

SERIES 'HIGHLIGHTS ON PULMONARY HYPERTENSION'
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Medical treatment of pulmonary hypertension in chronic lung disease

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ABSTRACT: In chronic respiratory diseases, especially chronic obstructive pulmonary disease (COPD) pulmonary arterial hypertension is generally mild to moderate, and the necessity for treating it can, therefore, be questioned. In fact, pulmonary hypertension, even when modest, may worsen markedly during acute episodes, exercise and sleep. These acute increases in mean pulmonary artery pressure (PAP) could contribute to the development of right heart failure. Therefore, the medical treatment of pulmonary hypertension is justified.

There are, at the present time, no selective pulmonary vasodilators, with the exception of inhaled nitric oxide. Indeed, vasodilators appear less effective in COPD compared to primary pulmonary hypertension. Thus, there is, at present, no justification for the long-term use of vasodilators in COPD patients.

Long-term oxygen therapy (LTOT) attenuates and sometimes reverses the progression of pulmonary hypertension, although the condition rarely returns to normal. We do not know whether the structural changes of the pulmonary vasculature in COPD patients are potentially reversible with LTOT. The longer the daily duration of LTOT the better are the haemodynamic results.

At present, LTOT remains the best treatment for pulmonary hypertension in COPD patient. In the future, treatment of this condition in COPD patients could combine LTOT and specific vasodilators.

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Chronic lung diseases with associated hypoxaemia lead to pulmonary arterial hypertension which, in turn, can lead to right heart failure. Therefore, the treatment of pulmonary hypertension in chronic lung diseases, particularly chronic obstructive pulmonary disease (COPD), is justified. We review first the rationale for the treatment of pulmonary hypertension and, secondly, the different treatments. As insufficient data are available on other chronic respiratory diseases (*e.g.* restrictive lung diseases), the review is confined to COPD patients.

Is it necessary to treat pulmonary hypertension in COPD?

Arguments against treatment

In chronic respiratory diseases, especially COPD, pulmonary hypertension is generally mild to moderate. The mean pulmonary artery pressure (PAP), when measured in a stable state of the disease is, in most patients, 20–35 mmHg [1]. This differs greatly from primary pulmonary hypertension and pulmonary thromboembolic disease. It differs also from pulmonary hypertension associated with left heart and congenital heart diseases. In these diseases, PAP exceeds 50 mmHg, and can reach levels comparable

to those of the systemic circulation. The necessity for treating a mild pulmonary hypertension can therefore, be questioned.

Prevention of right heart failure in pulmonary hypertension would be a valuable outcome of treatment. However, it can be questioned [2, 3] whether pulmonary hypertension leads to right heart failure in COPD patients. The mild degree of pulmonary hypertension in COPD, and the fact that cardiac index is generally found to be within normal limits in these patients, even during acute exacerbations of the disease and when the patients have marked peripheral oedema [4], raises a question about the role of pulmonary hypertension in right heart failure. MACNEE *et al.* [3] observed that PAP was no different in COPD patients with and without peripheral oedema. These authors concluded that right heart failure is not a result of increased PAP, but they did not undertake a longitudinal study. The cross-sectional basis of their work, where two different groups of patients were studied, weakens their conclusions [5].

Arguments in favour of treatment

The main argument in favour of treatment is that pulmonary hypertension, even when modest, may worsen

during acute episodes, during exercise and during sleep in COPD patients. These acute increases in PAP could contribute to the development of right heart failure in the presence of hypoxaemia.

Acute exacerbations of COPD are accompanied by transient, but sometimes marked, elevations of PAP [4, 6, 7]. These increases in PAP from baseline levels may exceed 20 mmHg. Since there is a good correlation between the rise in PAP and the arterial oxygen tension (P_{aO_2}) during such episodes, hypoxia is thought to be the mechanism [6, 7].

Similarly, PAP increases during exercise in COPD patients; *e.g.* a rise from 30 to 60 mmHg can be observed during a 30–40 W exercise. Such levels of exercise are associated with a twofold increase in cardiac output. As a result, pulmonary vascular resistance (PVR) rises rather than falls during exercise. It is conceivable that repeated and marked increases in PAP during exercise could lead to right heart failure. The rise in PVR, with exercise associated increases in cardiac output, also indicates a loss of the ability of the pulmonary vasculature to adapt to a rise in blood flow in these patients.

During sleep-related episodes of nocturnal hypoxaemia [8–11], PAP can rise acutely. These episodes occur mainly during rapid eye movements (REM) sleep. The peaks of pulmonary hypertension mirror dips in P_{aO_2} [10]. Again, as with exacerbations, these reflect acute pulmonary vasoconstriction. The acute worsening of pulmonary hypertension can be severe. COCCAGNA and LUGARESI. [8] reported rises in PAP from 30 to over 50 mmHg in their series, and we have also reported elevations of PAP by more than 25 mmHg [10]. Usually, PAP returns to baseline values after waking. However, repetitive increases in PAP could contribute to right ventricular hypertrophy, right ventricular dysfunction and right ventricular failure.

We studied 16 patients with COPD, during an episode of advanced peripheral oedema (table 1) [12]. Nine had elevated right ventricular end-diastolic pressure (>12 mmHg). These patients had enlarged heart size on chest radiographs, and increased right ventricular end-diastolic diameter on echocardiography. They satisfied most criteria for right ventricular failure. By comparison with baseline value, measured when stable, PAP values were significantly increased during the acute episode of oedema. This rise in PAP was a result of hypoxic vasoconstriction.

In some patients with COPD, we would conclude that right heart failure when assessed by clinical, haemodynamic, radiological and echocardiographic methods, is caused by a rise in PVR and PAP.

Methods of treatment of pulmonary hypertension in COPD

There are two treatment available, which are not mutually exclusive: vasodilators and long-term oxygen therapy.

Vasodilators

Experience with vasodilator therapy has come from the treatment of primary and severe pulmonary hypertension. It is based on the belief that pulmonary vasoconstriction is an important component of pulmonary hypertension. The ideal response to a vasodilator is a reduction of PAP with a rise in cardiac output [13]; in other words, a fall in PVR. Ideally, systemic arterial pressure and P_{aO_2} should be little affected [13]. However, most vasodilators are not selective to the pulmonary vasculature; they also act as systemic vasodilators. One newly applied vasodilator, prostacyclin (PGI_2), is a powerful nonselective vasodilator. Continuous intravenous infusion of prostacyclin has been used in patients with severe primary pulmonary hypertension, awaiting heart-lung transplantation [14, 15]. This treatment is still at an investigational stage and has not yet been given to COPD patients; moreover it is very expensive. Inhaled nitric oxide (40 ppm) is a selective pulmonary vasodilator [16, 17], and has been used in pulmonary arterial hypertension associated with adult respiratory distress syndrome (ARDS) [18]. However, its toxicology is not fully known, and it is difficult to administer.

Conventional vasodilator drugs can be administered orally. They include beta-adrenergic-agonists (*e.g.* isoproterenol), alpha-adrenergic-antagonists (*e.g.* urapidil, tolazoline, phentolamine, prazosin), calcium channel blocking agents (*e.g.* nifedipine and diltiazem), inhibitors of angiotensin converting enzyme, nitrates (such as trinitrine), and direct vasodilators (such as diazoxide and hydralazine). All of these drugs are nonselective, and act on the systemic and pulmonary circulation. Calcium channel blockers give good results in the treatment of primary

Table 1. – Arterial blood gases and pulmonary haemodynamics in 16 COPD patients changing from stable state (I) to an episode of marked peripheral oedema (II)

	P_{aO_2} mmHg		P_{aCO_2} mmHg		RVEDP mmHg		PAP mmHg		Q $l \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	
	I	II	I	II	I	II	I	II	I	II
Group 1 n=9	63±4	49±7**	46±7	59±1**	7.5±3.1	13.4±1.2**	27±5	40±6***	3.2±0.8	3.2±1.1
Group 2 n=7	66±7	59±7	42±6	45±6	5.5±2.4	5.1±1.5	20±6	21±5	3.6±0.4	3.3±1.3

Data are represented as mean±SD. Group 1: patients with an elevated (>12 mmHg) right ventricular end-diastolic pressure during an episode of oedema (right heart failure); Group 2: patients with a normal (<12 mmHg) right ventricular end-diastolic pressure during an episode of oedema (no right heart failure). P_{aO_2} : arterial oxygen tension; P_{aCO_2} : arterial carbon dioxide tension; RVEDP: right ventricular end-diastolic pressure; PAP: pulmonary artery mean pressure; Q: cardiac output. **: $p < 0.01$; ***: $p < 0.001$. (From APPRILL *et al.* [12]).

pulmonary hypertension [19, 20]. Less convincing results are seen in the treatment of pulmonary hypertension secondary to COPD. Although an acute vasodilating effect has been observed [21, 22], long-term studies (>6 months) have failed to demonstrate any improvement in pulmonary haemodynamics [23].

Indeed worsening of the fluid retention is observed, possibly as a result of the negative inotropic effects of the calcium channel blockers. Oral vasodilators may not only cause severe systemic hypotension, but can also be associated with a fall in P_{aO_2} [24]. Since there are no selective pulmonary vasodilators, with the exception of inhaled nitric oxide, and vasodilators appear less effective in COPD compared to primary pulmonary hypertension, there is, at present, no justification for the long-term use of vasodilators in COPD patients

Long-term oxygen therapy (LTOT)

One of the aims of long-term oxygen therapy (LTOT) in COPD patients is to attenuate the development of pulmonary hypertension, and to reduce the frequency of the episodes of right heart failure. Alveolar hypoxia is considered to be the major determinant of the rise of pulmonary vascular resistance in pulmonary arterial hypertension. Acute alveolar hypoxia induces pulmonary vasoconstriction in normal men, as well as in patients with chronic respiratory diseases. As we determined previously, acute hypoxia is marked during episodes of acute respiratory failure [4, 6, 7], or during sleep [8–11].

Chronic hypoxia is believed to cause structural changes in the pulmonary vascular bed. These include hypertrophy of the muscular media of small pulmonary arteries, muscularization of the pulmonary arterioles, as well as fibrosis of the intima. These structural changes probably account for the rise in PVR and PAP. The role of chronic hypoxia has, however, recently been questioned [25], as these structural changes could be due to chronic hypoxia, or the result of pulmonary hypertension itself.

Structural changes of the pulmonary vascular bed induced by chronic alveolar hypoxia have been observed in man, both native highlanders, or under experimental conditions (healthy "lowlanders" living at high altitude (>3,500 m)), as well as in a wide variety of experimental animals studied under conditions of hypoxia. The experimental changes to the pulmonary vessels are reversible when animals are returned to ambient air. Similarly, pulmonary hypertension in man disappears a few weeks or months after return to sea level. This suggests that the pulmonary vascular tree returns to normal. These data have raised the hope that a similar reversibility of pulmonary vascular changes occurs in COPD patients receiving LTOT. There are few data on the morphological changes of the pulmonary vascular tree, either before or after LTOT in these patients, and it is not known whether these changes are reversible with oxygen. By contrast, there are adequate haemodynamic studies of the effects of LTOT.

The first reports on the pulmonary haemodynamic effects of LTOT were made by groups in Denver [26] and Birmingham [27], in 1967–1968. Small groups ($n=6$ in

both studies) of patients were investigated, and pulmonary hypertension was moderate to severe in all patients. Some patients had had recent episodes of right heart failure, which raises the question of their stable state. Oxygen therapy was continuously administered, 24 h-day⁻¹ over 4–8 weeks and was provided by means of liquid oxygen. The PAP fell in all patients from the Birmingham study, mean PAP decreasing from 42 to 32 mmHg. In the Denver study, PAP improved in three patients and was stable or increased in the remaining three patients. It must be emphasized that in no patient did the PAP return to normal (<20 mmHg). It should be noted that there was no control group in this study. A later report from the group in Birmingham [28] indicated that the daily duration of oxygen therapy markedly influenced the haemodynamic results (which were much better with 18 h-day⁻¹ than with 12 h-day⁻¹), but the number of patients allocated to each therapeutic programme was small, and again there was no control group. Unlike earlier pioneering studies, the Medical Research Council (MRC) and Nocturnal Oxygen Therapy Trial (NOTT) studies, published in 1980–1981 [29, 30], were multicentred, controlled trials and included a large number of patients. Pulmonary haemodynamic data were available in both studies. The periods of follow-up were adequately long, up to 5 yrs.

In the MRC study [29], haemodynamic investigations were available in 42 patients, who survived more than 500 days. In 21 patients receiving LTOT (>15 h-day⁻¹) PAP did not change, whereas in the control group not receiving oxygen ($n=21$), the PAP rose by a mean of 2.7 mmHg-yr⁻¹. Thus, whilst LTOT did not improve pulmonary hypertension, it prevented the deterioration of PAP seen in patients not receiving oxygen.

In the NOTT study, the pulmonary haemodynamic data were available after 6 months of follow-up in 117 patients randomly allocated to either continuous oxygen therapy (>18 h-day⁻¹) or nocturnal oxygen therapy (10–12 h-day⁻¹) [31]. Continuous oxygen therapy decreased the resting and exercising PAP, slightly but significantly, by -3 and -6 mmHg, respectively. In line with this, the resting and exercising PVR improved. Whereas, all of the haemodynamic data were stable in patients receiving only nocturnal oxygen therapy. However, many patients had only mild pulmonary hypertension, with an initial PAP of 29 ± 10 (SD) mmHg.

We investigated the evolution of pulmonary hypertension in 16 severe COPD patients before (T0–T1) and during (T1–T2) LTOT. In this study, the patients served as their own controls [32]. LTOT was given during 15–18 h-day⁻¹. Period T0–T1 lasted at least one year and on average 4 yrs. Period T1–T2 lasted at least one year and on average 2.5 yrs. The overall period of haemodynamic follow-up ranged from 31–144 months, with a mean of 78 ± 37 months.

The prescription of LTOT at T1 was a consequence of a marked worsening of P_{aO_2} during T0–T1. Under LTOT (period T1–T2) arterial blood gases measured on ambient air remained stable (table 2). The PAP increased significantly before LTOT ($p<0.005$) and decreased during LTOT ($p<0.05$). Consequently, final PAP at T2 was similar (as a mean) to initial PAP at T0. The PAP did not

Table 2. – Pulmonary haemodynamics before (from T0 to T1) and during (from T1 to T2) long-term oxygen therapy (n=16)

	T0	T1	T2	Difference T0–T1	Difference T1–T2	Difference T0–T2
Pao ₂ mmHg	59.3±9.4	50.2±6.6	50.1±8.3	p<0.001	NS	p<0.001
Paco ₂ mmHg	43.2±6.2	51.0±6.4	50.7±8.5	p<0.01	NS	p<0.005
PAP mmHg	23.3±6.8	28.0±7.4	23.9±6.6	p<0.005	p<0.05	NS
PCW mmHg	5.9±1.4	5.5±2.7	5.7±2.4	-	-	-
Q l·min ⁻¹ ·m ⁻²	3.9±0.8	3.9±0.6	3.4±0.8	NS	NS	NS
PVR mmHg·l ⁻¹ ·min ⁻¹	2.41±0.76	3.27±0.71	2.68±0.51	-	-	-

Data are represented as mean±SD. PAP: pulmonary artery pressure; PCW: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance. T0–T1: period before LTOT, lasted at least one year and on average 4 yrs; T1–T2: period during LTOT, lasted at least one year and on average 2.5 yrs; LTOT long-term oxygen therapy. NS: nonsignificant. For further abbreviations see legend to table 1. (From WEITZENBLUM *et al.* [32]).

return to normal, but a reversal in the progression of pulmonary arterial hypertension was observed. The rate of yearly change of PAP was of +1.5±2.3 mmHg before the onset of LTOT instead of -2.1±4.4 during LTOT (p<0.01). The changes in PAP were due to changes in PVR, as both pulmonary wedge pressure and cardiac output remained stable (table 2).

In the NOTT study and in our own, the haemodynamic results were modest, but favourable. We have observed that LTOT could delay the progression of pulmonary hypertension in these patients. But PAP seldom returned to normal. There was no improvement of pulmonary hypertension in the MRC study, but control patients not receiving oxygen worsened. The daily duration of LTOT was important: it was less in the MRC study [29], compared with our patients [32] or the continuous oxygen group of the NOTT study [31], which suggests that there is a link between the daily duration of LTOT and the haemodynamic results. An improvement of PAP was seen in patients receiving oxygen for >16–18 h·day⁻¹.

Similarly, animal studies [33–35] have shown that whilst continuous normoxia could reverse pulmonary arterial hypertension and right ventricular hypertrophy induced by chronic hypoxia, intermittent normoxia for 16 h·day⁻¹ did not. We know from the study of SELINGER *et al.* [36] that removing oxygen for not more than 2–3 h in patients submitted to continuous oxygen therapy was associated with a significant increase of PAP. Although continuous oxygen therapy is probably to be recommended, this may not be acceptable to patients.

Recent data [37, 38] have suggested that there is a wide variation in the individual responses of the pulmonary circulation to either hypoxia or oxygen in COPD patient. At present it is not known whether short-term responders to oxygen and hypoxia will turn out to be good "responders" to long-term oxygen therapy.

Conclusions

LTOT attenuates, and sometimes reverses, the progression of pulmonary arterial hypertension. However, pulmonary artery pressure rarely returns to normal. We do not know whether the structural changes of the pulmonary vasculature in COPD patients are potentially reversible

with LTOT. The longer the daily duration of LTOT, the better the haemodynamic results. At present, LTOT is the best treatment for pulmonary hypertension in COPD patients. In the future, the treatment of this condition in COPD patients may combine LTOT and specific vasodilators.

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