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 (V_E/V_{O_2}) and carbon dioxide (V_E/V_{CO_2}) taken at baseline, 30 min following each dose of iloprost, and 2 h after the second dose. **Results:** Mean differences in V_E/V_{CO_2} and V_E/V_{O_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, 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 ilo-

prost, 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.

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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 Affairs Medical Center in Oklahoma City. Inclusion criteria were a prebronchodilator FEV₁ <65% of predicted and FEV₁ to FVC ratio <70%, baseline room air arterial 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 dilation 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 heparin 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 Affairs 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_lCO) 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 (Q_s/Q_t) 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 from the Enghoff modification of the Bohr equation using mixed expired and arterial CO₂ tensions [20] with adjustments made for the breathing valve dead space.

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, Q_s/Q_t, V_D/V_T, pulmonary function, D_lCO 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

Fig. 1. Effects of iloprost on 6MWT distance in 10 individual patients with COPD.

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 $59.0 \pm 3.9\%$.

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_LCO /alveolar volume (3.0 ± 1.1 vs. 3.1 ± 1.2 ml/mm

Table 1. Baseline patients' characteristics (n = 10)

Age	72.2 $\pm$ 7.3
BMI	26.5 $\pm$ 6.6
Medications	
Anticholinergic	10 (100%)
B ₂ Agonist	10 (100%)
ICS	6 (60%)
Theophylline	1 (10%)
NYHA	
I	0 (0%)
II	5 (50%)
III	4 (40%)
IV	1 (10%)
PO ₂ (torr.)	67.0 $\pm$ 5.8
PCO ₂ (torr.)	38.4 $\pm$ 4.5
D _{A-a} O ₂ (torr.)	30.7 $\pm$ 7.7
FEV ₁ , l	1.49 $\pm$ 0.44
FEV ₁ , %	47.4 $\pm$ 8.2
FVC, l	2.74 $\pm$ 0.65
FVC, %	64.2 $\pm$ 10.0
FEV ₁ /FVC, %	52.0 $\pm$ 7.0
RVSP, mm Hg	40.6 $\pm$ 3.2

BMI = Body mass index; ICS = inhaled corticosteroid; NYHA = New York Heart Association class; PCO_2 = arterial tension of carbon dioxide.

Table 2. Effects of iloprost on gas exchange

	Baseline	1st dose	2nd dose	2 h	p
VE, l	15.4 ± 3.0	12.7 ± 2.5	12.5 ± 2.8	14.4 ± 2.8	0.04
VO ₂ , l	0.204 ± 0.05	0.214 ± 0.05	0.207 ± 0.06	0.205 ± 0.04	0.99
VCO ₂ , l	0.201 ± 0.06	0.204 ± 0.05	0.202 ± 0.06	0.198 ± 0.05	0.99
VE/VO ₂	75.4 ± 21.0	59.1 ± 13.1 ¹	57.7 ± 13.7 ¹	70.0 ± 22.0	0.03
VE/VCO ₂	77.0 ± 20.9	63.0 ± 14.1 ¹	61.7 ± 12.0 ¹	72.7 ± 20.2	0.04
VD/VT	0.42 ± 0.03	0.38 ± 0.02 ¹	0.39 ± 0.04 ¹	0.41 ± 0.04	0.06
PO ₂ (torr.)	67.0 ± 5.8	68.5 ± 4.9	67.8 ± 5.5	68.9 ± 7.3	0.90
PCO ₂ (torr.)	38.4 ± 4.3	38.1 ± 5.0	38.2 ± 5.1	38.5 ± 5.2	1.00
D _{A-a} O ₂ (torr.)	30.7 ± 7.7	27.0 ± 6.8 ¹	26.9 ± 7.0 ¹	30.4 ± 8.5	0.01

R = Respiratory quotient. ¹ Comparison to baseline.

Table 3. Effects of iloprost on Q_s/Q_t, lung function and 6MWT

	Baseline	1st dose	2nd dose	2 h	p
Q _s /Q _t , %	15.7 ± 2.8	14.4 ± 3.3 ¹	14.6 ± 3.0 ¹	15.3 ± 3.5	0.06
FEV ₁ , l	1.49 ± 0.49	1.45 ± 0.47	1.40 ± 0.51	1.45 ± 0.50	1.00
FVC, l	2.74 ± 0.65	2.71 ± 0.61	2.67 ± 0.65	2.68 ± 0.63	1.00
D _L CO, ml/min/mm Hg	15.2 ± 8.5	15.0 ± 7.5	15.1 ± 7.6	15.9 ± 9.9	0.90
V _A , l	5.33 ± 0.85	5.17 ± 0.93	5.10 ± 0.92	5.33 ± 1.01	0.90
6MWT, m	269 ± 112	324 ± 135 ¹	330 ± 136 ¹	275 ± 117	0.02

V_A = Alveolar volume from helium dilution on D_LCO test.

¹ Comparison to baseline.

Fig. 2. Effects of iloprost on arterial oxygen saturation (SaO₂), mean arterial pressure (MAP) and heart rate (HR). SaO₂, MAP and HR measurements were averaged for all patients. T₁ and T₂ indicate time of administration of first and second dose of iloprost respectively, whereas T_{2h} represents vital signs 2 h after the last inhaled dose.

Hg/min/l), Q_s/Q_t (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, Q_s/Q_t 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

heart catheterization had a significant impact on survival in COPD [21]. RVSP higher than 35 mm Hg was also found to be an important prognostic indicator in patients receiving long term home oxygen therapy [22]. Given the importance of PH as a predictor of death in COPD, the treatment of PH in patients with lung disease has been an active area of interest and research over the last 3 decades. Several forms of vasodilator treatment were investigated but unfortunately, the results were disappointing. The positive effects of oral and intravenous vasodilators used in patients with PH on pulmonary hemodynamics in patients with diffuse parenchymal lung disease was offset by an increase in pulmonary shunt flow and thus gas exchange worsening in some of these studies [23, 24]. Because of these findings, the data currently do not support the routine use of vasodilators in patients with pulmonary arterial hypertension secondary to lung disease.

In this observational study, we evaluated and compared the acute effects of iloprost aerosol in patients with COPD. Iloprost was associated with improved gas exchange indices and exercise tolerance while preserving arterial gas tensions and lung function. Ventilatory equivalents for oxygen and carbon dioxide were used as surrogates of ventilatory efficiency. When lungs are very efficient at gas exchange, a subject will not need a very high V_E for each millimole of O_2 consumed or CO_2 produced. The decline in ventilatory equivalents for oxygen and carbon dioxide was mainly due to reduction in V_E (table 2). These findings along with narrowing of the $D_{A-a}O_2$ indicated a better ventilatory efficiency and improved V/Q matching in lung units after iloprost inhalation. A trend towards a reduction in shunt and V_D/V_T was also observed, while alveolar volume remained relatively unchanged. These findings suggest to some extent that targeted delivery of iloprost to ventilated areas was associated with favorable redistribution of blood flow in the lung and avoided unwanted adverse effects on pulmonary circulation reported previously with systemic vasodilators, while maintaining or even improving gas V/Q matching. The inhaled route of iloprost administration also avoided systemic effects of vasodilators and was without adverse hemodynamic consequences in our patients.

Clinically, the physiological improvement in gas exchange was accompanied by improved exercise tolerance as reflected by an increase in the distance walked on the 6MWT. This may be particularly important as both PH and a reduced ventilatory reserve contribute to the diminished functional status in COPD patients. The 19% improvement in 6MWT distance after iloprost represents a significant improvement in exercise performance and

cannot be explained by an initial learning effect with repeated 6MWT [25–27].

Multiple mechanisms can result in PH in patients with COPD. Hypoxic vasoconstriction is not the only mechanism involved. Impaired vasodilatation, remodeling of the pulmonary vasculature and other manifestations of endothelial dysfunction were shown to be present in emphysematous lung [28, 29]. Furthermore, prostacyclin (PGI_2) expression was proved to be altered in smoking-related lung disease [30]. Thus, treatment with inhaled PGI_2 may exert protective effects in the pulmonary vasculature of COPD patients ultimately leading to reduced pulmonary arterial pressures and improved outcome in these patients. Clinical studies to further test these assumptions are certainly needed.

The present study has certain limitations that need to be noted. We did not include a placebo group; however, it seems very unlikely that the results reported were unduly biased by placebo effect. We also recognize that accuracy and reliability of noninvasive estimation of Q_s/Q_t were typically reported previously in healthy and critically ill patients [31], nevertheless, a range between 4.0 and 5.0 ml/100 ml should be a reasonable assumed value for arterial-venous O_2 difference for most clinical purposes including COPD.

In conclusion, our findings suggest that iloprost has favorable acute effects on gas exchange and exercise tolerance in COPD patients. It can be used safely and may represent an important advance in the treatment of PH in these patients pending further randomized placebo controlled trials. These could include patients with more significant hypoxemia or subjects referred to a pulmonary rehabilitation program.

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