Improvement in Exercise Capacity With Nitric Oxide Inhalation in Patients With Precapillary Pulmonary Hypertension

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**Background**—Patients with precapillary pulmonary hypertension (PH) exhibit a poor exercise capacity due to an impaired vasodilatory response of their pulmonary arteries. By causing the pulmonary artery to dilate, inhaled nitric oxide (NO) may allow an increase in exercise capacity in patients with PH.

**Methods and Results**—On 2 separate days, 3 days apart, 14 patients with precapillary PH (10 primary PH, 4 residual PH after correction of an intracardiac shunt; age, 40±12 years; mean pulmonary artery pressure, 60±23 mm Hg) performed exercise, with and without inhalation of 20 ppm NO, on a cycle ergometer. The work rate was increased 15 W/min until their symptom-limited maximum, with breath-by-breath gas analysis. Patients were randomly and blindly selected to inhale NO on either their first or second test. Peak exercise load and anaerobic threshold tended to increase, but not significantly. Peak oxygen consumption (\( \overline{V}O_2 \)) and \( \Delta \overline{V}O_2/\Delta W \) ratio increased significantly, by 18% and 22%, respectively (peak \( \overline{V}O_2, 13.6±3.6 \) to 16.0±4.1 mL · kg\(^{-1}\) · min\(^{-1}\); \( \Delta \overline{V}O_2/\Delta W \) ratio, 5.8±2.4 to 7.1±2.3 mL · kg\(^{-1}\) · min\(^{-1}\) · W\(^{-1}\); both \( P<0.01 \)). Peak \( \overline{V}O_2 \) increased >10% in 12 of the 14 patients. However, respiratory quotient at peak exercise decreased from 1.22±0.15 to 1.09±0.15 (\( P<0.01 \)).

**Conclusions**—Inhaled NO substantially increases oxygen consumption at the same workload during exercise. This finding supports the possibility of ambulatory NO inhalation therapy in patients with precapillary PH. (Circulation. 2000;101:2066-2070.)

**Key Words:** nitric oxide ■ exercise ■ pulmonary heart disease ■ hypertension

The normal pulmonary circulation can accommodate an increase in blood flow during exercise with a minimal rise in pulmonary pressure. It can even allow a 50% decrease in pulmonary vascular resistance during heavy exercise through passive pulmonary vascular dilatation and recruitment. Patients with moderate precapillary resistance during heavy exercise through passive pulmonary vascular dilatation and recruitment.1 Patients with moderate precapillary pulmonary hypertension show a reduction in pulmonary vascular resistance of only 20%, and those with severe pulmonary hypertension with pulmonary vascular resistance of, say, >10 Wood units even show an increase in resistance due to a reduction in the pulmonary arterial bed for vessel recruitment and poor pulmonary vasodilatory capacity during exercise. Vasodilator agents have been used to treat these patients3,4 and may facilitate pulmonary artery dilatation and cause an increase in aerobic capacity during exercise.

Palmer et al5 reported in 1987 that nitric oxide (NO) is an endothelium-derived relaxing factor that dilates the pulmonary artery through the production of cGMP. Since then, NO has been used as a vasodilator agent for newborn infants with persistent pulmonary hypertension6,7 and patients with pulmonary hypertension associated with congenital heart disease8 as well as those with adult respiratory distress syndrome.9 It has been reported that NO inhalation improves exercise capacity in patients with left ventricular dysfunction and postcapillary pulmonary hypertension.10,11 However, there have been no reports concerning patients with precapillary pulmonary hypertension, although Channick et al12 reported that simple nasal delivery of inhaled NO at home improves pulmonary hypertension and the quality of life in patients with primary pulmonary hypertension.

Accordingly, the purpose of this study was to examine whether inhaled NO, a potent pulmonary artery dilator, is able to improve the exercise capacity on a cycle ergometer in patients with precapillary pulmonary hypertension, including primary pulmonary hypertension and residual pulmonary hypertension after surgical correction of an intracardiac shunt.

**Methods**

**Patients**
The study subjects were 14 patients with precapillary pulmonary hypertension (4 men and 10 women; age, 40±12 years, ranging from 25 to 59 years; mean pulmonary artery pressure, 60±23 mm Hg;
pulmonary vascular resistance, 16.1±9.8 Wood units; cardiac output, 4.2±1.9 L/min; mean right atrial pressure, 7.9±4.2 mm Hg; mean pulmonary capillary wedge pressure, 5.1±2.0 mm Hg). There were 10 patients with primary pulmonary hypertension and 4 with residual pulmonary hypertension after correction of an intracardiac shunt (3 atrial septal defect, 1 ventricular septal defect). Primary pulmonary hypertension was defined as pulmonary hypertension unexplained by any secondary cause, based on the National Institute of Health Registry criteria for primary pulmonary hypertension.\(^{13}\) A residual shunt could not be identified by cardiac ultrasonography in patients with pulmonary hypertension after correction of an intracardiac shunt. In these patients, mild to moderate precapillary pulmonary hypertension had been noted before surgery, which slowly worsened after the surgery. Patients who had additional left ventricular dysfunction and resultant postcapillary pulmonary hypertension were excluded. All patients had symptomatic right heart failure (2 patients were in New York Heart Association functional class II and 12 patients in class III) but were in a stable condition during hemodynamic and exercise tests. Hemodynamic parameters were obtained by means of right heart catheterization within 2 weeks after the exercise tests. Pulmonary hypertension was defined as a mean pulmonary artery pressure of >25 mm Hg. Arterial PaO\(_2\) and PaCO\(_2\) were 67±12 and 33±5 mm Hg, respectively. Eleven of the 14 patients studied received ambulatory oxygen therapy. All subjects gave informed consent in writing, and this study was approved by the Ethical Committee of the National Cardiovascular Center (No. 10-1).

**Exercise Protocol**

The patients performed exercise seated on a cycle ergometer. They first pedaled at 55 ppm without any added load for 1 minute. The work rate was then increased by 15 W/min up to their symptom-limited maximum. Breath-by-breath gas analysis was performed with an AE280 gas analyzer (Minato Medical Science) connected to a personal computer running analyzing software. Peak oxygen uptake was determined as the value of averaged data during the final 15 seconds of exercise. The ratio of change in oxygen uptake to change in work rate (ΔVO\(_2\)/ΔW ratio) was calculated as the slope of oxygen consumption per unit workload from 1 minute after the start of load addition until 85% maximal VO\(_2\). The exercise tests were performed on 2 separate days, 3 days apart, with and without inhalation of 20 ppm NO. Patients were randomly and blindly selected to inhale NO on either their first or second test. Patients first selected for NO inhalation were not different from those who received it on the second test. NO inhalation was started 2 minutes before the start of exercise when resting respiratory measurement was commenced. Blood pressure was measured at the brachial artery with a sphygmomanometer. The VE/VE\(_{\text{CO2}}\) slope, a parameter indicating the degree of dead-space ventilation, was determined as the linear regression slope of the VE and VO\(_2\)/VE\(_{\text{CO2}}\) relation from the start of exercise until the RC point (the time up until which ventilation is stimulated by CO\(_2\) output and end-tidal CO\(_2\) tension begins to decrease). The appearance of the VO\(_2\) plateau at maximal exercise was defined as (1) an invariant or <50-mL/min change in VO\(_2\) lasting at least 30 seconds with an increment in workload according to breath-by-breath analysis or (2) a rapid increment in VE despite VO\(_2\) decrement.\(^{14}\)

**NO Inhalation**

Figure 1 shows the NO delivery system. NO (800 ppm) (Kyoto Sanso Medical) was mixed with compressed air in an NO gas blender (NO-10, Taiyo Toyo Sanso Co Ltd) to obtain 20 ppm NO. The compressed air had the same composition as ambient air, and the volume of compressed air was manually altered according to the minute ventilation during exercise. NO concentration was monitored by an NO/NO\(_2\) analyzer (NOA-7000, Shimadzu Co Ltd) and manually brought to a concentration of 20 ppm by fine adjustment of the NO volume being introduced into the NO blender. Because the inspired NO was supplied from a cylinder with a high concentration of 800 ppm NO and constituted only a small fraction of the total inspired gas, inspired oxygen concentration was influenced very little. Inspired NO mixed with compressed air was stored for a short time in a 50-L reservoir bag. The inspired concentration of NO\(_2\) was negligible, being <1 ppm.

**Statistical Analysis**

All data are expressed as mean±SD. Comparison between variables with and without NO inhalation in the resting state and at peak exercise was performed by paired t test. Comparison of the number of patients with a VO\(_2\) plateau between with and without NO inhalation was performed by χ\(^2\) analysis. Linear regression analysis was used to correlate the hemodynamic variables with the percent peak VO\(_2\) change. A value of P<0.05 was considered statistically significant.

**Results**

Heart rate, systolic and diastolic blood pressures, and oxygen consumption before exercise and at peak exercise were not significantly different between NO inhalation and without NO inhalation. None of the variables in Table 1 showed significant differences between NO inhalation and without NO inhalation.

**Comparison of Exercise Parameters Between With NO Inhalation and Without NO Inhalation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>NO 20 ppm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR, bpm</td>
<td>82±14</td>
<td>83±15</td>
<td>NS</td>
</tr>
<tr>
<td>Resting SAP, mm Hg</td>
<td>114±14</td>
<td>117±17</td>
<td>NS</td>
</tr>
<tr>
<td>Resting VO(_2), mL · min(^{-1}) · kg(^{-1})</td>
<td>4.0±0.9</td>
<td>4.2±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>AT, mL · min(^{-1}) · kg(^{-1})</td>
<td>9.1±1.8</td>
<td>9.7±1.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>142±15</td>
<td>143±16</td>
<td>NS</td>
</tr>
<tr>
<td>Peak SAP, mm Hg</td>
<td>147±31</td>
<td>148±29</td>
<td>NS</td>
</tr>
<tr>
<td>Peak load, W</td>
<td>75±21</td>
<td>80±21</td>
<td>NS</td>
</tr>
<tr>
<td>Peak VO(_2), mL · min(^{-1}) · kg(^{-1})</td>
<td>13.6±3.6</td>
<td>16.0±4.1</td>
<td>0.00004</td>
</tr>
<tr>
<td>Peak RQ</td>
<td>1.22±0.15</td>
<td>1.09±0.15</td>
<td>0.0075</td>
</tr>
<tr>
<td>Peak Borg score (D/L)</td>
<td>18/17</td>
<td>18/18</td>
<td>NS</td>
</tr>
<tr>
<td>ΔVO(_2)/ΔW ratio</td>
<td>5.8±2.4</td>
<td>7.1±2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Ve-Ve(_{\text{CO2}}) slope</td>
<td>43.0±12.3</td>
<td>42.6±10.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Control indicates exercise without NO inhalation; NO 20 ppm, exercise with 20 ppm NO inhalation; HR, heart rate; SAP, systolic arterial pressure; RQ, respiratory quotient; Peak Borg score (D/L), Borg score at peak exercise (dyspnea/leg fatigue); ΔVO\(_2\)/ΔW ratio, VO\(_2\) increase per unit workload; and Ve-Ve\(_{\text{CO2}}\) slope, slope of regression line of relation between Ve and Ve\(_{\text{CO2}}\). All data are shown as mean±SD.
different between with NO inhalation and without NO inhalation (Table). Peak exercise load and anaerobic threshold (AT) did not change significantly with NO inhalation but tended to increase (peak exercise load, 75±21 increasing to 80±21 W; AT, 9.1±1.8 to 9.7±1.9 mL · kg⁻¹ · min⁻¹; P=NS). Nine of the 14 patients showed an increase in AT. Peak oxygen consumption and ΔVO₂/ΔW ratio, where W is work rate, increased significantly (18% and 22%, respectively, P<0.01 for both variables) after NO inhalation, although the respiratory quotient (index of exercise effort) decreased from 1.22±0.15 to 1.09±0.15 (P<0.01), which indicates increased oxygen consumption with less effort. Twelve of the 14 patients demonstrated an increase in peak VO₂ of ≥10% (Figure 2). A VO₂ plateau at peak exercise, indicating that exercise had been terminated by certain circulatory limitation, appeared in 11 patients, but this number was reduced to 5 by NO inhalation. The significant decrease (P=0.03) in the number of patients with circulatory limitation after NO inhalation during exercise implies that NO may improve pulmonary flow. These observations suggest that the hemodynamic improvements may have brought about a significant increase in peak oxygen consumption. The slope of Ve-VCO₂, an indicator of dead-space ventilation, was not significantly different between with NO inhalation and without NO inhalation (43.0±12.3 and 42.6±10.4, respectively).

Mean pulmonary arterial pressure, pulmonary vascular resistance, cardiac output, and mean right atrial pressure did not correlate with the percent increase in peak VO₂ with NO inhalation (Figure 3).

**Discussion**

The present study showed that NO inhalation significantly increased oxygen consumption at the same workload during exercise in patients with precapillary pulmonary hypertension. The improvement due to NO inhalation may be ascribed to pulmonary arterial dilatation with increased cardiac output, judging from the concomitant increase in ΔVO₂/ΔW ratio and the decrease in cases with a VO₂ plateau at peak exercise. The improvement in oxygen consumption at the same workload during exercise with NO inhalation did not correlate with the magnitude of hemodynamic abnormalities.

**Effects of NO Inhalation During Exercise**

Because of impaired pulmonary dilatation during exercise, pulmonary vascular resistance does not decrease in patients with precapillary pulmonary hypertension, whereas it decreases in normal subjects. NO inhalation is a unique form of treatment that uses selective pulmonary arterial dilatation, because it dilates the pulmonary arteries corresponding to the ventilated alveoli without affecting systemic arteries. Riley et al reported that during exercise, intrinsic NO production, as measured from the exhaled NO, failed to increase in patients with primary pulmonary hypertension. Likewise, it failed to increase in those with pulmonary fibrosis, whereas it increased in normal subjects. This lack of increase results in pulmonary endothelial dysfunction and impaired recruitment of the pulmonary vasculature during exercise. Thus, treatment with NO, as a selective pulmonary vasoreactive agent, can improve pulmonary arterial dilatation and thus increases cardiac output to bring about a resultant increment in peak oxygen consumption.

Matsumoto et al reported that NO inhalation improved the exercise capacity in 8 patients with left ventricular dysfunction and postcapillary pulmonary hypertension by alleviating both pulmonary hypertension and ventilation-perfusion mismatch. According to Koelling et al, after inhalation of 40 ppm NO, peak VO₂ increased in 8 of 14 patients with severe left ventricular failure and right ventricular dysfunction, with a mean increase of 3.4%. Our first report of an acute improvement in exercise capacity with NO inhalation in patients with precapillary pulmonary hypertension demonstrated that 86% of the patients showed an increase in oxygen consumption of >10% at the same workload during exercise for less effort, as represented by a lower peak respiratory quotient. From these results, we postulate that patients with precapillary pulmonary hypertension can benefit from NO inhalation during exercise.

In the present study, NO inhalation increased peak VO₂ and ΔVO₂/ΔW ratio significantly. The ΔVO₂/ΔW ratio indicates oxygen transport per unit workload to the exercising legs and is an index of circulatory capability. In this patient population, an acute change in ΔVO₂/ΔW ratio was considered to reflect change in cardiac output rather than other circulatory changes through pulmonary arterial dilatation with NO inhalation. A VO₂ plateau at peak exercise, indicating that exercise had been terminated by certain circulatory limitations, appeared in 11 patients, but this number decreased to 5 as a result of NO inhalation. In patients with precapillary pulmonary hypertension, failure of cardiac output to increase...
because of impaired pulmonary vasodilation is the most likely circulatory limitation. The significant decrease in the number of patients with circulatory limitation after NO inhalation during exercise suggests that NO may improve pulmonary flow. These results suggest that with NO inhalation, the increase in cardiac output may contribute to an increase in peak VO₂. The possible cardiac output increase can be explained by dilatation of pulmonary arteries. In addition, pulmonary hypertension and the resultant right ventricular pressure overload cause left ventricular diastolic dysfunction.\textsuperscript{19,20} NO dilates the pulmonary arteries, reduces right ventricular afterload, and improves left ventricular diastolic function, resulting in an increase in peak oxygen consumption during exercise.

Peak exercise load, AT, and the symptomatic load at peak exercise did not improve. Peak exercise load might have been increased intentionally by the examiner because he could not be blinded to whether NO was inhaled or not, because the examiner needed to perform meticulous adjustment of NO concentration and attend to the NO oxidant product. The fact that the respiratory quotient was decreased at peak exercise with NO inhalation means that the patients made less effort. They could have increased their workload if they had made more effort at the same level of respiratory quotient. This was confirmed by the finding that without NO inhalation, 11 of 14 patients finished their exercise in association with a VO₂ plateau, indicating circulatory limitation, and with NO inhalation, only 5 patients demonstrated this phenomenon, but the remaining 6 patients did not show a VO₂ plateau, and their exercise was limited by leg fatigue at the same workload. AT showed a tendency to improve (P=0.06), but the increase was not significant, partly because AT is influenced by muscle energetics,\textsuperscript{21} which are not improved immediately. The symptoms at peak exercise also did not improve, partly because the symptoms were determined after each exercise test with and without NO inhalation and were not compared with each other, and partly because the symptoms of leg fatigue and dyspnea are generally difficult for patients to differentiate.\textsuperscript{22}

The degree of increase in exercise capacity did not correlate with the resting hemodynamics, which suggests that NO reactivity might be related to some factors other than pulmonary artery rigidity, such as sensitivity to cGMP activity.\textsuperscript{23} Koelling et al\textsuperscript{11} argued that patients with elevated pulmonary pressure whose mean pulmonary pressure is <60 mm Hg and moderately high benefit with respect to exercise capacity from NO inhalation. In our study, peak VO₂ increased until it reached a mean pulmonary arterial pressure of 60 mm Hg and then declined.

Side Effects of NO

Because NO is a potentially poisonous gas, side effects had to be carefully monitored. NO was mixed with air and stored in a reservoir bag for a few seconds, which would have produced the highly harmful oxidation product NO₂. NO₂ was therefore measured before inhalation, but the level was found to be acceptable at a negligible concentration. The concentration of methemoglobin, another noxious product resulting from NO entering the blood, was <1%.

Clinical Implications

The short-term beneficial effects of inhaled NO on oxygen consumption support the possibility of long-term, home-based, ambulatory NO inhalation therapy. Kouyoumdjian et al\textsuperscript{19} reported that continuous inhalation of NO induced sustained pulmonary vasodilatation and pulmonary vascular remodeling in chronically hypoxic rats, which suggests that continuous inhalation may prevent the progression of thickening of the pulmonary vasculature in patients with pulmonary hypertension. If long-term NO inhalation has few side effects and is economically affordable, this therapy will be introduced more often and may improve the quality of life and even the prognosis in patients with precapillary pulmonary hypertension.

References

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