The optimization of iloprost inhalation under moderate flow of oxygen therapy in severe pulmonary arterial hypertension

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Abstract

Inhaled iloprost efficiently improves pulmonary hemodynamics, exercise capacity, and quality of life in patients with pulmonary arterial hypertension (PAH). However, the process of inhalation is laborious for patients suffering from resting dyspnea. We describe a 75-year-old man with idiopathic PAH and a low gas transfer. Investigations excluded significant parenchymal lung disease and airflow obstruction (presuming FEV1/FVC ration > 70%). The patient struggled to complete iloprost inhalation due to severe dyspnea and hypoxemia. As such, we optimized the methods of oxygen supply from the nasal cannula to the trans-inhalator during the inhalation. We successfully shortened the inhalation duration that effectively reduced the laborious efforts required of patients. We also recorded pulmonary hemodynamics during inhalation of nebulized iloprost. This revealed significant hemodynamic improvement immediately following inhalation but hemodynamics returned to baseline within 2 hours. We hope that this optimization will enable patients with severe PAH to undergo iloprost inhalation.

Introduction

Ever since randomized control studies of inhaled iloprost have proven its clinical efficacy in patients with pulmonary arterial hypertension (PAH),[1–3] this therapy has been indicated for PAH in Europe and the United States since 2001 and in Japan since 2016.[4] Inhalation of iloprost efficiently improves pulmonary hemodynamics, exercise capacity, and quality of life.[3] However, due to the drug's short half-life, patients are required to repeat the inhalation 6–9 times per day. Each inhalation usually lasts 3.2–6.5 min.[5] Sometimes, the process of inhalation is laborious for patients who are already suffering from resting dyspnea under moderate flow (4–6 L/min) of oxygen therapy. Severely dyspneic patients usually take rapid and shallow breaths, which often require a longer inhalation duration than prescribed. We encountered patients who struggled to complete iloprost inhalation therapy due to severe resting dyspnea. As such, we optimized the methods

of oxygen supply during inhalation. We successfully shortened the inhalation duration and enabled patients to complete iloprost therapy. We hope that this optimization will enable patients with severe PAH to undergo iloprost inhalation.

Case presentation

Background

A 75-year-old man was admitted because of progressive dyspnea over five months (World Health Organization

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functional class [WHO-FC] III). He had a 48-year smoking history (Brinkman index was 2640) before stopping ten years ago. In the previous hospital, he was diagnosed with chronic obstructive pulmonary disease (COPD) and was prescribed home oxygen therapy (HOT). Moreover, 58 mmHg tricuspid regurgitation pressure gradient (TRPG) was detected.

Investigations

In our hospital, we observed pulmonary hypertension (PH)-specific findings of electrocardiography (Fig. 1a) and echocardiography (Fig. 1b and c). We excluded the PH etiology from group $2 \sim 4$ by clinical images (Fig. 1b–g). Chest computed tomography (CT) demonstrated minor emphysematous changes but there no features of interstitial thickening and ground-glass opacities which excluded the possibility of combined pulmonary fibrosis and emphysema and pulmonary vascular obstructive disease (Fig. 1d and e). Lung functional tests indicated normal ventilation capacity (forced vital capacity [FVC] = 3.01 L, %FVC = 89.8%, forced expiratory volume in 1 s [FEV1] = 2.22 L, %FEV1 = 83.2%, FEV1/FVC ratio = 73.8%, residual volume [RV] = 1.43 L, total lung capacity [TLC] = 4.82 L, RV/TLC ratio = 29.7%) but severe diffusion disturbance (diffusing capacity of the lung carbon monoxide [DLco] = 4.88 mL/min/mmHg, %DLco = 33.2%). Ventilation perfusion lung scintigraphy showed no mismatched defects in bilateral lobes (Fig. 1f and g). Right heart catheterization (RHC) revealed PAH with a mean pulmonary arterial pressure (mPAP) of 45 mmHg, a pulmonary capillary wedge pressure (PCWP) of 6 mmHg, cardiac index (CI) of 2.47 L/min/m^2, and pulmonary vascular resistance (PVR) of 751 dyne*s/cm^5. We did not perform the nitric oxide challenge test. Blood testing did not identify any causes for PH in particular as anti-nuclear, centromere, double-strand DNA, caldiolipin, beta 2-glycoprotein I dependent anti-caldiolipin, human immunodeficiency virus antibodies were all negative. The level of lupus anticoagulant production, c-antineutrophil cytoplasmic antibodies (ANCA), p-ANCA, rheumatoid factor, bile acid, ammonia, and hepatitis serology were also normal. Trans-thoracic echocardiography excluded congenital heart disease.

Diagnosis

We diagnosed a new idiopathic PAH (IPAH) phenotype in predominantly elderly men with a low diffusing capacity of the lung for carbon monoxide (DLco), which was recently reported in the patients who were heavy cigarette smokers.[6]

Treatment and progress

We initiated sequential combination therapy with 40 mg tadalafil, 10 mg macitentan, and 360 µg beraprost. However, 16 months after the first admission, his symptoms deteriorated to WHO-FC IV with worsening of pulmonary hemodynamics (mPAP = 60 mmHg, CI = 1.98 L/min/m^2, PVR = 1136 dyne*s/cm^5) and exercise capacity (6-min walking
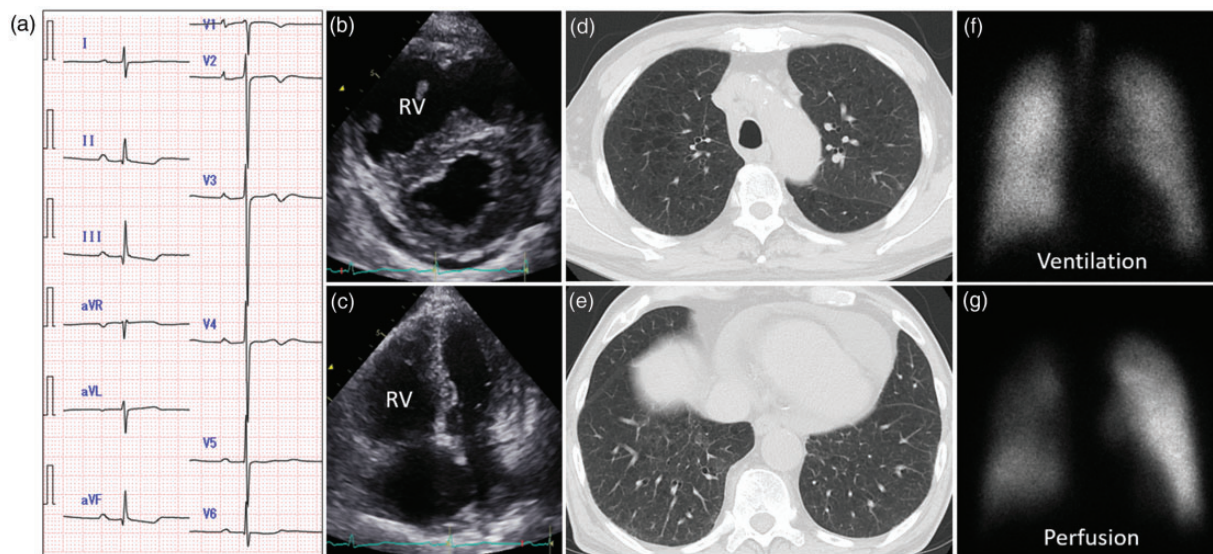
Fig. 1. Clinical images of the case. Electrocardiography revealed right axis deviation (92°), ISIIIQIIIT, and negative T in V1-V4 leads indicating right ventricular load. But small R wave in V1 implies subacute but not chronic phase after PAH development (a). Echocardiography shows enlarged right ventricle and D shape of left ventricle with pleural effusion (b, c). RV function is normal (TPASE = 18.5 mm). No dilated left atrium, normal left ventricular function (EF = 82.5%, E-deceleration time = 210 ms), and no significant left valvular heart diseases exclude left heart disease derived PH. Chest CT shows mild emphysema (d) and no sign of interstitial lung diseases and ground-glass opacities (e). No mismatched defects in lung scintigraphy denies the possibility of CTEPH (f, g).
CTEPH, chronic thromboembolic pulmonary hypertension; EF, ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

distance [6MWD] = 150 m to 90 m). We increased the oxygen level from 2 L/min to 5 L/min due to severe hypoxemia (peripheral saturation of oxygen [SpO$_2$] = 91% under 2 L/min oxygen therapy) and avoided introduction of intravenous epoprostenol due to his advanced age and the possibility of group 3 PH.

Nebulization and adaptations

From 31 August, we initiated iloprost inhalation therapy under moderate oxygen supply (5 L/min of O$_2$) via a trans-nasal cannula. Although the patient experienced dyspnea during inhalation, he inhaled 2.5 µg of iloprost within 15 min (Fig. 2). However, 5 µg of iloprost required an inhalation time of 20–45 min that was too taxing for the patient and he was not able to tolerate the higher dose. As he had previously experienced complete improvement of resting dyspnea following iloprost inhalation, the patient wished to increase the dose of iloprost. We modified the inhalation methodology from 9 September by attaching a nasal cannula into the inlet port of the inhalator (I-neb adaptive aerosol delivery [AAD] system®: Philips, Respironics, Inc., USA.) (Fig. 3a and b). This modification efficiently shortened the inhalation duration from 9.0 ± 2.4 min (Fig. 4a) to 3.3 ± 1.0 min (Fig. 4b), thereby allowing for an increase to 5 µg of iloprost from 13 September. The patient was able to tolerate inhalation of 5 µg iloprost within 8.3 ± 3.3 min (Fig. 4b) and his WHO-FC improved from IV to III and the 6MWD was 240 m. After the hospital discharge, he continued with iloprost inhalation therapy 6–7 times per day at home. However, he occasionally required a prolonged inhalation duration of > 10 min. Consequently, he sealed the inlet port using a rubber ampoule cutter that typically accompanies the ampoule of iloprost and connector joining the

oxygen tube (Fig. 3c and d). This sealing reliably reduced the duration required for inhalation from 8.3 ± 3.3 to 3.3 ± 1.3 min (Fig. 4c).

### Hemodynamic changes during nebulization with various regimens

We monitored pulmonary hemodynamics to observe the efficacy of the optimized inhaled iloprost therapy using the Swans-Ganz catheter during 8–9 November (Fig. 5). Continuous monitoring enabled us to analyze six iloprost-induced hemodynamic alterations by dissecting the baseline, during inhalation, and post inhalation (30 min, 1 h, 2 h) separately (Table 1). On the day of monitoring, the average duration of inhalation was 3.8 ± 1.2 min. The procedure of iloprost inhalation resulted in an elevated mPAP (65 ± 11 to 71 ± 7 mmHg, $P = 0.049$) and heart rate (79 ± 11 to 85 ± 8/min, $P = 0.03$) and decreased SpO$_2$ (92 ± 1 to 90 ± 4%, $P = 0.35$) compared with the baseline. This could be due to the laborious effort of inhalation (Table 1). However, a significant improvement in oxygenation (from 92 ± 1% to 99 ± 1% of SpO$_2$ at a peak of 7 ± 2 min after the inhalation) and hemodynamics (mPAP from 65 ± 11 to 43 ± 6 mmHg at 21 ± 7 min, CI from 2.0 ± 0.4 to 4.6 ± 1.2 L/min/m^2 at 36 ± 2 min, heart rate from 79 ± 11 to 60 ± 12/min at 41 ± 21 min) post inhalation significantly relieved his symptoms from WHO-FC IV to II. Unfortunately, we also observed that these improvements returned to baseline within 2 hours after each inhalation (Fig.5a, 5b, 5c, and Table 1). In addition, the cessation of iloprost inhalation during the night worsened his night hemodynamics (mPAP = 74 ± 5 mmHg, CI = 2.2 ± 0.4 L/min/m^2) compared with daytime hemodynamics (mPAP = 56 ± 10 mmHg, CI = 2.7 ± 0.9 L/min/m^2) (Table 1).
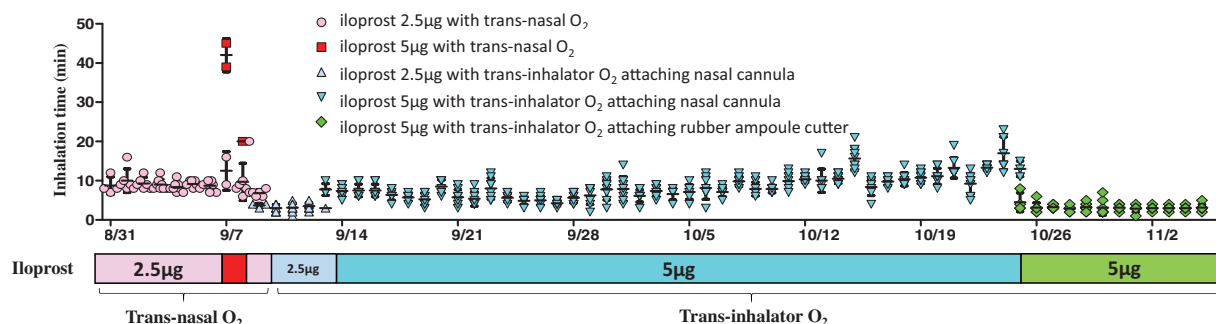

Fig. 2. Optimization of inhaled iloprost with moderate (5 L/min) flow oxygen supply. On 31 August, 2.5 µg of iloprost was introduced by I-neb AAD inhalator under trans-nasal 5 L/min oxygen flow. On 7 September, an increased dose to 5 µg required an intolerable inhalation duration (red square: 20, 38, and 45 min). The patient failed to complete the therapy at a higher dose and resumed 2.5 µg inhalation iloprost therapy. On 9 September, he optimized the system by switching the oxygen supply from the trans-nasal to trans-inhalator O$_2$ via the nasal cannula. This modification shortened the inhalation duration (pink circle to light blue triangle). From 13 September he succeeded completion of the higher dose of 5 µg inhalation iloprost therapy (blue triangle). On 25 October, he shortened the inhalation duration further (green lozenge) by introducing a more stable oxygen supply system via a rubber ampoule cutter.
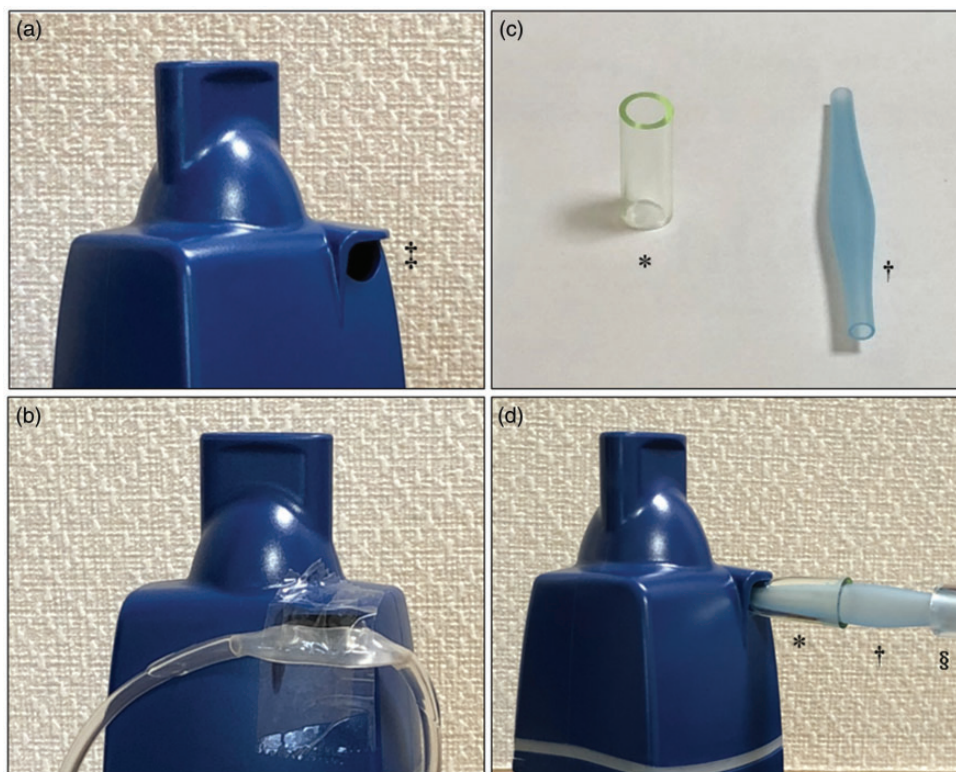
Fig. 3. Optimized trans-inhalator oxygen supply system. The I-neb AAD system has an inlet port for air (a; ‡). As trans-nasal 5 L/min oxygen flow disturbed inspiratory flow from the mouthpiece of I-neb, the patient switched the oxygen supply from trans-nasal to the trans-inhalator by attaching the nasal cannula to the inlet port (b). Furthermore, he optimized the oxygen supply system by inserting a rubber ampoule cutter (c, d; *) into the inlet port and attaching the connector (c, d; †) to the oxygen tube (d; §).
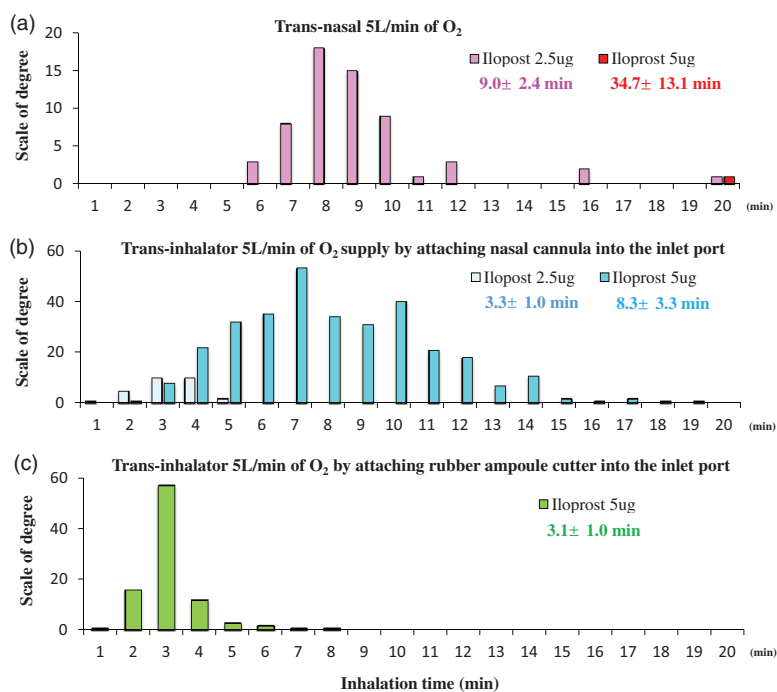
Fig. 4. The distribution of inhalation duration from different oxygen supply systems. Frequency of distribution under trans-nasal 5 L/min of O_2 is shown (a). The average inhalation duration was 9.0 ± 2.4 min for 2.5 µg of iloprost and 34.7 ± 13.1 min for 5 µg of iloprost. By the first optimization of attaching the nasal cannula to the inlet port, the average inhalation duration shortened to 3.3 ± 1.0 min for 2.5 µg of iloprost and 8.3 ± 3.3 min for 5 µg of iloprost (b). After the second optimization using the rubber ampoule cutter, the average inhalation duration was further reduced to 3.1 ± 1.0 min for 5 µg of iloprost (c).
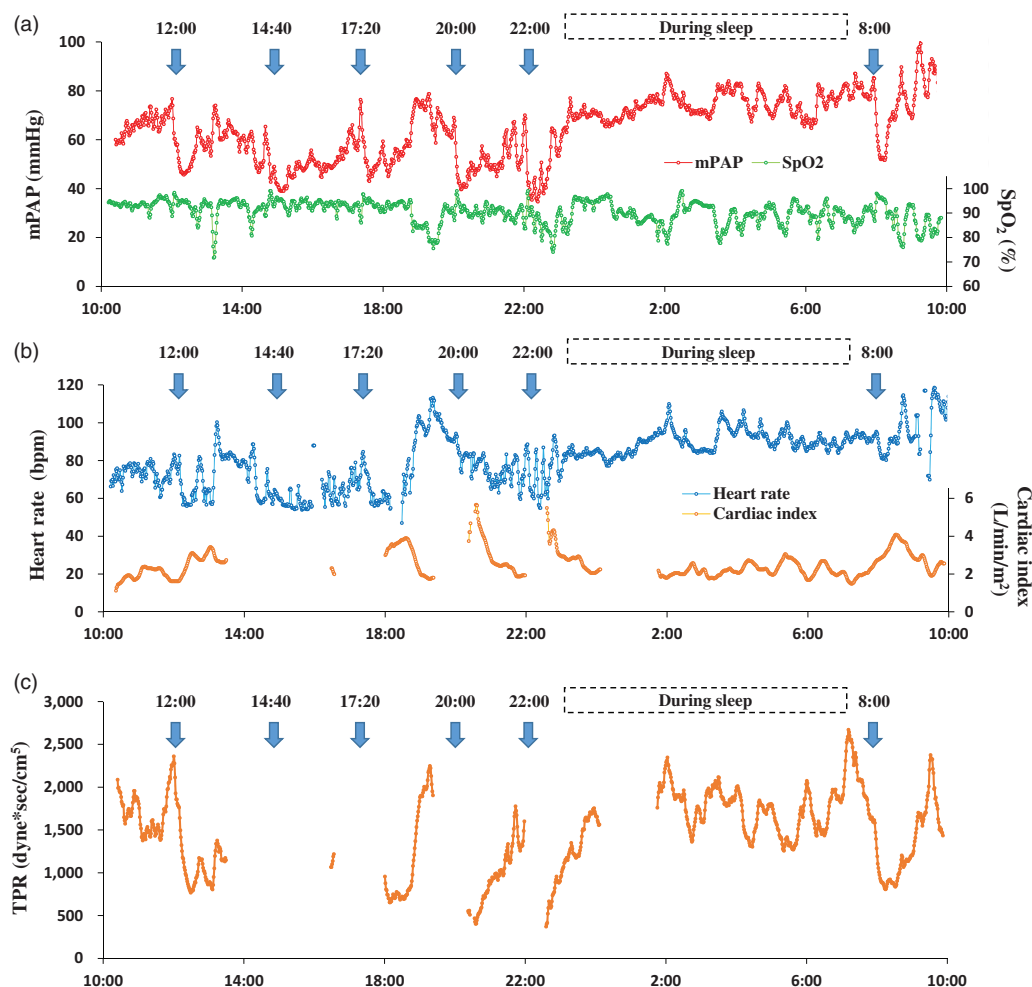
Fig. 5. Continuous Swan–Ganz monitoring under inhalation iloprost with the optimized trans-inhalator oxygen supply. Iloprost inhalation (a–c; ⇩) immediately improves mPAP without worsening hypoxemia (a). Moreover, a decreased heart rate and increased CI (b) after inhalation suggests substantial improvement in right ventricular afterload (c). However, the duration of action lasts < 2 hours and does not cover during sleep. mPAP, mean pulmonary arterial pressure; SpO_2, peripheral saturation of oxygen; CI, cardiac index. TPR. total pulmonary resistance

Table 1. Hemodynamic effects of iloprost inhalation on the case (n = 1).

	Baseline	During inhalation (3.8 ± 1.2 min)	30 min	1 h	2 h	Maximum effect	Time to maximum effect (min)	Average of day time	Average of night time
mPAP (mmHg)	65 ± 11	71 ± 7*	50 ± 10†	56 ± 8*	64 ± 11	43 ± 6‡	21 ± 7	56 ± 10	74 ± 5§
SpO_2 (%)	92 ± 1	90 ± 4	91 ± 3	93 ± 2	90 ± 6	99 ± 1‡	7 ± 2 in	91 ± 4	90 ± 4§
Heart rate (/min)	79 ± 11	85 ± 8*	70 ± 15*	67 ± 13*	85 ± 20	60 ± 12‡	41 ± 21	73 ± 13	90 ± 6§
CI (L/min/m^2)	2.0 ± 0.4	2.1 ± 0.5	4.0 ± 1.1*	3.2 ± 0.3*	2.1 ± 0.3	4.6 ± 1.2*	36 ± 2	2.7 ± 0.9	2.2 ± 0.4§
TPR (dyne*s/cm^5)	1783 ± 379	1798 ± 430	699 ± 250*	915 ± 155*	1672 ± 349	593 ± 239†	32 ± 9	1237 ± 477	1724 ± 315§

The values are averaged over the real-time continuous Swan–Ganz catheter data after inhaling iloprost six times on the monitoring day and are presented as the mean ± standard deviation.
*$P < 0.05$ vs. baseline.
†$P < 0.01$ vs. baseline.
‡$P < 0.001$ vs. baseline.
§$P < 0.001$ vs. average of daytime.
mPAP, mean pulmonary arterial pressure; SpO_2, peripheral saturation of oxygen; CI, cardiac index; TPR, total pulmonary resistance.

Discussion

Poor prognosis of IPAH with severely reduced DLco

Van der Bruggen et al. reported a retrospective analysis[7] that IPAH with severely reduced DLco shows a similar response to PH-specific vasodilatory therapy on the hemodynamics and exercise capacity with IPAH preserved DLco during two years of follow-up. However, at the same time, they also reported lower survival rates in IPAH with severely reduced DLco than the patients with preserved DLco in the latter years . The reasons for the discrepancy between the similar hemodynamic improvement and the survival differences are not well discussed and are still unclear. We speculated that severe hypoxemia might trigger the recurrent of PH worsening by pulmonary arterial vasospasm. In fact, we also observed a short-term improvement on hemodynamics and symptoms (data were not shown) after each initiation of sequential combination therapies, but which did not last > 6 months.

Difficulty of iloprost inhalation in severe PH patients

Drug delivery by inhalation has benefits over oral administration with respect to direct delivery to the target organ, lower doses, less systemic effects, and theoretically less VQ mismatch.[8] However, there have been several cases of patients with severe PH who were unable to undergo inhalation iloprost due to difficulties encountered. The I-neb AAD system is equipped with an efficient delivery system that can synchronize with the patient's respiratory pattern. I-neb monitors the first three tidal volumes to register the respiratory pattern. From the fourth inhalation, the inhalator releases misted iloprost only during the anterior half of the inspiration phase in order to avoid drug deprivation during the expiration phase. Although the provider recommends deep breaths for fast completion of the procedure, the I-neb AAD system is not suitable for patients with resting dyspnea, as they require intolerably long inhalation durations due to the small tidal volume. Even if the patients are able to maintain their vital capacity, some cases still require a long inhalation duration under moderate or high flow (≥ 5 L/min) oxygen therapy based on our experienced cases. Given that the source of inspiration flow into the lung is mainly trans-oral but shared trans-nasally, a moderate or high flow from the nasal cannula reduces the volume via trans-oral inspiration. In the data sheet[5] provided from the company, the average inhalation duration required is 3.2 min for 2.5 µg and 6.5 min for 5 µg of iloprost. Our patient required 45 min for 5µg of iloprost, which was too long for the patient to complete the therapy.

This case was our first patient for whom we applied the inhaled therapy because iloprost has only been approved in Japan since April 2016. We struggled to make the patient continue the inhaled therapy due to severe hypoxemia during the inhalation; we tried the ABC recommendation (hold I-neb at the proper Angles, Breathe in a slow and steady manner, Clean I-neb system every day) from the company,[9] but this did not reduce his inhalation time. The dosing option of using higher concentrations (20 µg/mL)[9] was recently reported to shorten the inhalation time and improve inhalation behavior.[10] The newly developed and approved BREELIB inhalator[11] for rapid iloprost inhalation (inhalation time < 5 min) should also be indicated in this case. However, both the dosing option and the new inhalator were not available in Japan. Besides, no other effective solutions were available from previous studies for this case. We discussed the trial approach of changing oxygen supply from trans-nasal to trans-mouthpiece with the patient. He agreed to try this optimization.

Beneficial aspects of optimized oxygen supply system

We changed the oxygen supply from trans-nasal to trans-inhalator oxygen by attaching the nasal cannula into the inlet port, thereby shortening the required inhalation duration. This optimization was intended to reduce trans-nasal inflow and increase the trans-mouthpiece inspiratory tidal volume. From lung functional tests, the tidal volume of the patient was 0.81 L and respiratory rate was 16/min, resulting in a 1-min ventilation of 12.8 L/min. Oxygen flow of 5 L/min from the nasal cannula was sufficient to reduce the trans-mouthpiece inspiratory volume. Although the cessation of oxygen via the nasal cannula during the inhalation might be an option to continue iloprost inhalation, the patient's SpO_2 decreased from 91% to 72% during the inhalation without oxygen and led to worsening dyspnea. As such, we were unable to opt for oxygen cessation for this patient.

Moreover, the tight seal provided by the rubber ampoule cutter as a second mode of optimization may further shorten the inhalation duration by increasing inspiratory resistance. Nikander et al.[12] compared two different breathing modes: the Tidal Breathing Mode (TBM), equipped with a bidirectional valve for respiration, versus the Target Inhalation Mode (TIM), equipped with a one-way valve for expiration only on the I-neb AAD system. They observed that the TIM valve restricted inhalation flow and prolonged tidal inspiratory time compared with TBM. TIM resulted in a tidal respiration that was slow and deep, significantly reducing the total treatment time (3.0 min by TIM versus 4.7 min by TBM). In our case study, the tight seal on the inlet port might have increased inspiratory resistance and prolonged tidal inspiratory time, thereby lengthening the iloprost release duration and reducing the total inhalation duration, which should have the merit of minimizing hemodynamic worsening (Table 1) and reducing the laborious efforts for the patients.

We further applied this optimization on three more patients with PH. The optimization worked well on two PH patients (combined pulmonary fibrosis and emphysema with 105% of %VC, cystic lung with 70.2% of %VC), but was not effective on one patient (destroyed lung by recurrent

pneumonia with 30.6% of %VC). The best indication of our optimization should be identified in further case experiences.

Acute hemodynamic response after iloprost inhalation

The data of acute hemodynamic response after iloprost inhalation were very limited and had a certain degree of variation.[4,13–15] The IBUKI study[4] (n = 27) reported the maximum effect on PVR was observed 5 min after the initiation of the inhalation. Similarly, Richter et al.[13] also reported 5 min from the end of inhalation with 5.0 µg iloprost (n = 12 of IPAH) as the maximum effect. However, they also reported the maximum effect of 2.5 µg iloprost was observed at 30 min (n = 8 of IPAH), which is similar with our data (Table 1). Besides, the maximum effect on mPAP was reported differently at 8[14] to 30[4,15] min. The maximum effect of 5 µg iloprost in our case on mPAP was observed at 21 ± 7 min after the initiation of inhalation, which was in the range of the peak timings from the previous reports.[4,14,15] The different peak timings among the reports might have several reasons: the different monitoring methods and intervals, limited sample number on the case report,[15] the different definition of 0 min (from initiation or finish of the inhalation), and different severity of PAH affects the results. In spite of the reported peak variance, we believe that we recorded the true peak by using continuous real-time monitoring with the Swan-Ganz catheter from our case.

Furthermore, we monitored a tremendous improvement of total pulmonary resistance (TPR) from 1783 ± 379 dyne*s/cm^5 to 593 ± 239 dyne*s/cm^5 at 32 ± 9 min after the initiation of inhalation (Table 1), which was a much stronger hemodynamic effect than those observed in the previous reports (124 dyne*s/cm^5 decrease from baseline 602 ± 269 dyne*s/cm^5 of PVR in the IBUKI study,[4] $12.7 \sim 16.5\%$ reduction from baseline $1032 \sim 1189$ dyne*s/cm^5 of PVR in Richter's study[13]). Although we do not know the effect of our optimization on drug stability, the drug delivery should be also affected by the patient's procedure and their respiratory status. This time, we could clinically observe non-inferiority of our optimization towards pulmonary hemodynamics. We speculated that the short and load-reduced inhalation would work in a favorable way as shown in the previous study.[11] Furthermore, we assume that the attempt to adjust hypoxemia by employing all available means in addition to short inhalation should be considered in the similar cases.

Limitations of inhaled iloprost efficacy

From our observations, the maximum effect on mPAP and CI was at 21 ± 7 min and 36 ± 2 min after the initiation of inhalation, respectively, which was not inferior to the potential from the provided data sheet.[5] However, the short duration of action is the most problematic feature of this drug. The hemodynamical improvements were completely abolished within 2 h after the therapy. Also, the clinical significance of fluctuating pulmonary hemodynamics in the daytime and nocturnally predominant PH under inhaled iloprost therapy was not investigated. This is an issue that needs to be solved by the new pulmonary vasodilator with a longer duration of action.

Special warning for our optimization

This time, we presented an unapproved modification of a medical device. Unfortunately, there is currently no supportive evidence to justify our optimization regarding the drug stability. Besides, according to the product sheet,[5] the benefit of iloprost has not been proofed in patients with concomitant COPD. Our optimization contained the challenging aspects which were not guaranteed by a randomized controlled trial. Although the attempt to clear up the concerns relating to the drug efficacy and side effects under our optimization should be executed, we observed an obvious advantage on inhaled procedure and non-inferior efficacy on pulmonary hemodynamics. We also monitored no apparent exacerbating side effects such as hypotension, headache, cough, or bleeding events in this case. We hope more-conceived inhaled optimization will be able to be applied on severer dyspneic patients.

Conclusion

We optimized the procedure of iloprost administration to shorten inhalation duration, which reduced laborious efforts required of patients with severe IPAH. Furthermore, despite its short-acting potential, we observed a dramatic improvement in pulmonary hemodynamics by iloprost. We hope that effortless inhalation with an efficient oxygen supply following our optimization protocol will reduce the burden of inhalation and that this therapy will be suitable for patients with severe PAH.

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