Effects of Inhaled Iloprost on Lung Mechanics and Myocardial Function During One-Lung Ventilation in Chronic Obstructive Pulmonary Disease Patients Combined With Poor Lung Oxygenation

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BACKGROUND: The ventilation/perfusion mismatch in chronic obstructive pulmonary disease (COPD) patients can exacerbate cardiac function as well as pulmonary oxygenation. We hypothesized that inhaled iloprost can ameliorate pulmonary oxygenation with lung mechanics and myocardial function during one-lung ventilation (OLV) in COPD patients combined with poor lung oxygenation.
METHODS: A total of 40 patients with moderate to severe COPD, who exhibited the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2/Fio_2) <150 mm Hg 30 minutes after initiating OLV, were enrolled in this study. Patients were randomly allocated into either ILO group (n = 20) or Control group (n = 20), in which iloprost (20 μg) and saline were inhaled, respectively. The Pao_2/Fio_2 ratio, dead space, dynamic compliance, and tissue Doppler imaging with myocardial performance index (MPI) were assessed 30 minutes after initiating OLV (pre-Tx) and 30 minutes after completion of drug inhalation (post-Tx). Repeated variables were analyzed using a linear mixed-model between the groups.
RESULTS: At pre-Tx, no differences were observed in measured parameters between the groups. At post-Tx, Pao_2/Fio_2 ratio (P < .001) and dynamic compliance (P = .023) were significantly higher and dead space ventilation was significantly lower (P = .001) in iloprost group (ILO group) compared to Control group. Left (P = .003) and right ventricular MPIs (P < .001) significantly decreased in ILO group compared to Control group.
CONCLUSIONS: Inhaled iloprost improved pulmonary oxygenation, lung mechanics, and cardiac function simultaneously during OLV in COPD patients with poor lung oxygenation. (Anesth Analg 2020;130:1407–14)

KEY POINTS

- **Question:** What is the impact of iloprost inhalation on lung mechanics and myocardial function during one-lung ventilation (OLV) in chronic obstructive pulmonary disease (COPD) patients combined with poor lung oxygenation?
- **Findings:** Partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2/Fio_2) ratio, lung mechanics, and biventricular function were improved by 20 μg of iloprost inhalation in patients who exhibited Pao_2/Fio_2 ratio <150 mm Hg during OLV.
- **Meaning:** We demonstrated that inhaled iloprost had a positive cardiopulmonary effect during OLV in patients with COPD combined with poor lung oxygenation.

GLOSSARY

ARDS = acute respiratory distress syndrome; **cAMP** = cyclic adenosine monophosphate; **CI** = confidence interval; **CO_2** = carbon dioxide; **CONSORT** = Consolidated Standards of Reporting Trials; **COPD** = chronic obstructive pulmonary disease; **CPAP** = continuous positive airway pressure; **CVP** = central venous pressure; **$Etco_2$** = end-tidal carbon dioxide; **FEV_1** = forced expiratory volume in 1 second; **Fio_2** = fraction of inspired oxygen; **FVC** = functional vital capacity; **GOLD criteria** = Global initiative for Chronic Obstructive Lung Disease criteria; **HPV** = hypoxic pulmonary vasoconstriction; **HR** = heart rate; **ILO group** = iloprost group; **LV** = left ventricular; **LV E** = peak early diastolic transmitral inflow velocity; **LV e′** = peak early diastolic mitral annulus velocity; **LV s′** = peak early systolic mitral annulus velocity; **MAP** = mean arterial pressure; **MPI** = myocardial performance index; **NO** = nitric oxide; **OLV** = one-lung ventilation; **$Paco_2$** = partial pressure of carbon dioxide; **PACU** = postanesthesia care unit; **PAH** = pulmonary arterial hypertension; **Pao_2** = arterial oxygen partial pressure; **PEEP** = positive end-expiratory pressure; **PGI_2** = prostaglandin I_2; **PIP** = peak inspiratory pressure; **post-Tx** = 30 minutes after completion of iloprost or saline inhalation; **pre-Tx** = 30 minutes after initiation of one-lung ventilation; **RV** = right ventricular; **RV E** = peak early diastolic transtricuspid inflow velocity; **RV e′** = peak early diastolic tricuspid annulus velocity; **RV s′** = peak early systolic tricuspid annulus velocity; **Spo_2** = oxygen saturation; **TDI** = tissue Doppler imaging; **V/Q** = ventilation/perfusion

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Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation.[1] These patients present with hypoxemia due to an increase of unequal ventilation/perfusion (V/Q) area and hypercapnia caused by inefficient carbon dioxide (CO_2) elimination.[2] The V/Q mismatch can be aggravated further during one-lung ventilation (OLV), although the intrinsic positive end-expiratory pressure (PEEP) caused by hyperinflation of ventilated lungs increases the functional residual capacity.[3] Furthermore, the protective mechanisms of hypoxic pulmonary vasoconstriction (HPV) during OLV are less effective and attenuated in COPD,[4] and the increase in stiffness and altered compliance of the pulmonary artery[5] limit the increase in perfusion by gravity. Recently, arterial oxygen partial pressure (Pao_2) was elucidated to have a significant correlation with mean pulmonary artery pressure,[6] and treatment of COPD exacerbation improved right ventricular function[7] in patients with COPD.

Iloprost, a stable carbacyclin derivative of prostacyclin (prostaglandin I_2 [PGI_2]), acts as a selective pulmonary vasodilator in patients with pulmonary arterial hypertension (PAH) to improve V/Q matching,[8] decrease pulmonary vascular resistance,[9] and improve or maintain right ventricular (RV) function.[10] We hypothesized that the use of iloprost in COPD patients with poor lung oxygenation could ameliorate Pao_2 level by improving V/Q matching and also improve cardiac function; however, no existing study has yet evaluated the effect of iloprost on oxygenation and relevant cardiac function during OLV.

The purpose of this study was to evaluate the effects of iloprost on gas exchange, lung mechanics, and cardiac function during OLV in COPD patients combined with poor lung oxygenation.

METHODS

Study Population

This prospective, randomized, controlled study was approved by the institutional review board of Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea (No. 4-2015-0283) in June 2015, and it was registered before patient enrollment at Clinicaltrials.gov (NCT 02490657, Principal investigator: Young Jun Oh, Date of registration: July 7, 2015). In addition, this article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. All participants provided written informed consent before participation. Inclusion criteria were as follows: (1) diagnosis of COPD according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[11] with the forced expiratory volume in 1 second (FEV_1) <80% predicted with a postbronchodilator FEV_1/functional vital capacity <0.7 according to the preoperative pulmonary function test results; (2) age between 40 and 80 years; (3) American Society of Anesthesiologist physical status class III or IV; (4) preoperative oxygen saturation (Spo_2) level ≤97% on room air (spontaneous ventilation); (5) ratio of Pao_2 to the fraction of inspired oxygen (Pao_2/Fio_2) <150 mm Hg 30 minutes after initiating OLV; and (6) video-assisted thoracoscopic surgery planned for single-lobe lobectomy. Exclusion criteria were heart failure (New York Heart Association class >II), previous arrhythmia, severe functional liver or kidney disease, decreased lung diffusion capacity for carbon monoxide <75% predicted, and Pao_2/Fio_2 ratio ≥150 mm Hg 30 minutes after initiating OLV.

Anesthetic Management

Anesthesia was induced using propofol, remifentanil, and rocuronium. Tracheal intubation was performed using a double-lumen tube (Broncho-cath; Mallinckrodt, Mulhuddart, Dublin, Ireland), which was positioned using a fiberoptic bronchoscope before OLV was provided. A radial artery was cannulated, and a 7F central venous catheter (Arrow; Teleflex Incorporated, Wayne, PA) was placed in the right internal jugular vein. Mechanical ventilation was provided using the autoflow pressure-controlled ventilation mode (Primus i ventilator; Dräger TM Medical, Lübeck, Germany). Anesthesia was maintained with 1.0–2.0 vol% sevoflurane and 0.05–0.1 μg/kg/min remifentanil targeted at bispectral index (BIS VISTA; Aspect Medical Systems, Norwood, MA) between 40 and 60. Intraoperatively, balanced crystalloids were administered at a rate of 3 mL/kg/h, and additional crystalloids were given to compensate for blood losses. Vasoactive drugs, such as ephedrine, were administered if the mean arterial pressure decreased and persisted by >20% from baseline arterial pressure.

During OLV, the tidal volume was set at 6 mL/kg, and PEEP was applied at 2 cm H_2O. The inspiratory–expiratory ratio was set to 1:2.5. The Fio_2 level was initially at 0.6, and in cases of desaturation (Spo_2 <90%),

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the F_{IO_2} level was increased by 0.2 up to 1.0. Surgeons insufflated neither CO_2 nor any other gas during the surgery, and the trial was completed before vascular clamping of the nondependent lung.

Study Design and Outcome Measurements

All enrolled patients were allocated to the study groups using a randomized sequence, and the surgeon and anesthesiologist were blinded to the patients' group allocation. In the inhaled iloprost group (ILO group), iloprost (20 μg [2 mL], Ventavis; Bayer AG, Leverkusen, Germany) was mixed with normal saline (3 mL) and aerosolized to the lung using an ultrasonic nebulizer (Pari Boy Sx; PARI GmbH, Starnberg, Germany), which was connected to the inspiratory limb of the ventilator system. A comparable volume (5 mL) of normal saline was aerosolized to the lung in Control group.

Thirty minutes after initiating OLV, respiratory, hemodynamic, and echocardiographic parameters were recorded for baseline value if the Pao_2/F_{IO_2} ratio was <150 mm Hg (30 minutes after initiation of one-lung ventilation [pre-Tx]). Then, interventional medications were administered over a period of 30 minutes, and 30 minutes after the drugs had been administered, the same aforementioned parameters were recorded (30 minutes after completion of iloprost or saline inhalation [post-Tx]). In addition, the Pao_2/F_{IO_2} ratio 20 minutes after arrival in postanesthesia care unit (PACU) was assessed.

The measured respiratory parameters were Pao_2/F_{IO_2} ratio, dead space ventilation, tidal volume, peak inspiratory pressure (PIP), and dynamic compliance. Pao_2 and partial pressure of carbon dioxide ($Paco_2$) levels were assessed using an arterial blood gas analyzer (GEM Premier 4000; Instrumentation laboratory, Lexington, MA) for the calculation of Pao_2/F_{IO_2} ratio and dead space ventilation, respectively. Dead space ventilation was calculated with $Paco_2$ and end-tidal carbon dioxide ($Etco_2$) according to the Hardman and Aitkenhead equation[12] [$1.14 \times (Paco_2 - Etco_2)/Paco_2 - 0.005$]. Dynamic compliance was automatically estimated by the following equation: [tidal volume/(plateau airway pressure − PEEP)]. The hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP).

Echocardiographic assessment was conducted by a single, blinded anesthesiologist who used a 4–7 MHz multiplane transesophageal echocardiography probe (6TC; GE, Vingmed Ultrasound AS, Horten, Norway), which was connected to a cardiac ultrasound system (Vivid E9; GE, Vingmed Ultrasound AS). To confirm RV and left ventricular (LV) function, the tissue Doppler imaging (TDI) was used to assess the transtricuspid and transmitral flow in the midesophageal 4-chamber view. Isovolumetric contraction, isovolumetric relaxation time, and ejection time were measured using TDI, and myocardial performance indices (MPIs) of right and left ventricle were defined as follows: (isovolumic contraction time + isovolumic relaxation time)/ejection time.[13] The peak early diastolic tricuspid annulus velocity (RV e′) and peak systolic tricuspid annulus velocity (RV s′) were estimated at the lateral tricuspid annulus. The ratio of peak early diastolic transtricuspid inflow velocity (RV E) to RV e′ (RV E/e′) was measured. The peak early diastolic transmitral inflow velocity (LV E) and the peak early diastolic mitral annulus velocity (LV e′) and peak systolic mitral annulus velocity (LV s′) were estimated at the lateral and septal annuli. The LV E/e′ was calculated by averaging the sum of lateral and septal LV E/e′.

Statistical Analysis

The primary outcome was change in Pao_2/F_{IO_2} ratio at 30 minutes after iloprost inhalation, and the secondary outcome was change in other lung mechanics and cardiac function, such as RV MPI evaluated by TDI. In addition, the Pao_2/F_{IO_2} ratio in the PACU between the groups was analyzed using unpaired Student *t* tests as a secondary outcome. Repeated variables were analyzed using a linear mixed model with group, time, and interaction between groups and time as a fixed effect and patient indicator as a random intercept. Post hoc analysis with Bonferroni correction for within-group comparison versus pre-Tx and between-group comparison versus Post-Tx was performed for multiple comparisons. Results are expressed as a mean (standard deviation), median [interquartile range], or number (proportion). To determine intra- and interobserver variabilities, a random sample of 25% of MPI and TDI data was reanalyzed twice by the first investigator (N.K.) and once by the second investigator (S.H.L.). Variabilities were measured as the absolute difference between 2 readings divided by the mean of the 2 readings, averaged across patients for each Doppler parameter. Statistical analyses were performed using SPSS 20.0 software (IBM Corp, Armonk, NY), and *P* values <.05 were considered statistically significant.

Taking into account the preliminary results for 10 patients who showed a mean difference of 55 and 60 mm Hg of standard deviation in Pao_2/F_{IO_2} ratio at 30 minutes after iloprost had been administered during OLV, we determined that 20 patients in each group would be required to detect a mean difference in this magnitude at a significance of .05 with a power of .80. Considering a 10% dropout, we included 44 patients in this study.

RESULTS

Demographic characteristics of the 40 patients in this study are shown in Supplemental Digital Content,

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Table, http://links.lww.com/AA/D36. Four patients had a Pao_2/FIo_2 ratio ≥150 mm Hg at pre-Tx; thus, they were excluded from the present study (Figure 1).

Effects on Gas Exchange, Lung Mechanics, and Hemodynamic Parameters

As shown in Table 1, no clinically relevant differences were observed between the 2 groups at pre-Tx. ILO group showed a significant increase in Pao_2/FIo_2 ratio (95% confidence interval [CI], 147.1–221.5; $P < .001$) and dynamic compliance at post-Tx compared to pre-Tx, resulting in significant differences between the 2 groups at post-Tx. Dead space ventilation and PIP of ILO group were significantly lower at post-Tx compared to pre-Tx, which led to significant differences between the 2 groups at post-Tx. Tidal volume, HR, MAP, and CVP were not changed at post-Tx compared to pre-Tx in both groups, leading to no significant difference between the 2 groups. Postoperative Pao_2/FIo_2 ratio in PACU was significantly higher in ILO group compared to Control group (Figure 2; $P = .041$).

Echocardiographic Assessment

As shown in Table 2, ILO group showed a significant decrease in RV MPI (95% CI, 0.275–0.316; $P < .001$) and a significant increase in RV e′ and RV s′ at post-Tx compared to pre-Tx and Control group. In addition, ILO group showed a significant decrease in LV MPI (95% CI, 0.388–0.460; $P = .003$) and a significant increase in LV e′ and LV s′ at post-Tx compared to pre-Tx, resulting in significant differences between the 2 groups at post-Tx. RV E/e′ and LV E/e′ at post-Tx were significantly decreased compared to pre-Tx, resulting in significant differences between the 2 groups at post-Tx.

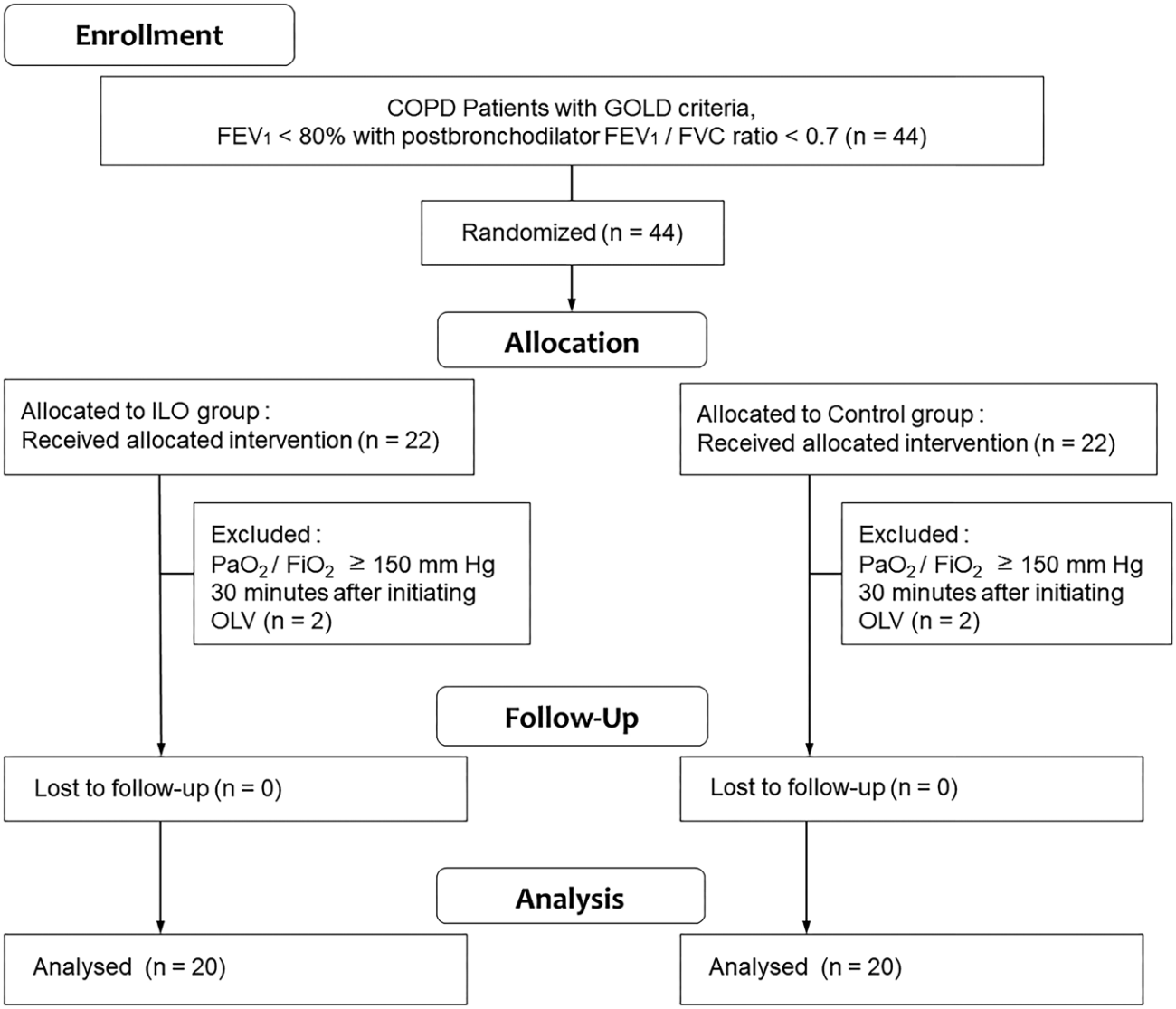

Figure 1. CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, functional vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; ILO group, iloprost group; OLV, one-lung ventilation; Pao_2/FIo_2, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.

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Table 1. Effects on Gas Exchange, Lung Mechanics, and Hemodynamic Parameters

Variables	ILO Group (n = 20)	Control Group (n = 20)	*P* Value
Pao_2/Fio_2 ratio (mm Hg)			<.001
Pre-Tx	98.4 [87.9–112.1]	98.3 [89.5–104.4]	
Post-Tx	184.2 [138.3–200.0][a,b]	96.6 [93.3–101.4]	
Dead space (%)			.002
Pre-Tx	30.4 ± 2.4	30.9 ± 3.3	
Post-Tx	20.1 ± 4.7[c,d]	31.7 ± 2.2	
Tidal volume (mL)			.856
Pre-Tx	405.7 ± 52.6	383.8 ± 48.0	
Post-Tx	402.8 ± 50.9	379.5 ± 48.2	
PIP (cm H_2O)			<.001
Pre-Tx	24.1 ± 5.3	21.2 ± 4.9	
Post-Tx	18.6 ± 4.7[b,e]	21.8 ± 5.3	
Dynamic compliance (mL/cm H_2O)			<.001
Pre-Tx	16.7 [14.3–21.2]	18.8 [15.1–22.0]	
Post-Tx	21.3 [19.0–28.0][b,e]	19.3 [15.0–20.9]	
HR (beats/min)			.059
Pre-Tx	73.0 [70.5–83.0]	80.0 [65.0–82.0]	
Post-Tx	74.5 [68.0–83.0]	82.0 [68.5–84.0]	
MAP (mm Hg)			.676
Pre-Tx	72.6 ± 5.9	75.2 ± 6.9	
Post-Tx	75.1 ± 6.4	76.6 ± 7.2	
CVP (mm Hg)			.079
Pre-Tx	12.5 [12.0–15.0]	12.5 [11.0–13.5]	
Post-Tx	12.5 [12.0–13.0]	12.5 [11.5–14.0]	

Data were presented as the mean (standard deviation) or median [interquartile range].

Abbreviations: CVP, central venous pressure; dead space, dead space ventilation; HR, heart rate; MAP, mean arterial pressure; Pao_2/Fio_2 ratio, the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; PIP, peak inspiratory airway pressure; post-Tx, 30 min after completion of iloprost or saline inhalation; Pre-Tx, 30 min after initiation of one-lung ventilation.

P values in the rightmost column represented *P*group × time, and adjusted *P* values after multiple comparisons were shown as follows:

[a]*P* < .001 compared with the Control group.

[b]*P* < .001 compared with the pre-Tx.

[c]*P* < .01 compared with the Control group.

[d]*P* < .05 compared with the pre-Tx.

[e]*P* < .05 compared with the Control group.

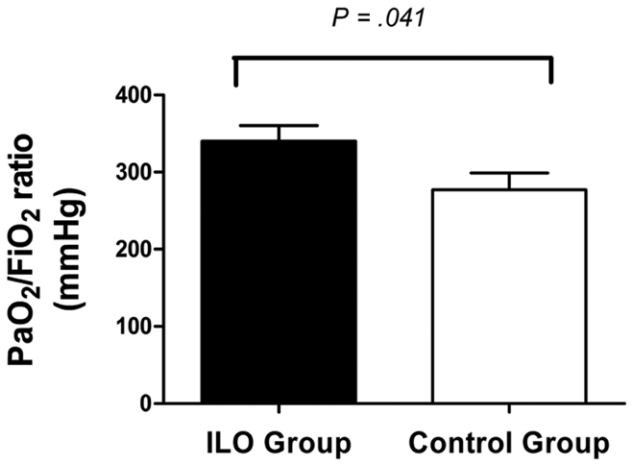

Figure 2. Gas exchange parameters in postanesthesia care unit. Boxes and error bars represent mean (standard deviation). ILO group indicates iloprost group; Pao_2/Fio_2 ratio, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.

Table 2. The Results of Echocardiographic Assessment

Variables	ILO Group (n = 20)	Control Group (n = 20)	*P* Value
RV e′ (cm/s)			.028
Pre-Tx	6.0 [4.0–8.0]	6.0 [4.5–8.0]	
Post-Tx	7.0 [6.5–8.0][a,b]	6.0 [5.0–7.5]	
RV s′ (cm/s)			.001
Pre-Tx	3.0 [2.5–4.0]	3.0 [2.0–4.0]	
Post-Tx	4.5 [3.0–5.0][c,d]	3.0 [3.0–4.0]	
RV E/e′			.073
Pre-Tx	7.4 [6.4–8.8]	6.2 [5.8–9.2]	
Post-Tx	6.1 [5.4–7.3][a,d]	7.9 [6.9–8.5]	
RV MPI			<.001
Pre-Tx	0.49 ± 0.08	0.47 ± 0.10	
Post-Tx	0.30 ± 0.04[d,e]	0.43 ± 0.09	
LV e′ (cm/s)			.011
Pre-Tx	5.35 ± 1.56	5.50 ± 1.60	
Post-Tx	6.60 ± 1.18[a,d]	5.45 ± 1.42	
LV s′ (cm/s)			<.001
Pre-Tx	3.35 ± 0.74	3.40 ± 1.23	
Post-Tx	5.55 ± 1.35[d,e]	3.60 ± 0.75	
LV E/e′			.147
Pre-Tx	12.0 ± 3.1	12.7 ± 3.0	
Post-Tx	10.1 ± 2.3[c,d]	12.3 ± 2.7	
LV MPI			.003
Pre-Tx	0.56 ± 0.11	0.54 ± 0.11	
Post-Tx	0.42 ± 0.08[c,d]	0.52 ± 0.13	

Data were presented as the mean (standard deviation) or median [interquartile range].

Abbreviations: LV, left ventricle; LV E, peak early diastolic transmitral inflow velocity; LV e′, peak early diastolic mitral annulus velocity; LV s′, peak systolic mitral annulus velocity; MPI, myocardial performance index; post-Tx, 30 min after completion of iloprost or saline inhalation; pre-Tx, 30 min after initiation of one-lung ventilation; RV, right ventricle; RV E, peak early diastolic transtricuspid inflow velocity; RV e′, peak early diastolic tricuspid annulus velocity; RV s′, peak systolic tricuspid annulus velocity.

P values in the rightmost column represented *P*group × time, and adjusted *P* values after multiple comparisons were shown as follows:

[a]*P* < .05 compared with the Control group.

[b]*P* < .05 compared with the pre-Tx.

[c]*P* < .01 compared with the Control group.

[d]*P* < .001 compared with the pre-Tx.

[e]*P* < .001 compared with the Control group.

Table 3. Intra- and Interobserver Variability for Echocardiographic Parameters

	Intraobserver Variability	Interobserver Variability
RV e′	1.1 (−3.0 to 5.2)	4.4 (−1.1 to 9.8)
RV s′	1.7 (−0.9 to 4.3)	1.4 (−4.4 to 7.2)
RV MPI	1.5 (−0.8 to 3.6)	3.5 (−2.7 to 9.6)
LV e′	1.6 (−3.3 to 6.4)	2.6 (−1.7 to 6.9)
LV s′	1.5 (−0.6 to 3.8)	2.7 (−3.1 to 8.4)
LV MPI	1.7 (−1.2 to 4.6)	4.1 (0.5 to 7.7)

Values are expressed as percentages (95% CI).

Abbreviations: CI, confidence interval; LV e′, peak early diastolic mitral annulus velocity; LV MPI, left ventricular myocardial performance index; LV s′, peak systolic mitral annulus velocity; RV e′, peak early diastolic tricuspid annulus velocity; RV MPI, right ventricular myocardial performance index; RV s′, peak systolic tricuspid annulus velocity.

However, biventricular E/e′ showed no statistical differences in linear mixed-model analysis adjusted for group and time.

Inter- and intraobserver variabilities of echocardiographic parameters are shown in Table 3.

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DISCUSSION

The present study demonstrated that inhaled iloprost improves oxygenation, dead space ventilation, and dynamic compliance during OLV in COPD patients with poor lung oxygenation. Furthermore, iloprost significantly ameliorated biventricular function, which indicates positive cardiopulmonary effects.

In general, treatment options for improving oxygenation during OLV are as follows: (1) PEEP application to the ventilated lung, (2) recruitment of both lungs and continuous positive airway pressure (CPAP) application to the nonventilated lung as an advanced ventilation strategy, and (3) modulation of perfusion.[14] However, in addition to the limitation of PEEP application to overcome the V/Q mismatch, the response to HPV is not effectively activated because of remodeling of the pulmonary vascular structure and altered pulmonary vascular reactivity in patients with COPD.[15] Furthermore, even in patients with early COPD without coexisting pulmonary hypertension, increased pulmonary artery stiffness can inhibit the activation of HPV.[5] Therefore, therapeutic options for hypoxemia and hypercapnia in these patients during OLV are limited, and although medical therapies such as β-agonist, prostacyclin, or dexmedetomidine are available,[16] limited studies support their use in such instances.

There have been several contradictory studies that attempted to enhance pulmonary oxygenation by improving V/Q mismatch using nitric oxide (NO), which can induce pulmonary vasodilation during OLV. According to Fradj et al,[17] there was little effect of correcting hypoxemia compared to the placebo group when 20 ppm of NO was given during OLV. On the other hand, NO inhalation effect on the patients with pulmonary hypertension showed significant improvement in pulmonary oxygenation compared to patients with normal pulmonary artery pressure.[18]

Iloprost acts as selective pulmonary vasodilator, with similar effects to inhaled NO.[19] Iloprost-mediated vasodilation is associated with the prostacyclin I receptor[20] and prostanoid E receptor,[21] and it increases cyclic adenosine monophosphate (cAMP) in the pulmonary vessels. Inhaled iloprost effectively decreases pulmonary vascular resistance and pulmonary arterial pressure[22] by selectively targeting pulmonary terminal capillaries surrounded by alveoli, and it can also redistribute the pulmonary flow from nonventilated lung to ventilated lung and decrease V/Q mismatching.[23] It can improve the Pao_2 level without causing systemic adverse events in acute respiratory distress syndrome (ARDS) patients, and, because these effects are not dose dependent, 10 μg of nebulized iloprost is sufficient for inducing maximal pulmonary vasodilation.[8]

Previous studies have shown that, although inhaled iloprost ameliorates the decreased exercise capacity in patients with COPD, there are conflicting results regarding gas exchange.[24–26] A recent open-label trial demonstrated that inhaled iloprost impaired resting oxygenation in patients with COPD.[24] In another observational study, arterial oxygenation and dead space ventilation were unchanged after treatment with inhaled iloprost, and V/Q mismatch was improved.[25] However, because these studies were performed during spontaneous ventilation, the effects of iloprost would be different than those in the current trial with mechanical ventilation. When the HPV response is attenuated in COPD patients during general anesthesia,[4] pulmonary blood flow redistribution is diminished, which may further worsen V/Q mismatch. This phenomenon is not influenced by the severity of PAH in patients with COPD, and it is common even in those with mild COPD.[27]

The benefit of Pao_2/Fio_2 ratio persisted in the iloprost group 2 hours after the inhalation of iloprost in the PACU, which is consistent with the mechanism of action of iloprost and with the result of the previous study.[8] Although the plasma half-life of iloprost is relatively short (20–30 minutes), cAMP levels may remain elevated for up to 4 hours.[28] The cAMP is the key factor not only for pulmonary vascular resistance, but also in airway remodeling,[29] and increase in cAMP is involved in the relaxation of airway smooth muscles.[30]

Interestingly, our results showed that inhaled iloprost improves RV e′, RV s′, and RV MPI, because iloprost affects the RV diastolic and systolic functions. These results are consistent with previous findings that Pao_2 has a significant correlation with mean pulmonary artery pressure[6] and PAH caused by pulmonary vascular remodeling augments RV diastolic impairment.[31] Even in mild cases of COPD without coexisting PAH, RV remodeling may develop.[32] Iloprost induces pulmonary vasodilation and indirectly reduces RV afterload.[33] Moreover, recent studies have indicated that iloprost may enhance RV function in a load-independent manner[10] and be involved in direct RV remodeling[34] with direct inotropic effect.[35] Furthermore, in this subset of patients, ventricular interdependence may induce impairment of LV function.[36] Previous experimental studies have demonstrated that iloprost increases myocardial cAMP, which preserves the early phase of active isovolumic relaxation and improves LV diastolic function[37] and contractility.[38]

There are some limitations of this study. In the current trial, we could not directly measure the pulmonary artery pressure. Although pulmonary

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artery stiffness could be observed in mild COPD patients, we could not confirm the presence of pulmonary hypertension; therefore, it cannot be concluded whether iloprost was effective with or without pulmonary hypertension. Second, most of the patients enrolled in our study were moderate to severe COPD patients, and the purpose of 2 cm H_2O PEEP application in the current trial was to minimize or eliminate the effects of PEEP to confirm the effect of iloprost inhalation. However, because levels of extrinsic PEEP around 3–5 cm H_2O or individualized PEEP[39] and CPAP to the nonventilated lung can be applied to augment pulmonary oxygenation during OLV, our study results can differ from conventional strategies for the management of hypoxemia. Third, if we could confirm the level of airway resistance as well as pulmonary compliance, it would be more clear to investigate the effect of iloprost inhalation on obstructive airway pathology, because overcoming airway resistance is more crucial in COPD patients. Fourth, the effects of iloprost on biventricular cardiovascular function during general anesthesia need to be clarified further. Although we measured the integrated biventricular function by using MPI from midesophageal 4-chamber view and MPI alone can serve as a diagnostic value,[40] it is necessary to understand RV function more comprehensively by using the parameter that measures the sizes of both right atrium and right ventricle, fractional area change, and tricuspid annular plane systolic excursion. Fifth, we only included moderate to severe COPD patients according to the GOLD criteria[11] with Pao_2/Fio_2 ratio <150 mm Hg. Further investigation is warranted to clarify the efficacy of inhaled iloprost in all categorical grades of COPD patients during OLV, because there are various responses of pulmonary circulation to hypoxia. Sixth, although we performed randomization for the study enrollment, there were more patients who underwent right lobectomy with no difference in operation sites between the ILO and the control group as shown in Supplemental Digital Content, Table, http://links.lww.com/AA/D36. We think that the effect of iloprost on left and right thoracotomy should be investigated further, because the Pao_2/Fio_2 ratio may differ between the 2 as shown by previous study.[14] Finally, it remains to be determined if the beneficial effect of iloprost on oxygenation will be maintained over time, and whether it would affect postoperative outcome.

In conclusion, the results of the current study support the use of iloprost inhalation as a novel rescue therapy for improving oxygenation and cardiac function during OLV in COPD patients combined with poor lung oxygenation.

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DISCLOSURES

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