

# Inhaled iloprost induces long-term beneficial hemodynamic changes in patients with pulmonary arterial hypertension receiving combination therapy

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## Abstract

Inhaled iloprost is an established treatment for pulmonary arterial hypertension (PAH). However, the long-term hemodynamic changes that inhaled iloprost induces are unclear. Here, we retrospectively enrolled 18 patients with PAH who received inhaled iloprost as add-on to oral combination therapy from December 2016 to January 2021 at our institute in Japan. We then examined the changes in hemodynamic parameters induced by iloprost in these patients during right heart catheterization (RHC). To examine the long-term effects of iloprost, we repeated the RHC examination at follow-up (median time to follow-up, 8.5 months). During both catheterization procedures, iloprost was administered by using an I-neb AAD system (Philips NV). In a comparison of pre-inhalation values at the first and follow-up RHCs, inhaled iloprost significantly improved mean pulmonary artery pressure (mPAP;  $39.9 \pm 7.8$  to  $32.5 \pm 7.2$  mmHg,  $p = 0.016$ ) and pulmonary vascular resistance (PVR;  $588.5 \pm 191.7$  to  $464.4 \pm 188.5$  dyn s cm<sup>-5</sup>,  $p = 0.047$ ). During the follow-up RHC, in a comparison of the pre-inhalation and best recorded values out to 30 min after the end of iloprost inhalation, iloprost significantly decreased mPAP ( $32.5 \pm 7.2$  to  $30.0 \pm 6.6$  mmHg,  $p = 0.007$ ) and PVR ( $457.8 \pm 181.4$  to  $386.2 \pm 142.8$  dyn s cm<sup>-5</sup>,  $p = 0.025$ ) and significantly increased cardiac output ( $4.19 \pm 0.91$  to  $4.64 \pm 1.01$  L/min,  $p = 0.035$ ). Iloprost may have not only acute vasodilation effects but also long-term hemodynamic benefits in PAH patients receiving combination therapy.

## KEYWORDS

aerosolized prostacyclin, efficacy, right heart catheterization

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease characterized by epithelial cell dysfunction and pulmonary vascular remodeling, leading to increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP). These pathological changes result in increased right ventricular load, right heart failure, and eventually death.<sup>1–6</sup>

In the last 30 years, many drugs have been developed for the treatment of PAH, and they have improved exercise tolerance and long-term patient survival rates.<sup>7–9</sup> The current recommendation in the *2015 European Society of Cardiology and European Respiratory Society Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension* is that patients with PAH should receive combination therapy and that this combination therapy can be administered in either a sequential or upfront fashion in accordance with risk stratifications.<sup>2,10,11</sup>

Pulmonary vasodilators are the recommended therapy for the treatment of PAH, and currently available therapies generally target one of three pathways: the nitric oxide pathway, the endothelin pathway, and the prostaglandin pathway. In Japan, several therapeutic agents targeting the prostaglandin I<sub>2</sub> (PGI<sub>2</sub>, prostacyclin) pathway via various administration routes (intravenous, subcutaneous, inhaled, or oral) are also approved for the treatment of PAH.<sup>12</sup> PGI<sub>2</sub> is produced mainly by lung endothelial cells and its production is reduced in PAH. Iloprost is a synthetic analog of PGI<sub>2</sub> formulated as an inhaled pulmonary vasodilator. When administered via a nebulizer, iloprost is deposited in the peripheral airways and alveoli, allowing it to rapidly exert its effects on the

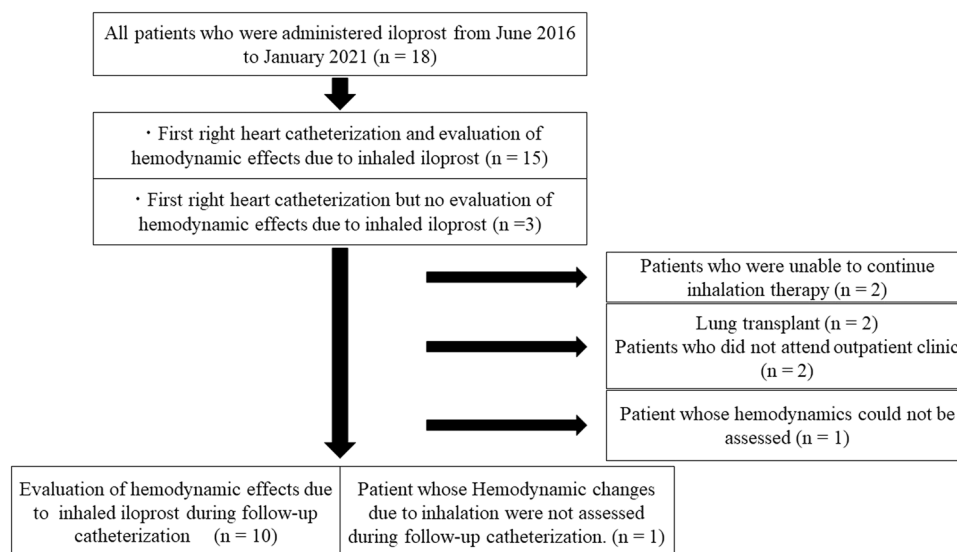
pulmonary arteries.<sup>13</sup> Because iloprost is administered via inhalation, lower doses can be given; this results in very few systemic side effects (e.g., headache, diarrhea, and vomiting) compared with those of other drugs that are administered via the intravenous, subcutaneous, or oral routes.<sup>14</sup> Past clinical studies have shown improvements in hemodynamic parameters and exercise tolerance in patients with PAH treated with inhaled iloprost.<sup>15,16</sup> Moreover, acute decreases in mean PAP (mPAP) and PVR, and an increase in cardiac index (CI), have been reported in patients with pulmonary hypertension (PH) that were administered nebulized iloprost via the I-neb Adaptive Aerosol Delivery system (I-neb AAD system (Philips NV)).<sup>17</sup>

Despite several reports detailing the acute improvements in hemodynamic parameters by inhaled iloprost,<sup>18–20</sup> there are few reports of the long-term hemodynamic effects of this therapy. Therefore, here, we retrospectively examined the acute hemodynamic effects of iloprost during right heart catheterization (RHC) in PAH patients receiving combining therapy. To examine the long-term effects of iloprost, RHC was repeated at long-term follow-up.

## METHODS

### Study design and patients

This was a retrospective study. A total of 18 subjects with PAH receiving combination therapy who were administered inhaled iloprost at Nagoya University Hospital from June 2016 to January 2021 were enrolled (Figure 1).



**FIGURE 1** Flow diagram showing patient enrollment in the study

During follow-up, all patients received inhaled iloprost at 5.0  $\mu\text{g}$  per inhalation, six to nine times per day, at intervals  $\geq 2$  h. If 5.0  $\mu\text{g}$  per inhalation was not tolerated, the dose was reduced to 2.5  $\mu\text{g}$  per inhalation. If patients could not perform inhalation six to nine times per day, the number of inhalations per day was reduced to a number that was achievable. Of the 18 patients enrolled, 3 had started inhaled iloprost in the outpatient setting and were not assessed for hemodynamic changes at the time of catheterization. As a result, 15 of the enrolled patients received inhaled iloprost and underwent RHC and were assessed for hemodynamic changes. Of the overall 18 patients, 2—one with a history of pneumonia who was reluctant to receive inhaled therapy, and one with shortness of breath that was exacerbated during exertion—discontinued iloprost therapy. Also, two patients underwent subsequent lung transplantation so pulmonary vasodilators were terminated, two patients stopped coming to our hospital during follow-up so follow-up catheterization could not be performed, and one patient continued inhaled iloprost but was unable to undergo follow-up RHC. As a result, 11 patients underwent follow-up RHC, and the long-term hemodynamic changes were evaluated in 10 of these; the remaining patient did not receive inhaled iloprost at the time of follow-up catheterization, so hemodynamic changes could not be assessed. Variables assessed at baseline and follow-up included World Health Organization Functional Classification (WHO-FC), 6-min walking distance (6MWD), brain natriuretic peptide (BNP), and risk.<sup>2</sup>

## RHC

RHC was performed under local anesthesia from the right jugular vein. A 6-Fr Thermodilution Catheter (Nipro Corporation) was used to measure RAP, PAP, PAWP, right ventricular pressure, cardiac output (CO). PVR and CI was calculated as follows:  $\text{PVR} = (\text{mPAP} - \text{PAWP})/\text{CO}$ ;  $\text{CI} = (\text{CO}/\text{body surface area})$ . All subjects were examined in the supine position, and the zero-reference level was set at mid-chest. Pressures were measured at end-expiration. To ensure the accuracy of the data, none of the patients inhaled oxygen during the examination. Pulmonary hemodynamics, saturation of arterial oxygen ( $\text{SaO}_2$ ) and  $\text{SvO}_2$  via blood gas were assessed at baseline and 10, 20, 30 min after the end of inhalation. Also, on the day of the follow-up examination, no inhalation of iloprost was performed before the examination.

## Inhalation method

The day before administration of iloprost, under the guidance of nurses and technicians from Philips Respironics, patients practiced the correct inhalation method using the I-neb AAD system by inhaling 2.5  $\mu\text{g}$  of iloprost. To check the accuracy of inhalation and the absence of side effects, patients were asked to inhale iloprost 2.5  $\mu\text{g}$ , and all patients were evaluated at 5  $\mu\text{g}$  during catheterization. During the RHC procedure, the patient was raised from the recumbent position to the sitting position, in which inhalation was performed. After inhalation, the patient resumed the supine position and we checked that the zero level was not shifted. Iloprost was administered by using the I-neb AAD system as practiced, and the administration was continued until the system gave a vibratory signal indicating the end of nebulization. mPAP, PVR, CO, PAWP, RAP, and CI were assessed at baseline and at 10, 20, and 30 min after the end of nebulization.

## Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics software (v.27.0; IBM). Categorical variables are expressed by using counts and percentages. Continuous variables are expressed as median (25th–75th percentile range) or as mean  $\pm$  SD. The Wilcoxon signed-rank test, which is a nonparametric test, was used to compare the hemodynamic changes between baseline and the maximum effect out to 30 min after the end of iloprost inhalation, as well as the hemodynamic changes at baseline between the two RHCs. Wilcoxon's signed-rank test was also used to calculate the two-sided 95% confidence interval of the changes in hemodynamic parameters between the two RHCs.  $p$  Values  $< 0.05$  were considered statistically significant.

## RESULTS

The baseline characteristics of the subjects at the time of the first RHC are shown in Table 1 ( $n = 15$ ). Mean age was 41 ( $\pm 15.7$ ) years, and 73.3% of the subjects were female. Nine patients had idiopathic PAH. One patient was classified as WHO functional class I, eight as functional class II, and six as functional class III. All patients were receiving double or triple combination therapy. In two patients, inhaled iloprost was added during continuous intravenous epoprostenol administration. The baseline

characteristics of the subjects at the time of the follow-up RHC are shown in Table 2 ( $n = 10$ ). During the follow-up period, 10 patients received iloprost: 9 patients (90%) received iloprost at a dose of 5  $\mu\text{g}$  per inhalation and 1 patient received iloprost at a dose of 2.5  $\mu\text{g}$  per inhalation;

**TABLE 1** Baseline characteristics before the first right heart catheterization

Variable	Value ( $n = 15$ )
Age (years), mean (SD)	41.0 (15.7)
Gender, M/F, $n$ (%)	4 (26.7)/11 (73.3)
Female	11 (73.3)
Male	4 (26.7)
Body mass index ( $\text{kg}/\text{m}^2$ ), mean (SD)	23.7 (4.8)
PAH etiology, $n$ (%)	
Idiopathic	9 (60.0)
PVOD	2 (13.3)
Other	4 (26.7)
WHO functional class, $n$ (%)	
I	1 (6.7)
II	8 (53.3)
III	6 (40.0)
Baseline PAH medication, $n$ (%)	
Dual combination therapy	12 (80)
Triple combination therapy	3 (20)
Macitentan	15 (100)
Sildenafil	1 (6.7)
Tadalafil	4 (26.7)
Riociguat	10 (66.7)
Epoprostenol	2 (13.3)
Selexipag	1 (6.7)
6-min walk distance (m)	401.2 (93.5)
BNP (pg/ml), median (25th–75th percentile range)	22.4 (7.7–76.6)
Hemodynamic parameters at right heart catheterization baseline	
Mean PAP (mmHg), mean (SD)	40.0 (7.1)
PAWP (mmHg), mean (SD)	8.5 (2.6)
RAP (mmHg), mean (SD)	5.5 (2.8)
CO (L/min), mean (SD)	4.59 (1.02)
CI (L/min/ $\text{m}^2$ ), mean (SD)	2.89 (0.68)
PVR ( $\text{dyn s cm}^{-5}$ ), mean (SD)	580.3 (214.3)
SvO <sub>2</sub> (%), mean (SD)	70.7 (5.4)
SaO <sub>2</sub> (%), mean (SD)	93.8 (4.5)

**TABLE 1** (Continued)

Variable	Value ( $n = 15$ )
Heart rate (beat/min), mean (SD)	77.9 (15.9)
Mean blood pressure (mmHg), mean (SD)	79.0 (10.9)

Abbreviations: BNP, B-type natriuretic peptide; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVOD, pulmonary vascular obstructive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SaO<sub>2</sub>, blood oxygen saturation; SvO<sub>2</sub>, mixed-venous oxygen saturation; WHO, World Health Organization.

7 patients (70%) inhaled iloprost 5 to 6 times a day and 3 patients inhaled iloprost 3 times a day. None of the patients died during follow-up.

During the first RHC, the changes in hemodynamic parameters between before and after inhalation of iloprost were evaluated in 15 patients (Figure 2, Table 3). Significant reductions in mPAP and PVR were observed between pre-inhalation (before iloprost inhalation) and the lowest recorded value out to 30 min after the end of iloprost inhalation (mPAP change from  $40.0 \pm 7.1$  mmHg to  $36.7 \pm 5.3$  mmHg,  $p = 0.002$ ; PVR from  $580.3 \pm 214.3$  dyn s  $\text{cm}^{-5}$  to  $463.6 \pm 177.9$  dyn s  $\text{cm}^{-5}$ ,  $p < 0.001$ ). Similarly, a significant increase in CO was observed between pre-inhalation and the highest recorded value out to 30 min after the end of iloprost inhalation (from  $4.59 \pm 1.03$  L/min to  $5.35 \pm 1.23$  L/min,  $p = 0.001$ ).

During the follow-up RHC, the changes in hemodynamic parameters between before and after inhalation of iloprost were evaluated in 10 patients (Figure 2, Table 4). Significant reductions in mPAP and PVR were observed between pre-inhalation and the lowest recorded value out to 30 min after the end of iloprost inhalation (mPAP from  $32.5 \pm 7.2$  to  $30.0 \pm 6.6$  mmHg,  $p = 0.007$ ; PVR from  $457.8 \pm 181.4$  to  $386.2 \pm 142.8$  dyn s  $\text{cm}^{-5}$ ,  $p = 0.025$ ). Similarly, a significant increase in CO was observed between pre-inhalation and the highest recorded value out to 30 min after the end of iloprost inhalation (from  $4.19 \pm 0.91$  to  $4.64 \pm 1.01$  liters per minute,  $p = 0.035$ ).

Comparison of the hemodynamic parameters between the first and follow-up RHCs revealed significant reductions in mPAP and PVR at follow-up (mPAP from  $39.9 \pm 7.8$  to  $32.5 \pm 7.2$  mmHg,  $p = 0.016$ ; PVR from  $588.5 \pm 191.7$  to  $464.4 \pm 188.5$  dyn s  $\text{cm}^{-5}$ ,  $p = 0.047$ ). However, unlike in the previous two comparisons, no significant change in CO was observed at follow-up (Figure 3, Table 5).

We investigated the efficacy of inhaled iloprost during follow-up RHC in 10 patients (Table S1). BNP

**TABLE 2** Characteristics of patients receiving inhaled iloprost and in whom hemodynamic changes were assessed at follow-up

Variable	Value (n = 10)
Age (years), mean (SD)	36.5 (12.0)
Gender, M/F, n (%)	1 (10)/9 (90)
Female	9 (90)
Male	1 (10)
Body mass index (kg/m <sup>2</sup> ), mean (SD)	24.5 (5.2)
PAH etiology, n (%)	
Idiopathic	9 (90)
PVOD	1 (10)
WHO functional class, n (%)	
I	1 (10)
II	5 (50)
III	4 (40)
Baseline PAH medication, n (%)	
Dual combination therapy	7 (70)
Triple combination therapy	3 (30)
Macitentan	10 (100)
Sildenafil	1 (10)
Tadalafil	2 (20)
Riociguat	7 (70)
Epoprostenol	1 (10)
Selexipag	1 (10)
Follow-up period (month), median (25th–75th percentile range)	8.5 (6–13)
Inhalation iloprost during follow-up	
A dose of 5 µg/2.5 µg per inhalation, n (%)	9 (90)/1 (10)
Inhaled iloprost of 2.5 µg 3 times a day, n (%)	1 (10)
6-min walk distance (m) <sup>a</sup>	444.3 (80.0)
BNP (pg/ml), median (25th–75th percentile range)	8.1 (5.8–25.5)
Hemodynamic parameters at right heart catheterization baseline	
Mean PAP (mmHg), mean (SD)	39.9 (7.8)
PAWP (mmHg), mean (SD)	9.0 (2.2)
RAP (mmHg), mean (SD)	6.9 (3.0)
CO (L/min), mean (SD)	4.39 (1.01)
CI (L/min/m <sup>2</sup> ), mean (SD)	2.78 (0.62)
PVR (dyn s cm <sup>-5</sup> ), mean (SD)	588.5 (191.7)
SvO <sub>2</sub> (%), mean (SD)	71.9 (3.7)

**TABLE 2** (Continued)

Variable	Value (n = 10)
SaO <sub>2</sub> (%), mean (SD)	95.3 (3.6)
Heart rate (beat/min), mean (SD)	77.4 (20.0)
Mean blood pressure (mmHg), mean (SD)	78.9 (11.2)

Abbreviations: BNP, B-type natriuretic peptide; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVOD, pulmonary vascular obstructive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SaO<sub>2</sub>, blood oxygen saturation; SvO<sub>2</sub>, mixed-venous oxygen saturation; WHO, World Health Organization.

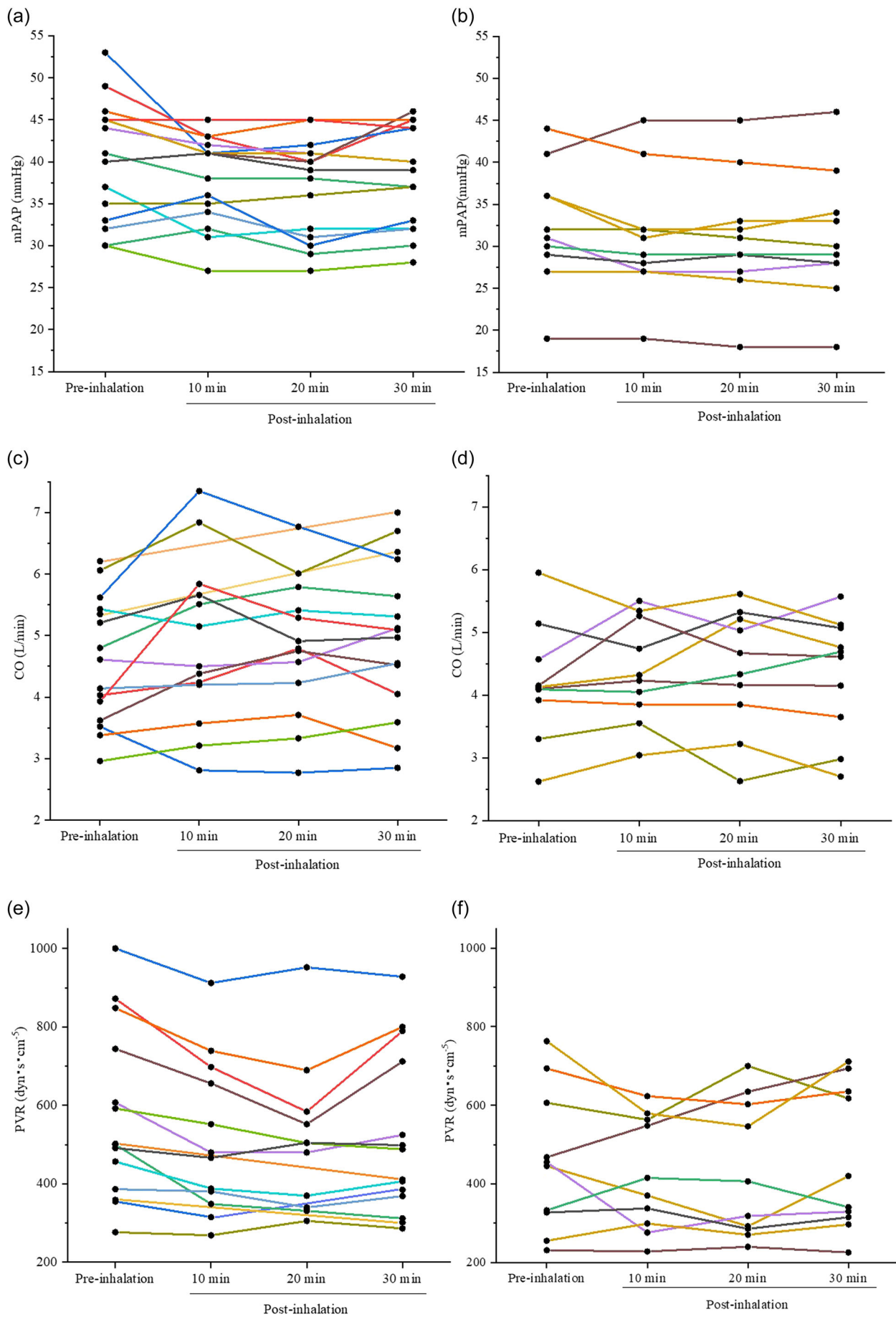
<sup>a</sup>Six-minute walk distance (n = 8).

and 6MWD did not change significantly between baseline and follow-up. In terms of WHO-FC, four of five patients who were WHO-FC III at baseline had changed to WHO-FC II at follow-up. Also, two of four patients who were WHO-FC II at baseline had changed to WHO-FC I at follow-up. In terms of risk classification, four patients were at intermediate risk and six patients were at low risk at baseline, and one patient was at intermediate risk and nine patients were at low risk at follow-up; thus three patients demonstrated an improvement in risk classification.

The incidence of adverse events related to inhaled iloprost was examined in all patients prescribed inhaled iloprost and in the patients whose hemodynamics were evaluated during follow-up RHC (Table S2). At follow-up, three patients had decreased their inhalation frequency owing to adverse events related to inhaled iloprost: one patient had reduced the number of inhalations from six to five times per day because of headache, one patient had reduced the number of inhalations from six to four times per day also because of headache; and one patient had reduced the number of inhalations from six to three or four times per day because of nausea. None of the patients reduced the dose per inhalation because of adverse events associated with inhaled iloprost.

## DISCUSSION

Here, in PAH patients receiving combination therapy (endothelin receptor antagonist (ERA), phosphodiesterase type-5 inhibitor (PDE5-I), soluble guanylate cyclase stimulator and/or prostacyclin receptor agonist), we found that inhaled iloprost induced favorable hemodynamic changes at both the time of initial administration and at long-term follow-up (median 8.5 months).



**FIGURE 2** (See caption on next page)

**TABLE 3** Hemodynamic parameters during the first right heart catheterization ( $n = 15$ )

Parameter	Pre-inhalation, mean (SD)	10 min, mean (SD)	20 min, mean (SD)	30 min, mean (SD)	Best mean, (SD) <sup>a</sup>	p Value
mPAP (mmHg)	40 ± 7.1	38 ± 5.3	37.6 ± 5.7	38 ± 6.0	36.7 ± 5.3	0.002
PVR (dyn s cm <sup>-5</sup> ) <sup>b</sup>	580.3 ± 214.3	517.1 ± 197.3	510.3 ± 189.3	515.1 ± 208.8	463.6 ± 177.9	<0.001
CO (L/min) <sup>c</sup>	4.59 ± 1.03	4.87 ± 1.35	4.79 ± 1.11	5.01 ± 1.26	5.35 ± 1.23	0.001
PAWP (mmHg) <sup>d</sup>	8.5 ± 2.6	8.9 ± 3.9	9.0 ± 3.6	8.1 ± 3.7		
RAP (mmHg) <sup>e</sup>	5.5 ± 2.8			6.6 ± 3.1		

Note: Pre-inhalation values are the values recorded before inhalation of iloprost. Values were then recorded at 10, 20, and 30 min after the end of inhalation of iloprost.

Abbreviations: CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

<sup>a</sup>Lowest (mPAP and PVR) or highest (CO) value recorded out to 30 min after the end of iloprost inhalation.

<sup>b</sup>PVR 10 min ( $n = 12$ ), PVR 20 min ( $n = 11$ ) and PVR 30 min ( $n = 14$ ).

<sup>c</sup>CO 10 min ( $n = 13$ ) and 20 min ( $n = 13$ ).

<sup>d</sup>PAWP 10 min ( $n = 14$ ), PAWP 20 min ( $n = 12$ ), and 30 min ( $n = 14$ ).

<sup>e</sup>RAP baseline ( $n = 14$ ) and RAP 30 min ( $n = 5$ ).

**TABLE 4** Hemodynamic parameters during follow-up right heart catheterization ( $n = 10$ )

Parameter	Pre-inhalation, mean (SD)	10 min, mean (SD)	20 min, mean (SD)	30 min, mean (SD)	Best, mean (SD) <sup>a</sup>	P Value
mPAP (mmHg)	32.5 ± 7.2	31.1 ± 7.4	31.0 ± 7.5	31.0 ± 7.7	30.0 ± 6.6	0.007
PVR (dyn s cm <sup>-5</sup> )	457.8 ± 181.4	424.0 ± 143.3	429.6 ± 173.9	458.6 ± 185.1	386.2 ± 142.8	0.025
CO (L/min)	4.19 ± 0.91	4.38 ± 0.82	4.40 ± 0.96	4.33 ± 0.95	4.64 ± 1.01	0.035
PAWP (mmHg)	9.9 ± 3.6	9.0 ± 3.5	8.5 ± 2.7	7.7 ± 1.9		
RAP (mmHg) <sup>b</sup>	6.4 ± 2.0			5.8 ± 2.2		

Note: Pre-inhalation values are the values recorded before inhalation of iloprost. Values were then recorded at 10, 20, and 30 min after the end of inhalation of iloprost.

Abbreviations: CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

<sup>a</sup>Lowest (mPAP and PVR) or highest (CO) value recorded out to 30 min after the end of iloprost inhalation.

<sup>b</sup>RAP 30 min ( $n = 5$ ).

A previous phase III, non-randomized, open-label study (IBUKI study) showed that, for patients with PAH, PVR was improved by  $-127 \pm 108$  dyn s cm<sup>-5</sup> from baseline after 12 weeks of iloprost inhalation; 70% of the patients were also treated with an ERA and a PDE5-I.<sup>21</sup> In addition, in IBUKI, PVR at 3 months after starting iloprost inhalation was decreased by 21% from baseline; this is comparable with what we found in the present study at follow-up (median 8.5 months). In contrast to the findings

from IBUKI, we also found significant improvements in mPAP (from  $32.5 \pm 7.2$  to  $30.0 \pm 6.6$  mmHg,  $p = 0.007$ ) and CO (from  $4.19 \pm 0.91$  to  $4.64 \pm 1.01$  L/min,  $p = 0.035$ ). This difference in findings between the present study and IBUKI may be attributable to different distributions of the different PAH etiologies in the study cohorts; however, at the very least, both studies suggest that inhaled iloprost has a positive effect on hemodynamic parameters in PAH patients receiving combination therapy. In a randomized,

**FIGURE 2** Hemodynamic parameters before and after inhalation of iloprost during right heart catheterization. Right heart catheterization was performed twice in each patient, once at baseline ( $n = 15$ ) and once at follow-up ( $n = 10$ ). Three parameters were assessed during each catheterization: mean pulmonary artery pressure (mPAP; a, at baseline; b, at follow-up); cardiac output (CO, c, at baseline; d, at follow-up); and pulmonary vascular resistance (PVR; e, at baseline; f, at follow-up)

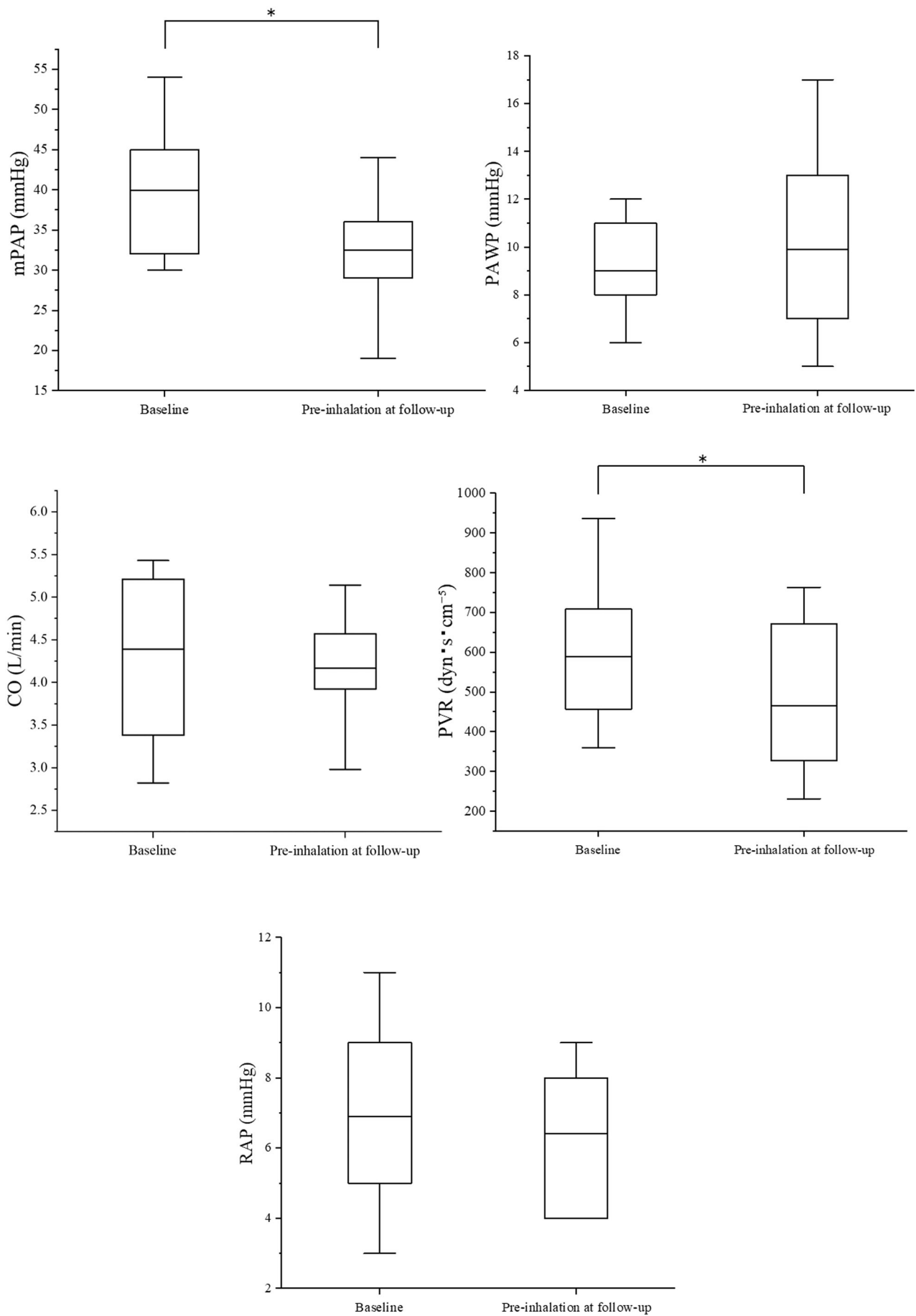


FIGURE 3 (See caption on next page)



**TABLE 5** Comparison of hemodynamic parameters at pre-inhalation between the first and follow-up right heart catheterizations (RHC) ( $n = 10$ )

Parameter	First RHC, mean (SD)	Follow-up RHC, mean (SD)	P Value
mPAP (mmHg)	39.9 ± 7.8	32.5 ± 7.2	0.016
PVR (dyn s cm <sup>-5</sup> )	588.5 ± 191.7	464.4 ± 188.5	0.047
CO (L/min)	4.39 ± 1.01	4.20 ± 0.91	0.508
PAWP (mmHg)	9.0 ± 2.2	9.9 ± 3.6	0.675
RAP (mmHg)	6.9 ± 3.0	6.4 ± 2.0	0.763
SvO <sub>2</sub> (%)	71.9 ± 3.7	70.5 ± 4.2	0.139
SaO <sub>2</sub> (%)	95.3 ± 3.6	94.3 ± 3.4	0.285
HR (beat/min)	77.4 ± 19.6	69.4 ± 11.1	0.123
MBP (mmHg)	78.9 ± 11.2	73.3 ± 9.6	0.014

Abbreviations: CO, cardiac output; HR, heart rate; MBP, mean blood pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO<sub>2</sub>, blood oxygen saturation; SvO<sub>2</sub>, mixed-venous oxygen saturation.

multicenter, double-blind trial in PAH patients receiving bosentan monotherapy, the addition of inhaled iloprost improved mPAP (−8 mmHg from baseline;  $p < 0.001$ ) and PVR (−254 dyn s cm<sup>-5</sup> from baseline;  $p < 0.001$ ) at follow-up 3 months after the start of iloprost inhalation, indicating that, in the short term, the addition of iloprost in these patients may be effective at inhibiting disease progression.<sup>22</sup> Together, these results suggest that adding inhaled iloprost to patients already receiving one or more pulmonary vasodilator may have a beneficial long-term hemodynamic effect.

Our results indicate not only that iloprost has beneficial effects on hemodynamic parameters in the short-term, but also that these effects are seen in the long term; that is, at long-term follow-up (median 8.5 months), we found improved mPAP and PVR values (Table 5). Hoeper et al. reported improvements in mPAP, PVR and CO after inhalation at 1 year's follow-up after the introduction of inhaled iloprost to the patients with primary PH (mPAP from 59 ± 10 mmHg to 52 ± 15 mmHg,  $p = 0.006$ ; PVR from 1205 ± 467 dyn s cm<sup>-5</sup> to 925 ± 469 dyn s cm<sup>-5</sup>,  $p < 0.001$ ; CO from 3.8 ± 1.4 L/min to 4.4 ± 1.3 L/min,  $p = 0.02$ ).<sup>23</sup> Although we used a different inhalation device and a different dose of iloprost compared with those in the study of Hoeper et al., the hemodynamic effects observed in the two studies were comparable.

A previous study showed that the acute hemodynamic effects of nebulized iloprost (2.5 or 5 μg) delivered via the I-neb AAD system for the patients with

PH significantly reduced mPAP and PVR and increased CI, compared with baseline (mPAP Maximum change from baseline,  $-10.1 ± 1.5%$ ; PVR maximum change from baseline,  $-15.6 ± 2.4%$ ; CI maximum change from baseline  $+6.4 ± 2.2%$ ).<sup>17</sup> We used the same administration device and saw comparable acute hemodynamic effects in patients already receiving combination therapy.

Regarding the long-term effects of inhaled iloprost, a previous experimental study has shown that repeated inhalation of iloprost improves hemodynamics (right ventricular systolic pressure, CI, and PVR) and vascular structural remodeling in Wistar rats with monocrotaline-induced PAH.<sup>24</sup> Another experimental study has demonstrated that inhaled iloprost partially reverses right ventricular fibrosis and improves right ventricular function by preventing collagen synthesis and inducing collagen degradation.<sup>25</sup> Together with these previous findings, our results suggest that continuous inhalation of iloprost has beneficial influences on hemodynamics in the long term (Figure 3).

This was a retrospective, uncontrolled study; therefore, there was a high risk that bias was introduced to the data. The limitations of our study include the small sample size and the heterogeneity of the study group. In the study, 18 patients were started on iloprost, but initial hemodynamic assessment was not performed in 3 patients and 8 patients could not be assessed at follow-up. Therefore, although the observed overall hemodynamic response to inhaled iloprost was favorable, selection bias cannot be ruled out.

**FIGURE 3** Pre-inhalation hemodynamic parameters at the baseline and follow-up right heart catheterizations (RHCs) ( $n = 10$ ). CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure. \* $p < 0.05$

In terms of hemodynamic assessment, the acute effect of iloprost may have overestimated by selecting the maximal change within 30 min after inhalation.

In conclusion, our analysis suggests that inhaled iloprost has not only acute vasodilation effects but also long-term beneficial effects on hemodynamic parameters in PAH patients receiving combination therapy.

### AUTHOR CONTRIBUTIONS

Toyoaki Murohara is the guarantor of the present study. Kenichiro Yasuda, Yoshihisa Nakano, and Shiro Adachi conceived the study. Kenichiro Yasuda, Shiro Adachi, Itsumure Nishiyama, Masahiro Yoshida, and Yoshihisa Nakano pooled the data. Kenichiro Yasuda and Shiro Adachi analyzed the data and wrote the manuscript. All authors contributed to drafting the manuscript, discussing the results, and reviewing the manuscript, and all approved the final manuscript.

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Not applicable.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.


### ETHICS STATEMENT

This study was approved by the Human Research Ethics Committee of Nagoya University Hospital (no. 2016-0372) and was performed in accordance with the Declaration of Helsinki and the ethical standards of the institutional committee on human experimentation. All participants gave written informed consent for the collection of data and samples.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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