Oxygen Therapy and Vasodilator Therapy in Patients with Chronic Lung Disease: The Effects on Episodic Pulmonary Hypertension During Sleep and Exercise Performance

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In patients with chronic lung disease, we estimated the effectiveness of nocturnal oxygen therapy in eliminating episodes of sleep hypoxemia and concomitant elevations in the pulmonary arterial pressure. We also assessed the effect of vasodilators (ISDN, nifedipine) in improving exercise tolerance. Our results support the efficacy of nocturnal oxygen therapy. Vasodilators examined were not confirmed as effective or safe for wide use.

COR pulmonale is an intractable condition which occurs in the terminal stage of chronic lung disease. In our previous study, half of the patients who apparently had cor pulmonale died within 4 years of its onset.¹ Oxygen therapy and vasodilator therapy are employed to treat this condition by relieving the underlying pulmonary hypertension.²⁻³ These therapies are also expected to improve exercise tolerance by reducing right ventricular afterload and increasing oxygen delivery. In order to assess the clinical usefulness of these therapies, we studied the effectiveness of oxygen therapy in reducing episodic pulmonary hypertension due to sleep hypoxemia, and the effect of vasodilators in improving exercise performance.

I. Sleep hypoxemia and oxygen therapy (Subjects and Methods)

Polysomnography was carried out using standard techniques in 38 patients with chronic lung disease who fell under the category of respiratory failure. In 8 of these 38 cases, a Swan-Ganz catheter was inserted into the pulmonary artery for serial recording of pulmonary arterial pressure and occasional determination

of cardiac output. In 9 cases in whom sleep hypoxemia occurred when they breathed the room air, second polysomnography was performed under low-flow oxygen breathing, in order to assess the effect of nocturnal oxygen therapy.

(Results and Discussion)

Figure 1 shows the polysomnographic records taken from a patient with respiratory failure after thoracoplasty. This patient suffered from sleep hypoxemia 3 times during a night. In this case, the mean pulmonary arterial pressure transiently elevated corresponding like a mirror image to a reduction in arterial oxygen saturation (SaO_2). The pulmonary arterial pressure rose to a higher level than that observed during exercise in the same patient. However, cardiac output during the sleep hypoxemia did not rise as high as it did during exercise. Therefore, these episodes of pulmonary hypertension were attributed chiefly to an increase in pulmonary vascular resistance caused by hypoxic pulmonary vasoconstriction. When the mean pulmonary arterial pressure values, taken every 30 sec throughout the night, were plotted against SaO_2 values taken at the same intervals (Fig. 2), there was a significant negative correlation, suggesting that SaO_2 is an important determinant of pulmonary arterial pressure.

Similar episodes of sleep hypoxemia occurred

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Fig.1. Polygraphic tracing showing three episodes of nocturnal desaturation with elevation in the pulmonary artery pressure.

in 76% of 38 cases studied. The frequency of episodic hypoxemia in a night ranged from 0 to 9 (mean: 3); the Sao_2 decreased by about 10%; and the minimum Sao_2 value was under 80% (70% in some cases), as shown in Table I. Such sleep hypoxemia and an accompanying transient pulmonary hypertension occurring every night seemed to cause right ventricular hypertrophy (i.e., cor pulmonale).⁴ We analyzed the relationship between the frequency of hypoxemic episodes per night and the percentage of patients who were diagnosed to have right ventricular hypertrophy by a myocardial cintigraphy (Fig. 3). This analysis disclosed that the incidence of right ventricular hypertrophy increased with the frequency of sleep hypoxemia and suggests a causal relationship between sleep hypoxemia and right ventricular hypertrophy.

Figure 4 shows a comparison of polysomnographic records taken from the above-mentioned patient breathing room air and low-flow oxygen (one litre/minute). Breathing low-flow oxygen, this patient developed no hypoxemia during sleep, and the Sao_2 remained at about 95% throughout the night. Thus, the severe pulmonary hypertension occurring when breathing room air was prevented by supplementary oxygen. Of the 9 cases who showed sleep hypoxemia when breathing room air, about half had no sleep hypoxemia when breathing low-flow oxygen, and the remaining half showed significantly fewer attacks of sleep hypoxemia per night (Table II). In addition, the minimum Sao_2 remained within a safe range in these 9 cases. These results support the efficacy of nocturnal oxygen therapy.

Fig.2. Relation between SaO_2 and pulmonary artery mean pressure (PAMP).

TABLE I NOCTURNAL DESATURATION IN PATIENTS WITH CHRONIC LUNG DISEASE (n = 38)

Baseline SaO_2 (%)	90.2 ± 3.4
Episodes of desaturation	2.9 ± 2.7
Maximal fall in SaO_2 (%)	9.5 ± 3.7
Lowest SaO_2 (%)	79.9 ± 5.3
mean $\pm$ SD	

similar to the subjects used for test I. This test aimed to assess the acute effects of vasodilators and oxygen on hemodynamics and tissue oxygenation. Subjects exercised in a supine position using a bicycle ergometer. The intensity of exercise was increased stepwise or kept at a sub-maximal level which the patient could maintain for 5 min or more. Eleven patients were given isosorbide dinitrate (ISDN) by intravenous drip infusion ($1 \mu\text{g/kg/min}$). Another 11 patients were given a sublingual 10 mg dose of nifedipine. Four of the latter 11 cases were treated with nifedipine for 3 weeks (20 mg/day) in order to assess the chronic effects of this agent. In 10 cases, the effect of oxygen therapy on the disturbed pulmonary hemodynamics and tissue oxygenation during exercise was assessed in a similar way.

(Results and Discussion)

During exercise, patients with chronic lung disease are known to show aggravation of disturbed pulmonary hemodynamics and tissue oxygenation. Fig. 5 shows the changes in each

II. Disturbed pulmonary hemodynamics during exercise and vasodilator therapy (Subjects and Methods)

An exercise test was performed in 32 patients

Fig.3. Prevalence of nocturnal desaturation in patients with right ventricular hypertrophy (RVH).

Fig.4. Effect of oxygen therapy on episodic pulmonary hypertension.

TABLE II EFFECT OF OXYGEN THERAPY ON NOCTURNAL DESATURATION

(n = 9)	Room air	Oxygen
Baseline SaO_2 (%)	87.9 ± 3.8	$92.9 \pm 4.7^{**}$
Episodes of desaturation	5.6 ± 2.1	$2.1 \pm 2.1^{**}$
Maximal fall in SaO_2 (%)	11.7 ± 3.1	$8.7 \pm 1.4^{**}$
Lowest SaO_2 (%)	76.1 ± 4.4	$84.2 \pm 4.4^{**}$

$^{**}p < 0.01$ mean $\pm$ SD

index of pulmonary hemodynamics and tissue oxygenation during exercise the intensity of which was increased stepwise. In these patients, the mean pulmonary arterial pressure rose from 22.8 mmHg at rest to 44.6 mmHg during maximal exercise. This change is chiefly attributable to the increase in pulmonary blood flow through vessels whose beds have become rigid. The pulmonary vascular resistance did not increase with exercise. Pao_2 tended to decrease during exercise, and $P\bar{v}O_2$ fell from 37.5 Torr at rest to

28.4 Torr during maximal exercise. It is still controversial whether or not such aggravation of disturbed pulmonary hemodynamics and tissue oxygenation works as a factor limiting the exercise capacity of patients. In any event, such a condition may prevent patients continuing exercise. Therefore, we studied whether vasodilator therapy could improve the disturbed pulmonary hemodynamics and tissue oxygenation during exercise.

ISDN was found to reduce venous return and

Fig.5. Changes in hemodynamic indices and tissue oxygenation during exercise.

Fig.6. Hemodynamic responses to isosorbide dinitrate at rest and during exercise (n = 11).

cardiac output, resulting in a reduction in pulmonary blood flow and pulmonary arterial pressure (Fig. 6). Treatment with ISDN also resulted in

a tendency for the systemic vascular resistance to rise, and so systemic blood pressure was reduced only slightly by ISDN. The ISDN-induced re-

Fig.7. Effect of isosorbide dinitrate on tissue oxygenation.

Fig.8. Hemodynamic responses to nifedipine at rest and during exercise ($n = 11$).

duction in cardiac output resulted in a decline of oxygen transport, while the $\text{P}\bar{\text{v}}\text{O}_2$ values decreased only within a permissible range in our patients (Fig. 7). Thus, ISDN was found to have

the advantages of suppressing the elevation of pulmonary arterial pressure during exercise and of reducing the right ventricular stroke work index. However, because this drug reduces

Fig.9. Effect of nifedipine on tissue oxygenation.

Fig.10. Chronic effect of nifedipine on exercise performance.

cardiac output, ISDN therapy involves difficulties over tissue oxygenation.

Nifedipine, on the other hand, caused an increase in cardiac output because it dilates the blood vessels of the systemic circulation system (Fig. 8). However, nifedipine therapy caused

a large drop in systemic blood pressure. In the pulmonary circulation system, the nifedipine-induced reduction in pulmonary arterial pressure was less than had been expected. The unexpectedly small reduction may be due to a nifedipine-induced increase in pulmonary blood

Fig.11. Effect of oxygen breathing on tissue oxygenation (n = 10).

Fig.12. Hemodynamic responses to oxygen breathing at rest and during exercise.

flow. The finding that P_{aO_2} was not reduced by nifedipine therapy suggests that nifedipine does not work as an active vasodilator in the pulmonary circulation system, and that the reduction of pulmonary arterial pressure following nifedipine therapy is an outcome of the reduction of systemic blood pressure induced by this drug. Although oxygen transport was increased by nifedipine therapy because of its effect of increasing cardiac output, there was no significant change in $P\bar{v}O_2$ values (Fig. 9). This finding indicates that tissue oxygenation probably cannot be sufficiently improved by nifedipine therapy. Thus, although nifedipine suppressed the elevation of pulmonary arterial pressure during exercise, it reduced systemic blood pressure and elevated the right ventricular stroke work index. Furthermore, the effectiveness of nifedipine in improving tissue oxygenation was not good enough. We expected a considerable improvement in cardiac function and exercise tolerance if the acute effect of nifedipine in reducing the right and left ventricular afterloads could be maintained for a long time. However, 3-week nifedipine therapy (20 mg/day) did not lead to any increase of right and left ventricular ejection fractions (determined by radioisotope angiography), and the distance some patients could walk in 10 min (an index of the exercise capacity) decreased as shown in Fig. 10.

Oxygen therapy, on the other hand, resulted in a marked improvement in tissue oxygenation (Fig. 11), although its acute hypotensive effect on pulmonary circulation system was weak (Fig. 12).

In treating disturbances of pulmonary hemodynamics in patients with chronic lung disease, we face a pathophysiological dilemma that an improvement of one parameter leads to an impairment of another. Whether the total effects of oxygen or vasodilator therapy are favorable or unfavorable depends on the condition of each individual case. Even when these therapies prove to have favorable acute effects, it does not neces-

sarily mean that they are effective in long-term use. Although the long-term effectiveness of oxygen has been confirmed by several studies done by the NOT trial group and others,⁵⁻⁶ none of the currently available vasodilators had been confirmed as effective and safe for wide use. At present, there seem to be no drugs for the treatment of chronic pulmonary hypertension that might be superior to oxygen. Therefore, we recommend that home oxygen therapy should come into wider use.² It is also desirable to establish a pulmonary vasodilator therapy that involves the use of new drugs more specific to the pulmonary circulation system, beginning at an earlier stage of the disease, in order not to disturb the delicate balance of the compensatory mechanism.⁷

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