

# **Pulmonary hemodynamics in patients with severe COPD**

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## **Abstract**

Worsening gas exchange during exercise and exacerbation in COPD contributes to systemic hypoxemia and restricts the quality of life. However, pulmonary hemodynamics under such conditions are not well understood. We performed right heart catheterization in six patients with severe COPD ( $\%FEV_1 < 50\%$ ) during rest, exercise and exacerbation. Pulmonary artery pressure (Ppa) was a little elevated at rest. The Ppa, as pulmonary artery wedge pressure (Pawp) and cardiac index were significantly increased during bicycle ergometer exercise. In contrast, pulmonary vascular resistance significantly increased during exacerbation accompanied by a slightly increased Ppa. Supplemental oxygen resulted in significant decreases in Ppa and Pawp during exercise and Ppa during exacerbation. These findings suggested that the pathological pulmonary hemodynamics are characterized by significant pulmonary hypertension due to dynamic hyperinflation during exercise and a prominent vasoconstrictive reaction under exacerbation. The principal pathophysiology of the pulmonary circulation between exercise and exacerbation might differ in severe COPD. Supplemental oxygen is beneficial in these situations as reflected by improved pathological pulmonary hypertension.

**Key words:** COPD, exacerbation, exercise, oxygen, right heart catheterization

**Short title:** Pulmonary hemodynamics in COPD

## **INTRODUCTION**

Pulmonary hypertension (PH) is a crucial cardiovascular complication of chronic obstructive pulmonary disease (COPD), and it might be associated with a poor prognosis.<sup>1</sup> It progresses rather slowly during the course of COPD, and usually develops at the advanced stage.<sup>2</sup> Although PH has been demonstrated during exercise in patients with COPD,<sup>3,4</sup> pulmonary hemodynamics at exacerbation are not well understood. Patients with advanced COPD under both exercise and exacerbation conditions develop equally severe hypoxemia resulting in restricted activities and a diminished quality of life. To investigate the pathophysiology of pulmonary circulation in severe COPD, we performed right heart catheterization in six patients with COPD and analyzed the hemodynamic parameters at rest, during exercise and under exacerbation. We also evaluated the effects of supplemental oxygen on these three conditions.

## **CASE REPORT**

### **Patients**

Pulmonary hemodynamic examinations were performed in 1 female and 5 male patients with COPD (average age, 74 y; Table 1). The overall clinical phenotype was classified as pulmonary emphysema. The ratio (%) of predicted forced expiratory volume in one

second (%FEV<sub>1</sub>) at stable status ranged from 17.0% to 48.6% (average, 31.8%). Therefore, the severity of COPD in all of the patients was assessed as stage III (Severe) or stage IV (Very Severe) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>5</sup> None had systemic hypertension and distinct heart disease under stable conditions.

### **Right heart catheterization**

A 7F Swan-Ganz thermodilution catheter was inserted through the right femoral vein into the pulmonary artery in the supine position. Pulmonary artery pressure (Ppa), pulmonary artery wedge pressure (Pawp) and cardiac output (CO) were measured as described.<sup>6,7</sup> Cardiac index (CI) was calculated as CO divided by body surface area and pulmonary vascular resistance index (PVRI) was calculated as  $[(Ppa - Pawp)/CI] \times 80$ . The institutional ethics committee approved the investigation, and written, informed consent was obtained from each patient to participate in all procedures associated with the study.

### **Exercise**

Stable COPD patients exercised on an electronically braked bicycle ergometer at a constant workload of 25 W. Pulmonary hemodynamics and arterial blood gas tension were measured at rest and 3 minutes after the start of exercise. Pulmonary

hemodynamic parameters were also obtained while breathing 2 L/min of oxygen.

### **Exacerbation**

All patients experienced exacerbation requiring medical intervention. The diagnosis of exacerbation was established according to the criteria of Anthonisen *et al.*<sup>8</sup> At the time of admission to our hospital, we examined both pulmonary hemodynamics and arterial blood gas tension. After treatment with oxygen, antibiotics, bronchodilators and corticosteroids, they were relieved of the exacerbation and returned to stable status.

### **Pulmonary hemodynamics**

We compared results at rest, exercise and exacerbation, as well as before and after providing supplemental oxygen, using the Student's paired *t* test. A *P* value below 0.05 was considered significant.

Table 2 shows the pulmonary hemodynamics. At rest, Ppa was a little elevated with normal Pawp, CI and PVRI. All hemodynamic parameters were significantly increased during exercise accompanied with significantly low PaO<sub>2</sub> and PvO<sub>2</sub>. In contrast, Ppa and Pawp were slightly increased and significantly decreased respectively, under exacerbation. Additionally, PVRI was significantly higher, whereas PaO<sub>2</sub> and PvO<sub>2</sub> were significantly decreased during exacerbation compared with those values at rest.

None of the pulmonary hemodynamic parameters was affected by oxygenation at

rest. The increased Ppa during both exercise and exacerbation was significantly decreased after oxygen inhalation (Fig. 1). Supplemental oxygen also significantly reduced the elevated Pawp during exercise (Fig. 2). However, CI and PVRI did not significantly change after oxygen administration under both conditions.

## **DISCUSSION**

It has been suggested that PH in occidental countries is the major cardiovascular complication in COPD and that it is associated with worsening clinical evolution and a poor prognosis.<sup>9</sup> Pulmonary hypertension usually develops at the latter stage of COPD.<sup>5</sup> Although pulmonary hemodynamics during exercise have been well investigated,<sup>7,10</sup> the present study examined differences in pulmonary hemodynamics during exercise and exacerbation status in patients with severe COPD. All pulmonary hemodynamic parameters were remarkably increased along with deteriorating oxygenation during exercise. The noteworthy finding is that pulmonary vascular resistance was remarkably increased following a slight increase in Ppa under exacerbation.

Exercise induces an abnormal increase in Ppa in COPD even when PH is not apparent at rest.<sup>11</sup> The reported incidence of exercise-induced PH is 76 of 131 patients (58%)<sup>11</sup>, or 31 of 151 patients (21%)<sup>12</sup>. However, all six patients with COPD in this

study developed remarkable PH during exercise, which coincided with the findings of our previous studies.<sup>7,10</sup> The discrepancy in the incidence of exercise-induced PH between our reports and those of others could be explained by our patients having relatively severe COPD.

Several mechanisms of exercise-induced PH have been identified including reactive pulmonary vasoconstriction, destruction/decrease of the pulmonary vascular bed, remodeling in the pulmonary artery, lung mechanic abnormalities and the disrupted production of vasorelaxing factors such as nitric oxide.<sup>9</sup> Among all of the possible mechanisms, hypoxic pulmonary vasoconstriction (HPV) might play an important role in inducing PH during exercise, because exercise-induced PH was improved by supplemental oxygen. The significant decrease of PvO<sub>2</sub> during exercise might enhance HPV resulting in significant PH. Another notable finding is that Pawp was two-fold higher during exercise than that at rest, which corresponded with previous reports.<sup>6,7,13</sup> Severe limitations in airflow might cause dynamic hyperinflation, which in turn induces an increase in alveolar and intrathoracic pressure that finally leads to this phenomenon.<sup>7,14</sup> The alveolar and intrathoracic pressure increases also induce an increase in Ppa. We emphasize that dynamic hyperinflation of the lung is an important factor in the modification of pulmonary hemodynamics during exercise.

The pathophysiology of COPD during exacerbation, especially pulmonary hemodynamics, has not been sufficiently investigated. Our results showed that mild PH considerably increased PVRI during exacerbation accompanied by significant hypoxemia. This may be the first report to precisely describe the pulmonary circulation under exacerbation in patients with severe COPD. The major physiological change during exacerbation is thought to be increased ventilation-perfusion ( $V'_A/Q'$ ) inequality rather than worsening of airflow obstruction.<sup>15,16</sup> Barbera *et al.* found using the inert gas technique in 13 COPD exacerbations that a  $V'_A/Q'$  inequality amplified by decreased  $PvO_2$  results in aggravated gas exchange.<sup>17</sup> The decrease of  $PvO_2$  arose from increased oxygen consumption, presumably due to increased work by the respiratory muscles.<sup>17</sup> The significantly low  $PaO_2$  and  $PvO_2$  at exacerbation in this report indicates that the disturbance in gas exchange was caused by respiratory muscle fatigue. In the meantime, the worsening  $V'_A/Q'$  relationship must result from several pathophysiological changes during exacerbation. An important cause of  $V'_A/Q'$  inequality might be the change of pulmonary blood flow distribution due to a vasoconstrictive reaction that includes HPV, endothelial dysfunction and inflammation.<sup>5,9</sup> The obviously increased PVRI and the attenuation of augmented  $Ppa$  by oxygen inhalation confirmed notable pulmonary vasoconstriction under this condition. Supplemental oxygen helped to relieve the HPV,

balance the  $V'_A/Q'$  relationship and improve the pathological pulmonary hemodynamics during exacerbation.

In summary, significant PH and considerably increased Pawp developed during exercise in patients with severe COPD, in contrast to the mild PH and remarkably increased PVRI observed during exacerbation. The pathological pulmonary hemodynamics are probably characterized by significant PH due to dynamic hyperinflation during exercise, while vasoconstrictive reaction becomes prominent under exacerbation. The principal change in pulmonary hemodynamics might differ between these two conditions for patients with severe COPD although supplemental oxygen equally improves the deterioration of PH. Further studies are required to confirm the pathophysiology of the pulmonary circulation under both conditions.

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**Table 1.** Patients' characteristics.

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|                           |              |
|---------------------------|--------------|
| n                         | 6            |
| Age (y)                   | 74.2 ± 2.7   |
| Smoking (pack-years)      | 64.4 ± 12.0  |
| FEV <sub>1</sub> (L)      | 0.67 ± 0.11  |
| %FEV <sub>1</sub>         | 31.8 ± 6.3   |
| FEV <sub>1</sub> /FVC (%) | 33.8 ± 5.0   |
| %VC                       | 83.4 ± 8.0   |
| %RV                       | 178.6 ± 18.0 |
| %DLco                     | 52.3 ± 8.2   |

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FEV<sub>1</sub>, forced expiratory volume in one second; %FEV<sub>1</sub>, the ratio of predicted forced expiratory volume in one second; FVC, forced vital capacity; %VC, the ratio of predicted vital capacity; %RV, the ratio of predicted residual volume; %DLco, the ratio of predicted diffusion capacity for carbon monoxide. Values are means ± SEM.

**Table 2.** Pulmonary hemodynamics at rest, during exercise and exacerbation in patients with severe COPD.

|   | Rest         | Exercise                  | Exacerbation  |
|---|--------------|---------------------------|---------------|
| Ppa (mmHg)  | 22.5 ± 2.4   | 47.8 ± 6.0* <sup>#</sup>  | 24.2 ± 1.7    |
| Pawp (mmHg)                                       | 11.2 ± 0.9   | 26.0 ± 5.1* <sup>#</sup>  | 6.8 ± 1.1*    |
| CI (L/min/m <sup>2</sup> )                        | 3.44 ± 0.36  | 5.46 ± 0.44* <sup>#</sup> | 3.52 ± 0.31   |
| PVRI (dynes·sec·m <sup>2</sup> /cm <sup>5</sup> ) | 268.0 ± 35.8 | 312.4 ± 29.4              | 404.8 ± 39.5* |
| PaO <sub>2</sub> (Torr)                           | 73.8 ± 4.0   | 56.9 ± 5.3*               | 57.6 ± 4.4*   |
| PaCO <sub>2</sub> (Torr)                          | 42.3 ± 1.7   | 45.2 ± 3.2                | 47.0 ± 5.4    |
| PvO <sub>2</sub> (Torr)                           | 36.7 ± 0.8   | 26.8 ± 1.0* <sup>#</sup>  | 31.5 ± 1.9*   |

Ppa, pulmonary artery pressure; Pawp, pulmonary artery wedge pressure; CI, cardiac index; PVRI, pulmonary vascular resistance index; PaO<sub>2</sub>, arterial blood oxygen tension; PaCO<sub>2</sub>, arterial blood carbon dioxide tension; PvO<sub>2</sub>, central venous blood oxygen tension. Values are means ± SEM; \**P* < 0.05 compared with rest; <sup>#</sup>*P* < 0.05 compared with exacerbation.

## **Figure legends**

**Figure 1.** Effect of supplemental oxygen on pulmonary artery pressure (Ppa) during rest, exercise and exacerbation in patients with severe COPD.

\* $P < 0.05$  compared with air.

**Figure 2.** Effect of supplemental oxygen on pulmonary artery wedge pressure (Pawp) during rest, exercise and exacerbation in patients with severe COPD.

\* $P < 0.05$  compared with air.