Pulmonary Hypertension and Right Heart Failure in Chronic Obstructive Pulmonary Disease

Robert Naeije

Department of Pathophysiology, Erasme Campus, Brussels, Belgium

Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD). The increase in pulmonary artery pressures is often mild to moderate. However, 5–10% of patients with advanced COPD may suffer from severe pulmonary hypertension and present with a progressively downhill clinical course because of right heart failure added to ventilatory handicap. The prevalence of clinically significant severe pulmonary hypertension in COPD is roughly estimated to be of 1–2/1,000. The cause of pulmonary hypertension in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy. However, recent pathologic studies point rather at extensive remodeling of all layers of the pulmonary arterial walls. These aspects account for minimal reversibility with supplemental oxygen. There may be a case for pharmacologic treatment of pulmonary hypertension in selected patients with advanced COPD and right heart failure. However, it will be a challenge for randomized controlled trials to overcome the difficulties of the diagnosis of right ventricular failure and the definition of a relevant primary endpoint in pulmonary hypertensive patients with COPD.

Keywords: pulmonary hypertension; chronic obstructive pulmonary disease; right heart failure

NATURE OF PULMONARY HYPERTENSION IN COPD

Pathologic studies that stemmed from long-term oxygen trials pointed to the fact that pulmonary vascular remodeling in chronic obstructive pulmonary disease (COPD) is more than just medial hypertrophy from long-lasting hypoxic vasoconstriction (1). This is now confirmed (2). In these patients, all vessel wall layers appear to be involved, with intimal changes actually being the most prominent (Figure 1). This peculiar pathologic picture is explained by inflammation-induced remodeling and angiogenesis, with inflammation being related to hypoxia, chronic infection, repeated stretching of hyperinflated lungs, and toxic effects of cigarette smoke (1, 2). Chronic hypoxia at high altitudes induces predominant medial hypertrophy (with sometimes longitudinal deposition of a few smooth muscle fibers in the intima) and is associated with complete reversal of pulmonary hypertension after a few weeks after return to sea level (3). Major remodeling of all pulmonary arterial vessel layers explains why pulmonary hypertension in COPD is often not, or minimally, reversible by supplemental oxygen, acutely (4) or chronically (5). Pulmonary artery pressures only loosely relates to arterial P_{O_2}, as well as to arterial P_{CO_2}, which is not really suggestive of a direct causal relationship (Figure 2) (6).

The pathobiology of pulmonary artery remodeling in advanced COPD remains incompletely explored. There are data supporting an endothelium-derived vasoconstrictor-dilator imbalance, mainly from a decreased endothelial nitric oxide expression (7, 8). There has been a more recent report of possible roles of increased vascular endothelial growth factor and serotonin transporter expressions (9, 10). Further studies are needed to determine similarities and differences in pathobiology of COPD-associated severe pulmonary hypertension and idiopathic pulmonary arterial hypertension.

SEVERITY AND INCIDENCE OF PULMONARY HYPERTENSION IN COPD

Pulmonary hypertension in COPD is generally limited to an increase in mean pulmonary artery pressure to 25–35 mm Hg in the face of a normal cardiac output (Table 1) (6). However, mean pulmonary artery pressures higher than 40 mm Hg (invasively measured) are not uncommon in advanced COPD, especially in patients with at least one previous episode of acute respiratory failure (Figure 2) (6, 10, 11). Patients with idiopathic pulmonary arterial hypertension in whom the disease process is limited to the pulmonary vasculature become symptomatic, with dyspnea, fatigue, and right heart failure when pulmonary artery pressures are higher than 35–40 mm Hg (12). It is thus possible that in a proportion of patients with advanced COPD, pulmonary hypertension contributes to the clinical picture because of right ventricular output limitation, and therefore would need to be identified and treated. This is even more true given the prognostic value of pulmonary hypertension in COPD, which is very similar to that of pulmonary arterial hypertension (Figure 3) (6).

The exact incidence of clinically significant pulmonary hypertension, defined as pulmonary hypertension that contributes to symptomatology and prognosis, is difficult to estimate in COPD. A prevalence of 10–30% in patients with at least one previous hospitalization seems reasonable minimum (6, 10, 11). Taken into consideration that each year in the United States, 500,000 patients with aggravated COPD are hospitalized and 100,000 patients with COPD die (13), it may be possible to estimate a prevalence of significant cor pulmonale of 2–6/1,000, corresponding to an incidence of 1–3/10,000, which represents 100 times the incidence of idiopathic pulmonary arterial hypertension (12).

The diagnosis of pulmonary hypertension in patients with COPD remains difficult. Systematic right heart catheterization is too invasive, in the face of absent evidence-based expected benefit, to be ethically acceptable. Echocardiography has made progress, but the performance of this apparently ideal noninvasive test remains less than optimal (14, 15). This may be improved by tissue Doppler echocardiography in the future. There is also perspective with magnetic resonance imaging of the right ventricle (16). Exercise in COPD may be associated with marked pulmonary hypertension in patients with COPD, in proportion to resting pulmonary artery pressure (17). Patients with exercise-induced pulmonary hypertension are particularly prone to developing resting pulmonary hypertension in the long term (17, 18). Exercise testing should theoretically allow for the detection of the cardiac limited patients who exceed the anaerobic threshold before reaching maximum ventilatory capacity ($FEV_1 \times 37.5$)

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Correspondence and requests for reprints should be addressed to R. Naeije, M.D., Department of Pathophysiology, Erasme Campus CP 604, Lennik Road, 808, B-1070, Brussels, Belgium. E-mail: rnaeije@ulb.ac.be

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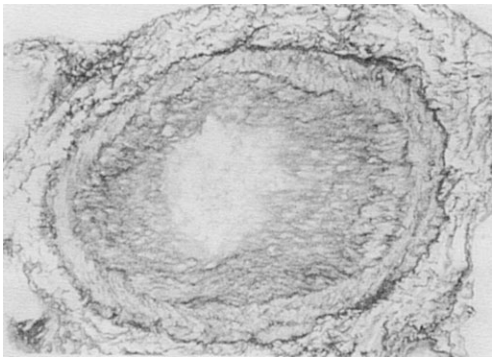

Figure 1. Section of a pulmonary arteriole from a patients with chronic obstructive pulmonary disease (COPD), showing remodeling of the entire vessel wall with striking intimal thickening. Reprinted by permission from Reference 2.

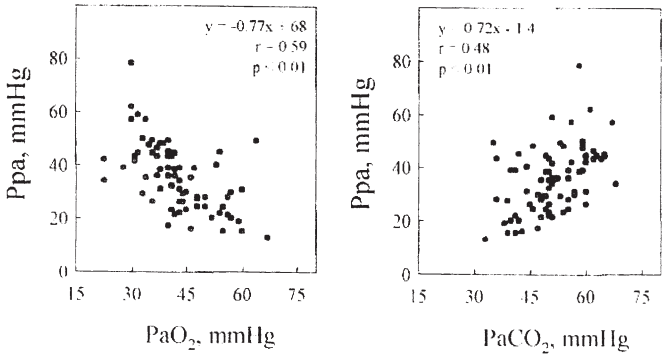

Figure 2. Mean pulmonary artery pressure (Ppa) as a function of Pa_{O_2} or Pa_{CO_2} in 74 patients with COPD. The correlations are significant but loose, and a proportion of patients has a Ppa higher than 40 mm Hg. Reprinted by permission from Reference 6.

(19). However, wasting of muscles of ambulation in COPD confuses the interpretation of cardiopulmonary exercise testing (20).

RIGHT VENTRICULAR FAILURE IN COPD

Severe pulmonary hypertension increases right ventricular afterload and eventually leads to the clinical syndrome of right heart failure with systemic congestion and inability to adapt right ventricular output to peripheral demand at exercise. Many patients with advanced COPD present with ankle edema but normal right atrial pressures (at rest). This apparent paradox has stimulated speculation that edema in COPD might be a renal rather than a right ventricular problem (21, 22). However, it is now better realized that edema in COPD is likely to be initially caused by repeated stretching of the right atrium from increased right ventricular diastolic pressures at exercise or conceivably with oxygen desaturation during sleep, causing increased sympathetic nervous system tone and activation of the renin-angiotensin-aldosterone system, with resultant renal salt and water retention. Renal salt and water retention may be aggravated by hypercapnia, which directly increases proximal tubular reabsorption of sodium, but also activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which causes additional distal tubular sodium reabsorption through amiloride-sensitive sodium channels. In summary, and as summarized in Figure 4, systemic congestion in COPD is caused by right heart failure, involving mechanisms that are very similar to those accounting for systemic and pulmonary congestion in left heart failure, but with an important additional contribution of hypercapnia (6).

TABLE 1. HEMODYNAMICS AT REST IN 74 PATIENTS WITH ADVANCED CHRONIC OBSTRUCTIVE PULMONARY DISEASE (6)

Variables	COPD	Range	Limits of Normal
Q, L/min/m^2	3.8 ± 0.8	2.2–5.2	2.6–4.6
Pra, mm Hg	4 ± 4	0–8	2–9
Pla, mm Hg	6 ± 4	2–10	4–14
Ppa, mm Hg	35 ± 12	11–59	8–20
PVR, dyne/s/cm^{-5}/m^2	660 ± 284	91–1228	40–200

Values are shown as mean ± SD.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; Pla = left atrial pressure (estimated by a pulmonary artery occluded pressure); Ppa = mean pulmonary artery pressure; Pra = right atrial pressure; PVR = pulmonary vascular resistance; Q = cardiac output.

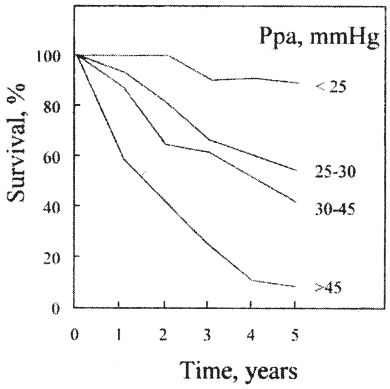

Figure 3. Prognosis of patients with COPD as a function of Ppa looks similar to reported in patients with PAH. Reprinted by permission from Reference 6.

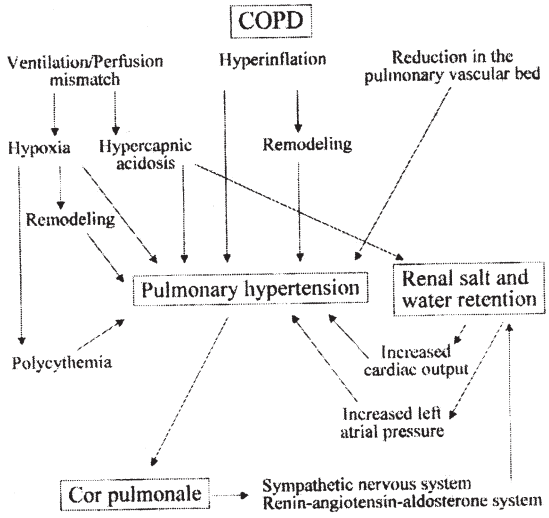

Figure 4. Pathogenesis of cor pulmonale in COPD, illustrating important roles of increased right heart filling pressures and hypercapnia. Reprinted by permission from Reference 6.

TREATMENT OF RIGHT HEART FAILURE IN COPD

What can be done to relieve the overloaded right ventricle in COPD? Standard measures aiming at improved lung mechanics and oxygenation and smoking cessation may be insufficient. Several systemic vasodilators, including calcium channel blockers, have been used in the past, with disappointing results (23). Based

on analogy to primary pulmonary hypertension, more specific interventions aiming at the restoration of endothelial vasoconstrictor-dilator imbalance could be undertaken. Randomized controlled trials of oral therapy endothelin receptor blockers (bosentan [Tracleer]) and phosphodiesterase 5 inhibitors (sildenafil [Viagra]) are being considered.

Conflict of Interest Statement: R.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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