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Vasoreactivity test using inhaled nitric oxide for pulmonary arterial hypertension accompanied by severe interstitial lung disease attributed to systemic sclerosis: a case report

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Abstract

A 70-year-old man with severe interstitial pneumonia attributed to limited cutaneous systemic sclerosis was referred to our institution because of worsening dyspnea. High-resolution computed tomography did not show considerable progression compared with previous images, whereas transthoracic echocardiography showed severe right ventricular dysfunction. Oxygen saturation was decreased to 84% at room air. A blood test showed an increase in the plasma brain natriuretic peptide level (289.4 pg/mL). Right heart catheterization (RHC) showed a remarkably high mean pulmonary arterial pressure (mPAP) of 48 mmHg at room air. A vasoreactivity test using inhaled nitric oxide showed improvement of mPAP, pulmonary vascular resistance (PVR), and partial pressure of arterial oxygen. These findings suggested that the patient responded to pulmonary hypertension (PH)-targeted drugs. We then prescribed tadalafil 10 mg and inhaled iloprost 5 μg six times daily. Three weeks after initiating PH-targeted drugs, RHC indicated hemodynamic improvement similar to hemodynamic changes in the vasoreactivity test (mPAP: 28 mmHg; PVR: 4.2 W.U.). He was discharged with improved symptoms. Inhaled nitric oxide during RHC might be helpful to consider the treatment strategy when they have PH comorbid with systemic sclerosis and severe interstitial lung disease.

Learning objective

In patients with pulmonary hypertension (PH) attributed to systemic sclerosis and interstitial lung disease, determining the indication of vasodilatory therapies for PH is clinically difficult. A vasoreactivity test using inhaled nitric oxide during right heart

catheterization might be useful for identifying patients who will respond to PH-targeted therapy.

Introduction

Pulmonary arterial hypertension (PAH) attributed to systemic sclerosis (SSc-PH) is classified as Group 1 pulmonary hypertension. Patients with SSc-PH are sometimes accompanied by other etiologies of PH, including interstitial lung disease (ILD), pulmonary veno-occlusive disease, and left ventricular dysfunction [1,2].

In patients with SSc-PH, ILD is an important comorbidity considering the indication of vasodilation therapy [1]. Vasodilation of PH-targeted therapy is sometimes exacerbated by hypoxia owing to increasing ventilation/perfusion (V/Q) mismatch in patients with severe ILD [1]. Additionally, PH-targeted therapies sometimes induce severe pulmonary congestion in patients with veno-occlusive lesions [3]. These comorbidities make clinical management of patients with SSc-PH more difficult.

Treatment of patients with SSc-PH accompanied by severe ILD should be administered with more caution than those with other types of PH. Little is known about clinical tests for estimating the safety and efficacy of PH-targeted therapies for these patients [1,4]. This is a case suggesting the usefulness of vasoreactivity test using inhaled nitric oxide for patients with SSc-PH accompanied by severe ILD.

Case report

A 70-year-old man, who was diagnosed with interstitial pneumonia (IP) attributed to

limited cutaneous SSc, presented to our institution because of worsening dyspnea at rest (WHO functional class IV). He received oxygen inhalation therapy owing to IP, but he did not have any history of cardiovascular disease. Blood pressure was 90/61 mmHg and heart rate was 111 bpm at a regular rhythm. The respiratory rate was 18 breaths/min and the oxygen saturation was decreased to 84% at room air. The 6-min walking test was not able to be performed because of severe dyspnea at rest and decreased physical ability. He had sclerodactyly, jugular vein distention, and pitting edema in both legs. A blood test showed a remarkable increase in the plasma brain natriuretic peptide level (289.4 pg/mL) and positive serum anti-nuclear antibody (×640, Centromere). Serum anti-topoisomerase I, anti-Sm, anti-U1 ribonucleoprotein, and anti-Jo-1 antibodies were negative. A chest X-ray showed poor permeability of interstitial patterns **(Figure 1A)**. An electrocardiogram showed sinus rhythm and a negative T wave in I, aVL, and V4–6 leads **(Figure 1B)**. Transthoracic echocardiography showed mild tricuspid regurgitation with a high pressure gradient (68 mmHg), right atrial and ventricular dilation, and oppressed left ventricle by a dilated right ventricle (RV) **(Figure 1C, D)**. High-resolution computed tomography (HR-CT) showed severe bilateral fibrotic changes, but these changes had not progressed compared with the previous examination **(Figure 1E, F)**. Right heart catheterization (RHC) showed a remarkable increase in mean pulmonary arterial pressure (mPAP) of 48 mmHg and a pulmonary vascular resistance (PVR) of 9.0 Wood units (W.U.) at room air **(Table 1)**. A vasoreactivity test using an inhaled nitric oxide (iNO) dose of 20 ppm with an oxygen mask at 2 L/min for 10 minutes of administration showed that the mPAP, PVR, and partial pressure of arterial oxygen (PaO_2) were improved to 27 mmHg, 5.3 W.U., and 129 Torr, respectively **(Table 1)**. These findings indicated the effectiveness of the combination of oxygen and iNO,

which suggested that the patient might have responded to vasodilation of PH therapy in the condition of oxygenation. Therefore, we decided to prescribe tadalafil 10 mg and inhaled iloprost 5 μg six times daily. After 3 weeks from initiating vasodilation therapy, RHC showed hemodynamic improvement using iloprost and oxygenation (mPAP: 28 mmHg and PVR: 4.2 W.U., immediately after inhalation of iloprost 5μg) **(Table 2)**. His plasma brain natriuretic peptide level was decreased to 183.7 pg/mL at discharge. He was successfully discharged with improved symptoms. He had physical therapy without severe oxygen desaturation after discharge. Unfortunately, after 3 months, he suddenly died of refractory pneumothorax, which might have been induced by severely progressed ILD.

Discussion

PAH is a common comorbidity in patients with SSc and its prevalence is between 7% and 12% [1]. Although PAH is recognized as an important prognostic comorbidity of patients with SSc, other comorbidities, such as ILD and pulmonary veno-occlusive disease, make clinical treatment of SSc-PH more difficult [1,3]. A clinical test that can identify patients who respond to PH-targeted therapy in those with SSc-PH needs to be established.

A vasoreactivity test is useful for isolating responders of a calcium channel blocker in patients with idiopathic and heritable pulmonary hypertension [1]. Some protocols of vasoreactivity tests have been reported, but the utility of these examination in patients with SSc-PH comorbid with severe ILD have not been validated [1]. Intravenous epoprostenol or adenosine as alternative agents of iNO can be used in vasoreactivity

tests for patients with idiopathic and heritable pulmonary hypertension. However, these protocols have some problems in patients with SSc-PH comorbid with ILD concerning lung edema, hypotension, and hypoxia from an increased V/Q mismatch induced by the test drugs. Plazak et al reported that vasoreactivity of iNO was observed only in patients with limited cutaneous SSc (5/14 patients with SSc were reactive to iNO), but not diffuse cutaneous SSc. Therefore, a vasoreactivity test should be considered, especially in patients with limited cutaneous SSc [4]. Although a few patients in whom pulmonary congestion was provoked by iNO have been reported, iNO might be a safer agent for patients with severe ILD compared with intravenous agents [5]. This is because iNO has a shorter half-life of 3 to 6 seconds with a lower incidence of side effects in vasoreactivity tests than other agents.

The reactivity of iNO probably reflects the residual activity of the NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate pathway, which is one of the mechanisms of vasodilation in the pulmonary artery *in vivo*. This concept suggests potential utility of phosphodiesterase type 5 inhibitors and a stimulator of sGC for PH-targeted drugs for patients who show positive results for iNO [1]. The PATENT 1 and PATENT 2 trials showed the efficacy of riociguat (as a stimulator of sGC) in patients with SSc-PH, but there was no information on whether these clinical trials included patients with severe ILD [6]. The RISE-IIP trial, which was a randomized, controlled trial that assessed the efficacy of riociguat in patients with PH attributed to IP, reported a worse prognosis in the riociguat group compared with the placebo group [7]. Additionally, there is concern about a stimulator of sGC having a pharmacological vasodilatory effect without the presence of nitric oxide, resulting in severe hypoxia due to an increased V/Q mismatch. In patients with idiopathic pulmonary fibrosis, sildenafil

(a phosphodiesterase type 5 inhibitor) does not have the clinical effect for improving exercise capacity. However, sildenafil is effective in improving patients' symptoms with few severe adverse events [8]. These clinical trials suggest that the efficacy of oral agents of PH therapy is good in a limited patient population. Additionally, we should use these oral agents more carefully by screening responders in patients with SSc-PH accompanied by severe ILD.

In patients with PH comorbid with severe ILD, the administration route of PH-targeted drugs is an important issue. The results of a vasoreactivity test using iNO suggested the safety and efficacy of inhaled PH therapy in the present case. Inhaled iloprost improves exercise capacity in patients with PAH, whereas the safety and efficacy for patients with severe ILD have not been established [9]. Additionally, the half-life of inhaled iloprost *in vivo* is short. Therefore, the long-term prognosis of patients using inhaled iloprost has not been established [9]. In the present case, the solitary effect of iloprost was not validated because the improved hemodynamics shown by RHC were observed after iloprost and oxygenation. However, his symptoms at rest and during physical therapy were improved with oxygenation, which was already used because of IP. The long-term clinical effects were unclear because of the patient's unfortunate death from pneumothorax. Inhaled treprostinil has a clinical effect on improvement of exercise capacity and preventing clinical worsening in patients with ILD [10]. These investigations suggest that treprostinil should be prioritized as inhaled therapy for patients with SSc-PH accompanied by severe ILD. However, inhaled treprostinil has not been approved in Japan to date.

At present, there is little evidence of use of vasoreactivity tests for patients with SSc-PH comorbid with severe ILD. A vasoreactivity test using iNO would be useful to

consider the treatment strategy in this patient population. Further large studies on this issue are required.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1. Right heart catheterization, vasoreactivity test of an inhaled nitric oxide dose of 20 ppm, and partial pressure of arterial oxygen at baseline.

Right heart catheterization (Pre-treatment)			
	Room air	O_2 2L mask	O_2 2L mask NO 20ppm
PAWP (mmHg)	11	6	7
PAP (mmHg)	73/31/48	66/31/44	46/18/27
RVP (mmHg)	61/1	51/5	44/3
RAP (mmHg)	4	3	2
CO (L/min)	4.09	3.63	3.75
CI (L/min/ $m^{2)}$	2.69	2.29	2.37
PVR (W.U.)	9.0	10.5	5.3
ABG	pH 7.445 pCO_2 45.1 Torr pO_2 50 Torr BE 6.1 mEq/L HCO^{3-} 30.5 mEq/L	pH 7.435 pCO_2 44.3 Torr pO_2 97 Torr BE 4.9 mEq/L HCO^{3-} 29.3 mEq/L	pH 7.424 pCO_2 46.1 Torr pO_2 129 Torr BE 5.0 mEq/L HCO^{3-} 29.7 mEq/L

PAWP = pulmonary arterial wedge pressure; PAP = pulmonary arterial pressure; RVP = right ventricular pressure; RAP = right atrial pressure; CO = cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance; W.U. = wood units; ABG = arterial blood gas. CO was measured by thermodilution methods. Evaluation of each phase was performed after 10 minutes of administration of oxygenation only and oxygenation and NO 20 ppm.

Table 2. Right heart catheterization after treatment of tadalafil 10 mg and inhaled iloprost 5 μg.

Right heart catheterization (Post-PH therapy)			
	Room air Tadalafil 10mg	O_2 2L mask Tadalafil 10mg	O_2 2L mask Tadalafil 10mg Inhaled iloprost 5μg
PAWP (mmHg)	12	16	9
PA (mmHg)	67/27/42	70/30/44	42/20/28
RV (mmHg)	71/15	61/12	41/3
RA (mmHg)	8	4	3
CO (L/min)	4.13	5.35	4.55
CI (L/min/ $m^{2)}$	2.72	3.52	2.99
PVR (W.U.)	7.3	5.2	4.2
ABG	pH 7.465 pCO_2 39.7 Torr pO_2 44 Torr BE 4.5 mEq/L HCO^{3-} 28.2 mEq/L	pH 7.445 pCO_2 41.2 Torr pO_2 66 Torr BE 4.0 mEq/L HCO^{3-} 27.9 mEq/L	pH 7.420 pCO_2 44.1 Torr pO_2 92 Torr BE 3.7 mEq/L HCO^{3-} 28.1 mEq/L

Tadalafil improved hemodynamic parameters compared with baseline, although the partial pressure of arterial oxygen (PaO_2) was slightly decreased at room air. Similar to the vasoreactivity test, PaO_2 was improved in accordance with hemodynamic improvement by inhalation of iloprost. Evaluation using an O_2 mask at 2L/min was performed after 10 minutes of oxygenation. Additionally, evaluation during oxygenation

and inhaled iloprost 5 μg was immediately performed after inhalation of iloprost, which might indicate peak data.

PH = pulmonary hypertension; PAWP = pulmonary arterial wedge pressure; PAP = pulmonary arterial pressure; RVP = right ventricular pressure; RAP = right atrial pressure; CO = cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance; W.U. = wood units; ABG = arterial blood gas. CO was measured by thermodilution methods.

Figure legends

Figure 1: **(A)** Chest X-ray on admission. **(B)** Electrocardiogram on admission. **(C, D)** Transthoracic echocardiogram shows considerable right atrial and ventricular dilation and oppressed left ventricle by the dilated right ventricle (C: Parasternal short axis view, D: Apical four-chamber view). **(E, F)** High-resolution computed tomography (HR-CT) shows severe bilateral fibrotic changes. (E: HR-CT images at admission (1: right upper lobe; 2: right middle and lower lobe; 3: left upper lobe; 4: left lower lobe). F: HR-CT images 3 months before admission. (1: right upper lobe; 2: right middle and lower lobe; 3: left upper lobe; 4: left lower lobe).

Figure 1