Iloprost Improves Gas Exchange and Exercise Tolerance in Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease

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Key Words
Iloprost · Pulmonary hypertension · Chronic obstructive pulmonary disease · Ventilation perfusion mismatch · Six-minutes walk test

Abstract
Background: Nonselective systemic vasodilators worsen ventilation perfusion (V/Q) matching and gas exchange in patients with chronic obstructive pulmonary disease (COPD). Inhaled iloprost has the potential to act preferentially in ventilated regions of the lung, thereby reducing pulmonary hypertension (PH) while alveolar ventilation is still maintained.

Objectives: To investigate the acute effects of inhaled iloprost on V/Q matching in patients with COPD and PH.

Methods: Ten males with COPD and PH on echocardiography were evaluated before and after inhaling 2 doses of iloprost (2.5 μg). Measurements included lung function, arterial blood gas, 6-min walk test (6MWT) as well as ventilatory equivalents for oxygen (Ve/VO2) and carbon dioxide (Ve/VCO2) taken at baseline, 30 min following each dose of iloprost, and 2 h after the second dose.

Results: Mean differences in Ve/VCO2 and Ve/VO2 were −13.3 (95% CI −36.5 to −2.7; p = 0.002) and −15.0 (95% CI −36.7 to −0.4; p = 0.02), respectively, and the mean change in (A-a) gradient was −3.7 mm Hg (95% CI −6.1 to −1.0; p = 0.01) after a single dose of iloprost, whereas mean improvement in 6MWT was 49.8 m (95% CI 14.8 to 84.7; p = 0.02). Arterial blood gas, venous admixture, dead space fraction and lung functions were maintained after iloprost. The effects of iloprost were reproducible after the second dose. All measurements returned to baseline 2 h after the last dose. No adverse effects on systemic blood pressure or oxygen saturation were seen.

Conclusions: Iloprost inhalation was safe in patients with COPD and PH, and was associated with improved V/Q matching and exercise tolerance.

Chronic obstructive pulmonary disease (COPD) is the fourth most common cause of mortality in the United States [1]. As obstructive airway disease becomes more severe, hypoxemia develops which in turn can lead to pulmonary hypertension (PH) and secondary right heart failure [2–5]. The development of PH and right heart failure is associated with a significant reduction in survival [6–8].

Oxygen therapy has been shown to reduce pulmonary arterial pressures, attenuate symptoms and improve survival in hypoxic patients with COPD [9, 10]. Vasodilator therapy has become a mainstay of therapy for patients with left ventricular failure as it has been shown to im-
prove both functional capacity and survival in patients with left ventricular failure. Conversely, vasodilator therapy in patients with PH associated with chronic lung disease resulted in worsening gas exchange and intensification of symptoms despite a decrease in pulmonary vascular resistance and arterial pressures [11–13].

Iloprost, an inhaled prostanoid approved for the treatment of patients with pulmonary arterial hypertension, is a potent acute pulmonary vasodilator with duration of action of about 60 min, but also exerts additional long-term benefit through antiproliferative and antithrombotic effects [14]. As an inhaled agent, iloprost has the potential to act preferentially in well ventilated regions of the lung which would receive the highest dose of iloprost, and thereby maintain or even improve ventilation perfusion matching while reducing pulmonary arterial hypertension. Nevertheless, the effects of iloprost on gas exchange and ventilation perfusion matching have not yet been investigated in patients with COPD. In this study we examined the hypothesis that aerosolized iloprost improves ventilation perfusion matching in patients with COPD as reflected by an improvement in gas exchange indices measured by expired and blood gas analysis that occurs while preserving lung function.

Methods

This study was conducted at the Veterans Affair Medical Center in Oklahoma City. Inclusion criteria were a prebronchodilator FEV1 <65% of predicted and FEV1 to FVC ratio <70%, baseline room air oxygen tension between 60 and 75 mm Hg, PH documented by echocardiography demonstrating an estimated right ventricular systolic pressure (RVSP) greater than 35 mm Hg plus findings of right ventricle (RV) morphologic changes, and the ability to provide informed consent. The presence of RV dilatation and/or hypertrophy on echocardiography was a necessary inclusion criteria for study subjects given the known limitations associated with echocardiography in the diagnosis of PH [15]. Exclusion criteria included clinical instability as evidenced by an acute exacerbation requiring an intensification of therapy and/or the need for hospitalization within the preceding 3 months, presence of an additional cause of lung disease as suggested by history, clinical, radiographic findings or pulmonary function tests, presence of left ventricular dysfunction and/or left atrial enlargement by echocardiography or catheterization, and hepatic allergy. The study protocol was approved by the local Institutional Review Board, and all patients gave written informed consent.

Study Design

This was a single-day study in which each patient’s baseline measurements obtained prior to iloprost administration were compared to measurements obtained 30 min and 2 h after iloprost inhalation. Patients reported to Veterans Affair Medical Center research laboratory and were asked to abstain from inhaled bronchodilator use for at least 2 h prior to arriving in the laboratory.

After informed consent was obtained and an Allen’s test was performed, a 22-gauge polyethylene catheter for obtaining arterial blood gases was introduced into the radial artery using sterile technique. Patency of the catheter was maintained by infusing 2 ml/h of heparinized normal saline (1 U/ml) via a standard infusion system. Blood gas tensions were corrected for patient’s body temperature. Patients performed spirometry, diffusing capacity for carbon monoxide (D L CO) and alveolar volume measured by helium dilution according to standard techniques [16–17]. Patients then inspired on room air through a 2-way breathing valve and their oxygen consumption (VO2), carbon dioxide production (VCO2), minute ventilation (V E ) and mixed expired carbon dioxide were measured with a metabolic cart (Vmax 229; Sensormedics, Yorba Linda, Calif., USA). Gas exchange was monitored over a minimum of 5 min and, once a steady state was reached as evidenced by values that changed by less than 5%, data from the last 3 min was averaged to establish baseline resting VO2, VCO2 and V E . Finally, patients were asked to perform a 6-min walk test (6MWT) according to the American Thoracic Society guidelines [18].

The ventilatory equivalents for oxygen (V E /VO2) and carbon dioxide (V E /VCO2) were calculated as the V E divided by VO2 and VCO2, respectively. The respiratory quotient (R) was calculated as the VCO2 divided by VO2. The alveolar to arterial oxygen gradient (D a- a O2) was calculated by standard formula using the value of R obtained from the metabolic measurements. Venous admixture (Ql/QO2) was estimated noninvasively using an assumed arterial-venous O2 difference of 4.5 ml/100 ml [19]. Dead space fraction (V D/V T ) was derived form the Enghoff modification of the Bohr equation using mixed expired and arterial CO2 tensions [20] with adjustments made for the breathing valve dead space.

Results

After baseline measurements were obtained, enrolled patients inhaled 2.5 µg iloprost via an approved nebulizer. Vital signs including blood pressure and heart rate, respiratory rate and arterial saturation by pulse oximetry were monitored at baseline and every 5 min after the inhalation of iloprost. Thirty minutes after the administration of iloprost the gas exchange, pulmonary function, arterial blood gas measurements and 6MWT were repeated as described above. Patients who remained clinically stable as evidenced by a fall in arterial oxygen tension (PO2) <5 mm Hg, fall in systemic blood pressure of <10% and increase in heart rate of <10 beats/min as well as the absence of symptoms 30 min after the inhalation of 2.5 µg of iloprost received a second dose of 2.5 µg to reach the FDA-approved maximal dose of 5.0 µg. Vital signs continued to be monitored every 5 and 30 min after the second dose of iloprost, and all pulmonary measurements were repeated. All patients were again monitored with vital signs every 15 min for at least 2 h and pulmonary testing were repeated for a final time 2 h after the last administration of iloprost.

Data Analysis

The primary outcome variables were the change in D A-a O2, V E /VCO2 and V E /VO2 as measures of gas exchange. Secondary outcome measures included PO2, Ql/QO2, V D/V T , pulmonary function, D L CO and change in 6MWT. All comparisons were performed using Student’s paired t test with Bonferroni correction for multiple comparisons, whereas nonparametric tests (Wilcoxon rank-sum test) were applied when necessary for data that do
not follow Gaussian distribution. The sample size of 10 was chosen on the basis of our initial power analysis to provide an α of 0.05 with a power of 0.9 to detect a 15% reduction in $D_{A-a}O_2$, $V_E/VCO_2$ and $V_E/VO_2$. Mean, median and standard deviation (SD) were calculated as well as 95% confidence intervals (CI). A p value less than 0.05 was considered statistically significant.

**Results**

Ten males with moderate to severe COPD were enrolled. All subjects completed the study procedure. Demographic characteristics, arterial blood gases and lung function at baseline are shown in table 1. The mean RVSP was 40.8 ± 3.2 mm Hg (36–45 mm Hg) and RV morphologic changes including either RV hypertrophy or dilation were present in all subjects on echocardiography. The mean left ventricular ejection fraction was 59.0 ± 3.9%.

After iloprost administration, $V_E$ decreased by a mean of 2.7 liters (95% CI −5.4 to −0.07; p = 0.04). The mean differences in $V_E$/$VCO_2$ and $V_E$/$VO_2$ were −13.3 (95% CI −36.5 to −2.7; p = 0.002) and −15.0 (95% CI −36.7 to −0.4; p = 0.02) respectively (fig. 1) and the mean change in $D_{A-a}O_2$ was −3.7 mm Hg (95% CI −6.1 to −1.0; p = 0.01) after a single dose of iloprost (table 2). Arterial $PO_2$ (67.0 ± 5.8 vs. 68.5 ± 6.9 mm Hg), $PCO_2$ (38.4 ± 4.3 vs. 38.1 ± 5.0 mm Hg), $V_D/V_T$ (0.42 ± 0.03 vs. 0.38 ± 0.02), $D_L$CO/alveolar volume (3.0 ± 1.1 vs. 3.1 ± 1.2 ml/mm

<table>
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<th>Table 1. Baseline patients' characteristics (n = 10)</th>
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<td><strong>BMI</strong></td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>Anticholinergic &amp; 10 (100%)</td>
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<td>B2 Agonist &amp; 10 (100%)</td>
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<td>ICS &amp; 6 (60%)</td>
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<td>Theophylline &amp; 1 (10%)</td>
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<td><strong>NYHA</strong></td>
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<td>II &amp; 5 (50%)</td>
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<td>III &amp; 4 (40%)</td>
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<td>IV &amp; 1 (10%)</td>
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<td><strong>PO2 (torr.)</strong></td>
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<td><strong>PCO2 (torr.)</strong></td>
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<td><strong>RVSP, mm Hg</strong></td>
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BMI = Body mass index; ICS = inhaled corticosteroid; NYHA = New York Heart Association class; $PCO_2$ = arterial tension of carbon dioxide.
Hg/min/l), Qs/Qt (15.7 ± 2.8 vs. 14.4 ± 3.3%) and lung function were all unchanged after iloprost. The effects of iloprost on 6MWT are shown in figure 1. Mean improvement was 49.8 m (95% CI 14.8 to 84.7; p = 0.02) after the initial dose and was maintained but not further increased after the second dose. The effects of iloprost on gas exchange, Qs/Qt and lung function were unchanged after the second dose, whereas these measurements returned nearly to baseline 2 h later (table 3). There were no significant effects on mean arterial pressure, heart rate or oxygen saturation (SaO2) (fig. 2), and none of the patients developed an increase in their sense of dyspnea.

### Discussion

PH commonly complicates chronic obstructive airway disease and is usually associated with a dire clinical outcome. Bishop et al. reported more than 3 decades ago that elevated mean pulmonary artery pressure on right
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