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【 CASE REPORT 】

Exercise-induced Right-to-left Shunt in a Patient with Combined Pulmonary Fibrosis and Emphysema

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Abstract:
Combined pulmonary fibrosis and emphysema (CPFE) is characterized by emphysematous lesions in the upper lung field and pulmonary fibrosis in the lower lung field and is often associated with pulmonary hypertension and severe exercise-induced hypoxemia (EIH). We herein report a 62-year-old man with CPFE who presented with severe EIH despite relatively preserved lung volumes. Cardiopulmonary exercise testing suggested exercise-induced right-to-left shunt (EIS) through a patent foramen ovale (PFO). EIS was attributed to exercise-induced pulmonary hypertension. In this case report, we highlight the possibility of EIS using PFO for CPFE. We also discuss potential treatments including pharmaceutical interventions and PFO closures.

Key words: combined pulmonary fibrosis and emphysema (CPFE), exercise-induced right-to-left shunt (EIS), patent foramen ovale (PFO), exercise-induced hypoxemia (EIH), exercise-induced pulmonary hypertension

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Introduction

Combined pulmonary fibrosis and emphysema (CPFE) was first described in 1990 (1) and subsequently recognized as a syndrome (2, 3). CPFE is diagnosed through chest imaging and manifests as the coexistence of emphysematous lesions in the upper lung field and pulmonary fibrosis in the lower lung field. CPFE is frequently associated with pulmonary hypertension and lung cancer (3). In terms of clinical and physiological characteristics, CPFE is marked by significant dyspnea and severe exercise-induced hypoxemia (EIH), despite relatively preserved lung volumes (3).

Several research groups have examined the disparity between exacerbated self-reported symptoms or reduced arterial oxygen saturation and maintained lung volume measurements in patients with CPFE. Costa et al. reported that poor ventilatory efficiency, as indicated by an increased carbon dioxide (CO_2) ventilation equivalent and increased dead space to tidal volume ratio, and hyperventilation, as shown by the decreased partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) on cardiopulmonary exercise testing (CPET), are the main determinants of exertional dyspnea in patients with CPFE (4). This study suggests that poor ventilatory efficacy, which may be associated with ventilation-perfusion mismatch, is the cause of severe EIH, and ventilatory-metabolic uncoupling is the cause of severe self-reported symptoms among patients with CPFE compared to patients with COPD alone or pulmonary fibrosis alone. Coexisting pulmonary hypertension might also have an impact on disproportionate exertional dyspnea related to lung volume through a combination of cardiac output impairment and abnormal gas exchange during exercise (5).

Exercise-induced right-to-left shunt (EIS) through the patent foramen ovale (PFO) has been observed in patients with pulmonary arterial hypertension (PAH). EIS among patients with PAH is recognized during CPET using the following criteria: 1) an abrupt and sustained increase in the partial

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pressure of end-tidal oxygen ($P_{ET}O_2$) with a simultaneous sustained decrease in $P_{ET}CO_2$; 2) an abrupt and sustained increase in the respiratory exchange ratio; and 3) an associated decline in oxygen saturation on pulse oximetry, with high sensitivity (90%) and specificity (96%) (6). However, EIS has not yet been reported in patients with CPFE.

CPFE is prone to comorbid pulmonary hypertension (PH), and EIS occurs not only in PAH but also in other forms of PH. We herein report a patient with CPFE in whom EIS was the primary contributor to severe dyspnea on exertion.

Case Report

A 62-year-old man was referred to our hospital following the detection of emphysematous changes on chest radiography. He had never complained of dyspnea at rest; however, he experienced significant dyspnea with moderate exertion, such as cycling on a flat road. He had comorbid hypertension and dyslipidemia and had previously undergone cholecystectomy due to gallstones. He had a smoking history of 60 cigarettes per day from 16 to 42 years old.

Chest computed tomography (CT) revealed emphysematous changes, predominantly in the bilateral upper lobes. In addition, subpleural reticular opacities and traction bronchiectasis were observed, predominantly in the bilateral lower lobes. On pulmonary function testing, the forced vital capacity was 4.72 L (100.7% of predicted value), forced expiratory volume in 1 second was 3.34 L (93.3% of predicted value), forced expiratory volume % in 1 second was 76.43%, and the diffusing capacity of the lung for carbon monoxide was 11.89 mL/min/mmHg (61.9% of predicted value). Echocardiography at rest showed that the tricuspid regurgitation pressure gradient (TRPG) was approximately 30 mmHg, and there was no evidence of PH at rest. The left ventricular ejection fraction was 61%. Trivial mitral and aortic valve regurgitation were noted. All of these findings supported the diagnosis of CPFE (3); however, the degree of patient exertional dyspnea was greater than expected from typical CPFE patients with normal ventilatory volumes, slightly low diffusing capacity of the lung, and no obvious PH.

We performed CPET to investigate the cause of severe exertional dyspnea. We used the Sheffield treadmill protocol, which starts with a slow walk up a slight slope, and the pace and incline were increased every three minutes. Soon after starting the test, percutaneous oxygen saturation (SpO_2) suddenly declined (Fig. 1A, Table). An expired gas analysis during exercise showed a sharp increase in the respiratory exchange ratio at approximately 1 min into the exercise. Simultaneously, $P_{ET}O_2$ increased rapidly and $P_{ET}CO_2$ decreased (Fig. 1A, Table). These findings are consistent with the characteristic features of EIS in CPET (6). Therefore, it was presumed that EIS was present.

To establish a diagnosis of intracardiac EIS, we performed a bubble test. After the intravenous injection of saline, bubbles were visualized in the left atrium during the Valsalva maneuver on transesophageal echocardiography (Fig. 1B). Transesophageal Doppler echocardiography also revealed an intracardiac right-to-left shunt during the Valsalva maneuver (Fig. 1B), which confirmed the presence of a right-to-left shunt due to PFO. Finally, we performed stress echocardiography during exercise, which showed that the TRPG increased from 27 mmHg at rest to 58 mmHg during exercise at 75 W (Fig. 1C). Based on these results, exercise-induced PH was diagnosed, which was determined to be the cause of the patient's exertional dyspnea.

Discussion

To our knowledge, this is the first reported case of CPFE with PFO-mediated EIS. Originally, severe EIH was considered an important limiting factor for exercise, and it has been associated with a poor prognosis among patients with chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (7, 8). However, the contribution of PFO-mediated EIS to severe EIH among these patients has not been clearly established, although PFO-mediated EIS has been reported in patients with COPD, especially those with PH (9). Patients with CPFE frequently develop PH (10); therefore, we believe that the clinical impact of PFO-mediated EIS on severe EIH is greater in CPFE than in COPD or idiopathic pulmonary fibrosis alone. Therefore, PFO-mediated EIS should be considered in cases of severe EIH among patients with CPFE.

In the present case, the characteristic features of CPET included a decrease in SpO_2, an increase in respiratory exchange ratio, an increase in $P_{ET}O_2$, and a decrease in $P_{ET}CO_2$, which suggested the need for further investigation (6). Although these features may be observed in cases of ventilation-perfusion mismatch with hyperventilation, "abrupt" changes in these features strengthen the confidence in the presence of EIS. If CPET is not feasible, the absence of an improvement in EIH even with the administration of large amounts of oxygen suggests the need for further investigation to search for EIS.

Pulmonary vascular pathology in patients with CPFE is diverse (11), and the cause of PH in CPFE is not fully understood. In the present case, we identified an abrupt narrowing of the right pulmonary artery on contrast-enhanced chest CT (Fig. 2A). We also identified a blood flow deficit on lung perfusion scintigraphy (Fig. 2B). Therefore, anticoagulant therapy was initiated with rivaroxaban for chronic thromboembolic PH. However, it had no significant therapeutic effect, suggesting a greater likelihood that the perfusion defect on lung perfusion scintigraphy observed in this patient was due to a decreased vascular bed associated with emphysematous lesions. In previous reports, certain pharmaceutical interventions, such as inhaled nitric oxide, supplemental oxygen, and phosphodiesterase-5 inhibitors, have shown effectiveness in ameliorating PFO-mediated EIS in patients with COPD (9, 12). In particular, inhaled treprostinil has shown promise in patients with group 3 PH

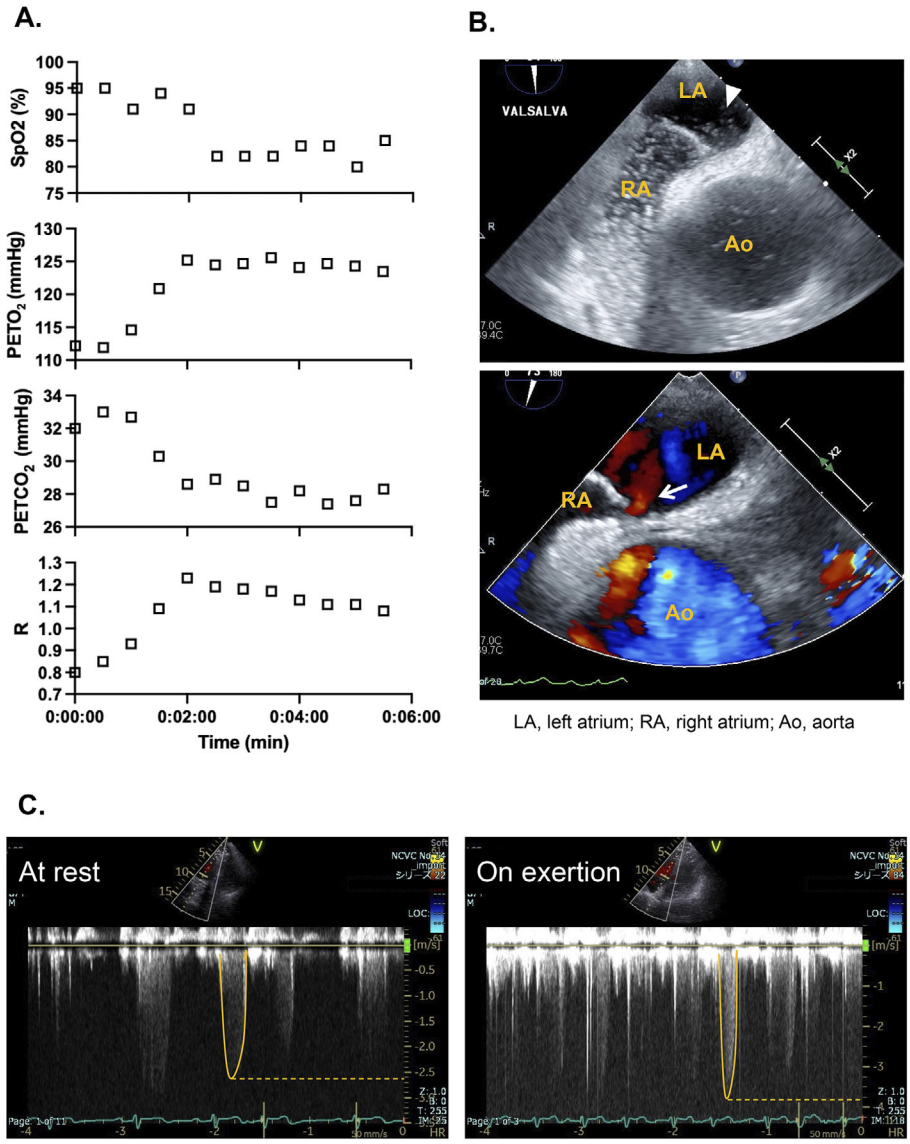

Figure 1. **(A) Temporal changes in SpO_2 (%), $P_{ET}O_2$ (mmHg), $P_{ET}CO_2$ (mmHg), and respiratory exchange ratio. The test was terminated at 5 minutes and 38 seconds due to dyspnea. The Borg rating of perceived exertion scale score was 5 at the time of termination. (B) TEE images obtained during the bubble test (upper). Bubbles filled the RA and were also observed in the LA, suggesting that bubbles produced in the RA flowed into the LA via the PFO. TEE color Doppler images (lower) showing blood flow from the RA into the LA (arrow). At rest, TRV was approximately 2.6 m/s, and TRPG was calculated as 27 mmHg. On exertion, TRV was approximately 3.8 m/s, and TRPG was calculated as 58 mmHg. LA: left atrium, $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide, $P_{ET}O_2$: partial pressure of end-tidal oxygen, PFO: patent foramen ovale, R: respiratory exchange ratio, RA: right atrium, SpO_2: percutaneous oxygen saturation, TEE: transesophageal echocardiography, TRPG: tricuspid regurgitation pressure gradient, TRV: tricuspid regurgitation velocity, Ao: aorta**

according to the World Health Organization classification (13). Thus, these agents were potential candidates for pharmaceutical treatment of the patient in the present case.

PFO closure is another treatment option for this patient to ameliorate symptoms and reduce the risk of mortality in the event of a potential acute exacerbation of pulmonary fibrosis (14), although Japanese health insurance coverage for PFO closure is limited to the secondary prevention of stroke. However, PFO-mediated EIS may be necessary to relieve the excessive pulmonary arterial pressure during exercise. In a large retrospective study, PFO closure was performed in a group of patients with chronic lung disease without improvement in the New York Heart Association functional class or hypoxemia (15). As pulmonary arterial vasculopathy may progress prior to the clinical detection of PH in CPFE (11), PFO closure must be carefully performed with a hemodynamic assessment by temporarily closing the PFO before permanently closing it (16). However, performing an exercise stress test while temporarily closing the PFO under catheter insertion from the lower limbs is challenging

Table. **Exercise data.**

Time min:s	HR /min	f /min	V'_E L/min	V'_{CO2} mL/min	V'_{O2} mL/min	V_E/V'_{CO2} mL/mL	V_E/V'_{O2} mL/mL	R	SpO_2 %	$P_{ET}CO_2$ mmHg	$P_{ET}O_2$ mmHg	V_D/V_T
0:00	95	23.2	13.7	252	314	54.5	43.6	0.8	95	32	112.2	0.41
0:30	116	24.9	28.6	669	787	42.8	36.3	0.85	95	33	111.9	0.35
1:00	125	30	42.9	1,004	1,082	42.7	39.6	0.93	91	32.7	114.6	0.35
1:30	143	36.2	70	1,537	1,408	45.5	49.7	1.09	94	30.3	120.9	0.35
2:00	152	39.8	82.8	1,710	1,391	48.4	59.5	1.23	91	28.6	125.2	0.35
2:30	154	40.7	81.3	1,635	1,378	49.7	59	1.19	82	28.9	124.5	0.37
3:00	153	42.4	82.4	1,646	1,400	50	58.9	1.18	82	28.5	124.7	0.37
3:30	151	42.3	85.9	1,644	1,405	52.3	61.1	1.17	82	27.5	125.6	0.37
4:00	151	40.2	76.9	1,503	1,333	51.2	57.7	1.13	84	28.2	124.1	0.37
4:30	154	43.2	82.2	1,552	1,398	53	58.8	1.11	84	27.4	124.7	0.38
5:00	154	41.2	81.1	1,561	1,406	51.9	57.7	1.11	80	27.6	124.3	0.37
5:30	160	39.9	79.9	1,576	1,459	50.7	54.8	1.08	85	28.3	123.5	0.37

f: respiratory rate, HR: heart rate, $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide, $P_{ET}O_2$: partial pressure of end-tidal oxygen, R: respiratory exchange ratio, SpO_2: percutaneous oxygen saturation, V'_{CO2}: carbon dioxide production, V_D/V_T: dead space gas volume to tidal volume ratio, V'_E: minute ventilation, V'_{O2}: oxygen consumption

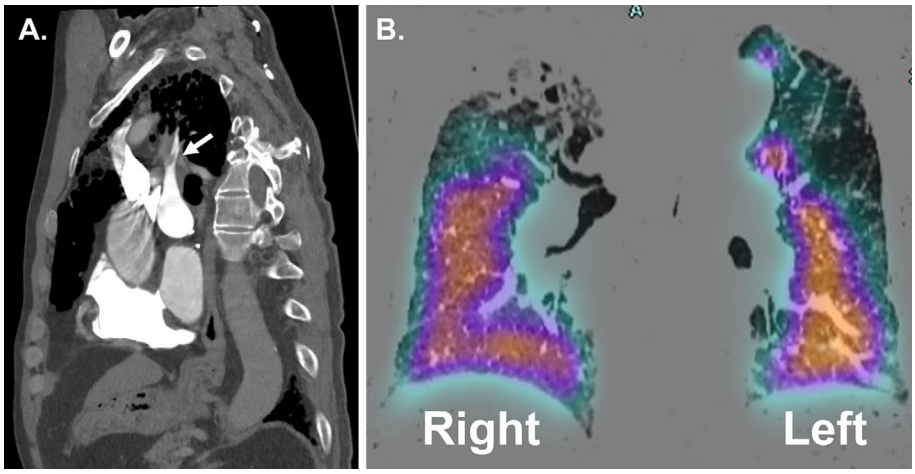

Figure 2. **(A) Re-constructed chest contrast enhanced CT shows abrupt narrowing of the right A_1 pulmonary artery (arrow). (B) Lung perfusion scintigraphy was performed. The orange area indicates abundant pulmonary blood flow, while the light blue area signifies poor pulmonary blood flow. Unhighlighted areas indicate interruption of pulmonary blood flow. In this patient, the pulmonary blood flow was notably reduced, particularly at the apex of the right lung and at the upper and lateral areas of the left lung. CT: computed tomography**

and risky. In our case, the patient chose not to take this risk, considering the uncertain benefits of PFO closure.

Subsequently, the patient was hospitalized because of acute exacerbation of pulmonary fibrosis. After recovering from the acute exacerbation with steroid pulse therapy, the patient's exertional dyspnea worsened, requiring 4 L/min of oxygen via a nasal cannula during exertion. If the eligibility criteria are met, lung transplantation with PFO closure should be considered (17, 18).

The present case study had limited generalizability. Additional research is essential to investigate the involvement of PFO-mediated EIS in severe EIH in CPFE patients.

The authors state that they have no Conflict of Interest (COI).

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