertension who underwent study are shown in Table 1. Only patients with isolated pulmonary vascular disease were included. Pulmonary function tests and high-resolution chest CT were performed to exclude significant airways or parenchymal lung disease. A mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg at rest was required for study entry. Chronic pulmonary emboli were excluded by normal or low probability ventilation/perfusion nuclear scintigraphy in all patients. Five patients had primary pulmonary hypertension, 6 had pulmonary hypertension associated with collagen vascular disease, 2 had pulmonary hypertension associated with hepatic cirrhosis, and 1 patient had veno-occlusive disease. The diagnosis of veno-occlusive disease was made clinically before the study, and was subsequently confirmed on

<table>
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<th>Table 1—Study Population*</th>
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<td>Patient</td>
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<td>14</td>
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</tbody>
</table>

*All values are obtained while breathing air, except patient 7, who was breathing at 3 L/min via nasal prongs. M = Male; F = Female; PAWP = pulmonary artery wedge pressure; CI = cardiac index; PPH = primary pulmonary hypertension; SLE = pulmonary hypertension associated with systemic lupus erythematosis; MIX = pulmonary hypertension associated with mixed connective tissue disease; CRST = pulmonary hypertension associated with CREST syndrome; CIRR = pulmonary hypertension associated with hepatic cirrhosis; VOD = veno-occlusive disease.
autopsy. The study was approved by the Massachusetts General Hospital Subcommittee on Human Studies. All patients gave informed consent before the study.

Hemodynamic Measurements

All vasodilators, including calcium-channel antagonists, were discontinued at least 24 h before the study. Right heart catheterization was performed with a triple-lumen balloon-tipped catheter via the internal jugular vein. A micromanometer-tipped catheter (Millar Instruments; Houston, Texas) was placed in the RV through a separate insertion site in the internal jugular vein. Systemic arterial pressure was obtained through a radial artery catheter.

The following hemodynamic variables were recorded: heart rate; right atrial pressure, high-fidelity RV pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and systemic arterial pressure. The position of the pulmonary artery catheter was confirmed by fluoroscopy and by the detection of a blood oxygen saturation of > 95% in blood drawn from the distal port of the wedged catheter. The rate of change in RV pressure (RV dp/dt) was determined by electronic differentiation. Cardiac output was determined by the Fick oxygen technique. Oxygen consumption was measured with an MRM-2 oxygen consumption monitor (Waters Assoc; Rochester, MN) at baseline on room air. Measurement of oxygen consumption was repeated at the conclusion of the study and did not differ significantly from the initial measurement. Thus, oxygen consumption was assumed to be constant throughout the study. Derived variables were calculated by standard formulas as follows:

\[
\text{pulmonary vascular resistance (dynes cm}^{-5}\text{)} = 80 \\
\left(\text{pulmonary artery mean pressure} - \text{pulmonary artery wedge pressure}\right) / \text{cardiac output}
\]

(1)

\[
\text{cardiac index (L/min/m}^2\text{)} = \text{cardiac output} - \text{body surface area}
\]

(2)

\[
\text{transpulmonary gradient (mm Hg)} = \text{pulmonary artery mean pressure} - \text{pulmonary artery wedge pressure}
\]

(3)

Blood Gas Measurements

Oxygen saturations were determined on a co-oximeter (model 482; Instrumentation Laboratories; Lexington, MA), and blood gases and pH were analyzed on a blood gas analyzer (model 1630; Instrumentation Laboratories). Pulmonary shunt fraction was determined by the standard formula:

\[
\frac{Qs/Qt}{1} = 0.003 (PAO_2 - PaO_2) / 0.003 (PAO_2) + (CaO_2 - Cvo_2)
\]

(4)

where PAO_2 is the partial pressure of alveolar oxygen, PaO_2 is the partial pressure of arterial oxygen, CaO_2 is the arterial oxygen content, and Cvo_2 is the mixed venous oxygen content.

Gas Delivery System

All gas mixtures were delivered by a nonrebreathing circuit consisting of a large bore aerosol tubing and a modified continuous positive airway pressure mask (Respirronics Inc; Murrysville, PA). Gas entry into the system was controlled by two standard high-flow flowmeters (Timeter Instruments; Lancaster, PA) in parallel. One flowmeter delivered 100% oxygen and the other a mixture of NO gas (800 ppm by volume in N_2; Airco; Riverton, NJ) and room air obtained from a standard low-flow blender (Bird Blender; Bird; Palm Springs, CA). Flow from each flowmeter was titrated to achieve a total flow of 45 L/min at > 90% oxygen concentration adding either 0, 20, 40, or 80 ppm NO. High flow was used to reduce the residence time of NO with oxygen to minimize the oxidation of NO to nitrogen dioxide (NO_2). The inspired concentration of NO and NO_2 was measured by chemiluminescence (model 14A; Thermo Environmental Instruments; Franklin, MA) and by polarimetry (Hudson Oxygen Meter; Temecula, CA). NO_2 levels were < 1 ppm at all doses of NO. Exhaled gases were scavenged and discarded to atmosphere. Blood methemoglobin levels were determined spectrophotometrically at baseline and during the inhalation of NO at 80 ppm.

Study Protocol

All measurements were made with the patient supine breathing through a face mask under the following sequential conditions: room air, > 90% oxygen, NO at 80 ppm by volume (ppm) in addition to > 90% oxygen, a second period of > 90% oxygen without NO, IV sodium nitroprusside plus > 90% oxygen, a third period of > 90% oxygen alone, and lastly, the administration of sublingual nifedipine plus > 90% oxygen. Measurements were taken 5 min after the beginning of each study period, or 5 min after the administration of the final dose of medication. The nitroprusside infusion was titrated to a systolic BP of 100 mm Hg, or a maximum dose of 300 μg/min. Ten milligrams of nifedipine was given sublingually every 10 min until the systolic BP was reduced to 100 mm Hg, or a maximum dose of 30 mg was reached.

Statistics

All results are expressed as mean ± SEM. Comparisons of the effects of oxygen alone are made by paired t test. One patient was unable to tolerate room air because of hypoxia; therefore, the comparison between room air and oxygen excludes one patient. Comparisons of the effects of NO, nitroprusside, and nifedipine were made by two-way analysis of variance for repeated measures followed by Fisher’s protected least-significant difference test, (StatView, version 5.1.2; SAS Institute Inc; Cary, NC). The Wilk-Shapiro test was used to test the normality of the data before analysis of variance. Values are compared with the previous baseline, unless otherwise noted. Comparisons of patients categorized by response to NO were by χ^2 test. A p value of ≤ 0.05 was considered significant.

RESULTS

Room Air

The mPAP (52 ± 2 mm Hg), pulmonary vascular resistance (882 ± 76 dyn cm/5) and RV end-diastolic pressure (RVEDP; 12 ± 2 mm Hg) were markedly elevated at baseline (Table 2). The cardiac index (2.4 ± 0.1 L/min/m^2) and stroke volume index (29 ± 2 mL/m^2) were low, but mean systemic arterial pressure (MAP; 102 ± 5 mm Hg) was normal. One patient was oxygen dependent and could not tolerate room air. This patient is not included in the values on room air.
Table 2—Hemodynamic Effects of Supplemental Oxygen*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>21% O₂</th>
<th>&gt; 90% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>83 ± 3</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>102 ± 5</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>12 ± 2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>PA, mm Hg</td>
<td>52 ± 2</td>
<td>48 ± 2†</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>7 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>45 ± 2</td>
<td>40 ± 2†</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>29 ± 2</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>SVR, dyn·cm⁻⁵</td>
<td>715 ± 43</td>
<td>720 ± 40</td>
</tr>
<tr>
<td>PVR, dyn·cm⁻⁵</td>
<td>882 ± 76</td>
<td>796 ± 65</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>1.27 ± 0.12</td>
<td>1.16 ± 0.12†</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM. See Table 1 for other abbreviations not given in text. TPG = transpulmonary gradient; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.
†p ≤ 0.05 vs room air.

Inhalation of > 90% Oxygen

Inhalation of > 90% oxygen reduced pulmonary artery pressure 7 ± 3% (p = 0.012), transpulmonary gradient 10 ± 4% (p = 0.016), and the ratio of pulmonary to systemic vascular resistance 9 ± 3% (p = 0.046). Heart rate, cardiac index, mean arterial pressure, RVEDP, and stroke volume index were unchanged (Table 2).

Nitric Oxide Inhalation

Inhalation of 80 ppm NO with > 90% oxygen reduced the pulmonary artery pressure by 10 ± 3% (p < 0.001), the transpulmonary gradient by 13 ± 4% (p < 0.003), pulmonary vascular resistance by 19 ± 4% (p < 0.001), and the ratio of pulmonary to systemic vascular resistance by 22 ± 4% (p < 0.001; Table 3). RVEDP decreased by 17 ± 5%, (p < 0.001), and stroke volume index increased by 12 ± 4% (p = 0.008). Heart rate, cardiac index, mean arterial pressure, and pulmonary artery wedge pressure were unchanged.

Nitroprusside Infusion

The infusion of nitroprusside (228 ± 47 µg/min) resulted in a 27 ± 4% decrease in MAP (p < 0.001) and a 16 ± 3% increase in heart rate (p < 0.001; Table 3). The pulmonary artery pressure and transpulmonary gradient were unchanged. Cardiac index increased by 18 ± 8% (p < 0.05), and pulmonary vascular resistance decreased with nitroprusside infusion by 16 ± 3% (p < 0.001). Nitroprusside infusion decreased RVEDP by 41 ± 6% (p < 0.001). Stroke volume, cardiac index, the ratio of pulmonary to systemic vascular resistance, and pulmonary artery wedge pressure were unchanged.

Nifedipine Administration

After the sublingual administration of nifedipine (24 ± 1 mg), mean arterial pressure fell 8 ± 1% (p < 0.001), and heart rate increased 11 ± 3% (p < 0.001). The ratio of pulmonary to systemic vascular resistance increased 21 ± 7% (p < 0.01), as did RVEDP (11 ± 4%; p < 0.001). Pulmonary artery pressure, pulmonary vascular resistance, transpulmonary gradient, cardiac index, and stroke volume index did not change with nifedipine (Table 3).

Effects of NO, Nitroprusside, and Nifedipine on RV Contractility and Relaxation

There were no changes in peak positive rate of change in right ventricular pressure (RV dP/dt), RV

Table 3—Hemodynamic Effects of NO, Nitroprusside, and Nifedipine While Breathing >90% Oxygen*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>O₂</th>
<th>NO, 80 ppm</th>
<th>O₂</th>
<th>Nitroprusside, 228 ± 47 µg/min</th>
<th>O₂</th>
<th>Nifedipine, 24 ± 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate, beats/min</td>
<td>77 ± 3</td>
<td>74 ± 3</td>
<td>78 ± 3</td>
<td>91 ± 4†</td>
<td>75 ± 3</td>
<td>84 ± 3† §</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>102 ± 5</td>
<td>103 ± 5</td>
<td>105 ± 5</td>
<td>76 ± 5†</td>
<td>103 ± 5</td>
<td>94 ± 5† §</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>12 ± 1</td>
<td>10 ± 1†</td>
<td>12 ± 1</td>
<td>7 ± 1†</td>
<td>12 ± 1</td>
<td>14 ± 2† §</td>
</tr>
<tr>
<td>PA, mm Hg</td>
<td>49 ± 2</td>
<td>44 ± 2†</td>
<td>48 ± 2</td>
<td>45 ± 3</td>
<td>49 ± 2</td>
<td>50 ± 2† §</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>9 ± 1</td>
<td>7 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>41 ± 2</td>
<td>36 ± 2†</td>
<td>39 ± 1</td>
<td>38 ± 2</td>
<td>40 ± 2</td>
<td>42 ± 2† §</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.3 ± 0.1</td>
<td>2.5 ± 0.2</td>
<td>2.3 ± 0.1</td>
<td>2.6 ± 0.2†</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>31 ± 2</td>
<td>35 ± 3†</td>
<td>30 ± 2</td>
<td>29 ± 2</td>
<td>32 ± 3</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>SVR, dyn·cm⁻⁵</td>
<td>715 ± 37</td>
<td>741 ± 39</td>
<td>738 ± 38</td>
<td>546 ± 41†</td>
<td>723 ± 41</td>
<td>645 ± 41† §</td>
</tr>
<tr>
<td>PVR, dyn·cm⁻⁵</td>
<td>829 ± 68</td>
<td>669 ± 64†</td>
<td>791 ± 53</td>
<td>665 ± 53†</td>
<td>791 ± 63</td>
<td>833 ± 70† §</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>1.21 ± 0.12</td>
<td>0.94 ± 0.10</td>
<td>1.12 ± 0.10</td>
<td>1.30 ± 0.13†</td>
<td>1.14 ± 0.12</td>
<td>1.39 ± 0.17† §</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM. O₂ = > 90% oxygen alone; NO, 80 ppm = oxygen plus NO at 80 ppm; Nitroprusside = oxygen plus nitroprusside; Nifedipine = oxygen plus nifedipine. See Table 1 for other abbreviations not used in text.
†p ≤ 0.05 vs previous O₂.
‡p ≤ 0.05 vs NO.
§p ≤ 0.05 vs nitroprusside.
dP/dt at 15 mm Hg developed pressure (RV +dP/dt at DP15), or peak negative RV dP/dt during NO inhalation. Nitroprusside infusion increased peak positive RV dP/dt 25 ± 12% (p < 0.001) and RV +dP/dt at DP15 10 ± 6% (p < 0.001). There was no change in peak negative RV dP/dt with nitroprusside infusion. The administration of nifedipine caused a decrease in RV +dP/dt at DP15 (9 ± 3%; p < 0.001); other measured indexes of myocardial contractility and relaxation were unchanged (Table 4 and Fig 1).

Gas Exchange

Six patients had PaO₂ < 60 mm Hg on room air (PaO₂ = 67.5 ± 4 mm Hg; range, 45 to 87 mm Hg). All patients had PaO₂ > 300 mm Hg on 90% oxygen. There was no significant change in PaO₂ during the administration of NO or nitroprusside. Shunt fraction was 0.08 ± 0.1 at baseline. The shunt fraction did not change while breathing NO (0.10 ± 0.01), but increased with the infusion of nitroprusside (0.12 ± 0.02; p = 0.03).

Characteristics of Patients Who Responded to NO

The pulmonary artery pressure, pulmonary vascular resistance, and RV dP/dt at a developed pressure of 20 mm Hg in individual patients receiving 100% oxygen, 80 ppm inhaled NO and oxygen, IV nitroprusside and oxygen, and oral nifedipine and oxygen are shown in Figure 1. A decrease in mPAP of ≥10% was arbitrarily used to define a pulmonary vasodilator response to treatment. The baseline pulmonary artery pressure was lower in patients who responded to NO (49 ± 1 vs 56 ± 3 mm Hg, p ≤ 0.05), but there was no difference in pulmonary artery pressure between responding and nonresponding patients while breathing oxygen (48 ± 3 vs 51 ± 4 mm Hg). A vasodilator response was seen in five of the six patients with collagen vascular disease, but in only one of the five with primary pulmonary hypertension and none of the two patients with cirrhosis. The single patient with pulmonary veno-occlusive disease had a 25% fall in pulmonary artery pressure with NO. All four of the patients who responded to nitroprusside infusion had responded to inhaled NO. There were no differences in demographics or baseline hemodynamics between those patients who responded to inhaled NO but not to IV nitroprusside and those who responded to both agents.

Discussion

In this study, we compared the short-term effects of inhaled NO, IV nitroprusside, and sublingual nifedipine on pulmonary and systemic hemodynamics, RV performance, and gas exchange in 14 patients with chronic pulmonary hypertension unrelated to LV dysfunction.

Hemodynamic Effects

Of the agents studied, only inhaled NO caused selective pulmonary vasodilation associated with augmented RV stroke volume and reduced RVEDP. In contrast, at doses that lowered pulmonary vascular resistance to a similar degree, nitroprusside caused systemic arterial hypotension as well as a decrease in RV preload, consistent with its known effect as a balanced vasodilator.20 The short-term administration of sublingual nifedipine did not cause pulmonary vasodilation. Nifedipine administration was associated with an increase in RVEDP without any change in stroke volume. The lack of a pulmonary vasodilator response to the relatively low dose of nifedipine has been reported: higher doses are usually required to demonstrate pulmonary vasodilation in the few patients who do respond.14 The increase in RVEDP in the absence of an increase in stroke volume even at this low dose suggests that nifedipine may have an adverse effect on RV myocardial function.

Inhaled NO has previously been reported to reduce the pulmonary artery pressure in patients with chronic pulmonary hypertension who were not receiving supplemental oxygen.4,21 Inhaled NO is also

| Table 4—Effects of NO, Nitroprusside, and Nifedipine on RV Contractility and Relaxation* |
|---|---|---|---|---|
| Variable | O₂ | NO, 80 ppm | O₂ | Nitroprusside, 228 ± 47 µg/min | O₂ | Nifedipine, 24 ± 1 mg |
| RV +dP/dt at DP15, mm Hg/s | 428 ± 18 | 399 ± 18 | 425 ± 22 | 465 ± 29† | 432 ± 24 | 389 ± 21‡ |
| RV peak +dP/dt, mm Hg/s | 496 ± 25 | 456 ± 27 | 490 ± 25 | 611 ± 60† | 495 ± 30 | 517 ± 37‡ |
| RV peak −dP/dt, mm Hg/s | 596 ± 37 | 552 ± 39 | 591 ± 34 | 585 ± 48 | 594 ± 39 | 614 ± 36 |

*Values given as mean ± SEM. RV peak + dP/dt = RV peak positive dP/dt; RV peak − dP/dt = RV peak negative dP/dt.
†p < 0.05 vs previous O₂.
‡p < 0.05 vs NO.
§p < 0.05 vs nitroprusside.

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132

Clinical Investigations

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Figure 1. Pulmonary artery pressure (top, A), pulmonary vascular resistance (middle, B), and RV +dP/dt at D15 (bottom, C) in pulmonary hypertension patients given 100% oxygen (O₂), >90% oxygen with 80 ppm nitric oxide (NO), 100% O₂ and IV nitroprusside (NTP), and 100% O₂ and oral nifedipine (NIF).
known to reverse hypoxic pulmonary vasoconstriction. In the current study, pulmonary vasodilation in response to supplemental oxygen was noted: both pulmonary artery pressure and transpulmonary gradient fell when oxygen was administered, despite the fact that oxygen saturation was > 90% on room air. Therefore, the current study differs from previous reports in that we observed additional pulmonary vasodilation when inhaled NO was added to a high inspired concentration of oxygen. Thus, inhaled NO appears to have vasodilating actions that are in addition to that of reversal of hypoxic vasoconstriction.

The target for NO in pulmonary vascular smooth muscle is thought to be the heme receptor of cytoplasmic soluble guanylate cyclase, where binding of NO leads to an increase in the conversion of cytoplasmic soluble guanylate cyclase, where binding of NO leads to an increase in the conversion of guanosine triphosphate to cyclic guanosine monophosphate. The relaxation effect of the increase in intracellular cyclic guanosine monophosphate in smooth muscle cells appears to be mediated by both an active extrusion of intracellular calcium and promotion of the phosphorylation of calcium channels. Phosphorylation leads to the inactivation of the calcium channels, resulting in a decrease in both voltage- and receptor-mediated calcium influx into the cell. Our observation that the vasodilator response to inhaled NO exceeds that of oxygen alone supports the hypothesis that some of the vasomotor effects of oxygen in the pulmonary circulation are endothelium independent and, as has been suggested by the studies of Madden et al., the location of the hypoxia sensor is within the smooth muscle cell.

Effects on RV Contractility

There is increasing evidence, both in vitro and in vivo, that NO has negative inotropic effects. Isolated cardiac myocyte contraction is attenuated by NO gas. Production of NO by NO synthase-3 within cardiac myocytes is associated with reduced contractility during endotoxemia. NO may also mediate the myocardial depressant effects of other cytokines. Endogenous NO reduces myocardial contractility and reduces myocardial lactate formation during myocardial ischemia in dogs. Furthermore, Hare et al. have demonstrated that the inhibition of NO synthase augments the positive inotropic response to intracoronary dobutamine infusion in heart failure patients. This suggests that local NO production in the heart inhibits the positive inotropic effect associated with dobutamine infusion.

The possibility that inhaled NO affects myocardial function is less certain. NO is rapidly bound to and inactivated by hemoglobin, and therefore should have no systemic effects. In patients with severe heart failure, inhalation of NO reduces the transpulmonary gradient but is associated with an increased pulmonary artery wedge pressure and no change in stroke volume. Loh et al. reported that inhaled NO increased LV end-diastolic pressure and decreased stroke volume in patients with left heart failure. Both of these observations are consistent with a negative inotropic effect.

The current study demonstrates that inhaled NO given at doses sufficient to lower pulmonary vascular resistance has no effect on RV contractility. Inhaled NO lowered pulmonary artery pressure and RV dP/dt at DP15. This likely reflects the extremely short half-life of NO in the presence of hemoglobin and the fact that, when given by inhalation, NO does not reach cardiac myocytes. Thus, the beneficial hemodynamic effects of breathing NO in patients with pulmonary hypertension appear to be related to an improvement in cardiac performance caused by a decrease in RV afterload, not a change in myocardial contractility.

IV nitroprusside, in contrast, was associated with an increase in RV contractility. The increased contractility is likely related to an increase in sympathetic nervous system activation, as indicated by the increase in heart rate that occurred during nitroprusside infusion. Despite the increase in contractility, RV performance was unchanged during nitroprusside infusion, probably because of the simultaneous fall of RV preload caused by systemic venodilation.

We observed that the administration of sublingual nifedipine caused a decrease in RV contractility associated with a rise in RV dP/dt. In vitro, nifedipine blocks transmembrane calcium transport in myocardium and results in depression of myocardial contractility. In humans with severe LV dysfunction, Fifer et al. observed a negative inotropic effect of nifedipine. In that study, sublingual nifedipine caused a decrease in peak LV dP/dt, associated with an increase in LV end-diastolic pressure. In patients with pulmonary hypertension, Packer et al. found that both nifedipine and verapamil administration lowered pulmonary artery pressure; however, both were associated with worsening RV performance as indicated by an increase in right atrial pressure with no change in cardiac output. Our observation that RV dP/dt decreased after sublingual nifedipine administration supports and extends the studies of Fifer et al. and Packer et al. We also measured RV dP/dt at a constant developed pressure to verify that our observation of a decrease indicated a negative inotropic effect regardless of the simultaneous change in ventricular preload. The negative inotropic effects of calcium-channel agonists may limit their utility in some patients with pulmonary hyper-
tension and RV dysfunction. However, in those patients in whom the pulmonary vasodilator effects predominate, the negative inotropic effect on the RV may be offset by the decrease in RV afterload. Indeed, improvement in RV function has been observed with the long-term use of calcium-channel antagonists in patients with a pulmonary vasodilator response.32

Cause of Pulmonary Hypertension and Effect of NO

The single patient with veno-occlusive disease had a 15% decrease in pulmonary artery pressure, which was associated with improvement in RV function and no change in clinical status or oxygenation. This response may indicate that there is NO-responsive tone in the pulmonary venules as well as the arterioles. If only the arterial circulation had undergone vasodilation, pulmonary edema would likely have developed because of increased pulmonary capillary pressure. Inhaled NO may provide a short-term therapy in this difficult to treat disorder.

Limitations of the Study

Several potential limitations to this study should be considered. The investigators in this study were not blinded, and the order in which the treatments were given was not randomized. Because of the obvious and possibly dangerous hemodynamic effects of nitroprusside, we did not want to administer this drug blindly. Given the short half-lives of both NO and nitroprusside and that the protocol called for at least a 5-min period of oxygen alone between measurements, it is unlikely that randomizing the sequence of administration would have changed the outcome. Nifedipine, which has a longer half-life, was given last by design because its effects would be expected to influence subsequent measurements.

Because a low dose of nifedipine was administered and only the short-term effects were recorded, we cannot compare the effects of NO with a fully titrated dose of this calcium-channel antagonist. All of the 14 patients did go on to enter prolonged high-dose calcium-channel blocker trials according to the protocol of Rich et al.14 Only two patients responded with a fall in pulmonary artery pressure. It is intriguing that both of these patients also had responded to inhaled NO. A vasodilator response to inhaled NO predicts a response to IV epoprostenol.21 It is likely that a response to inhaled NO will identify the subset of patients who are more likely to respond to high-dose calcium-channel antagonists.33,34

Conclusions

Inhaled NO is a selective pulmonary vasodilator in patients with chronic pulmonary hypertension that improves cardiac performance without changing RV contractility. At doses that caused a similar degree of pulmonary vasodilation, IV nitroprusside caused systemic hypotension, associated with increased RV contractility. The short-term administration of sublingual nifedipine did not cause pulmonary vasodilation, but did result in an increase in RV EDP and a decrease in RV contractility. This action may limit the use of nifedipine in patients with pulmonary hypertension.

References

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