Commentary

Pulmonary hypertension associated with COPD

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Abstract

Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease (COPD). The increase in pulmonary artery pressures is often mild to moderate, but some patients may suffer from severe pulmonary hypertension, and present with a progressively downhill clinical course because of right-sided heart failure added to ventilatory handicap. The cause of pulmonary hypertension in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy. However, recent pathological studies point, rather, to extensive remodeling of the pulmonary arterial walls, with prominent intimal changes. These aspects account for minimal reversibility with supplemental oxygen. There may be a case for pharmacological treatment of pulmonary hypertension in selected patients with advanced COPD and right-sided heart failure. Candidate drugs include prostacyclin derivatives, endothelin antagonists and inhaled nitric oxide, all of which have been reported of clinical benefit in primary pulmonary hypertension. 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 COPD patients.

Keywords chronic obstructive pulmonary disease, dobutamine, exercise, nitric oxide, oxygen, pulmonary hypertension, right ventricular failure

The article by Vizza and colleagues in this issue of *Critical Care* (page 355) raises interesting questions about the clinical relevance of pulmonary hypertension in chronic obstructive pulmonary disease (COPD) [1]. This form of pulmonary hypertension is generally believed to be hypoxic in origin and to be associated with only mild to moderate increases in mean pulmonary artery pressures (Ppa), amenable to supplemental oxygen. However, recent studies suggest a rather more complex pathobiology, leading to severe pulmonary hypertension in some patients, who might therefore benefit from more active and specific therapy.

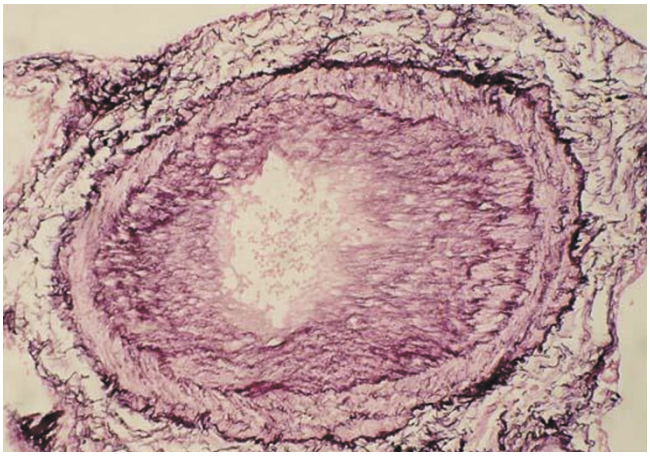
Nature of pulmonary hypertension in COPD

Pulmonary vascular remodeling in COPD is more than just medial hypertrophy from long-lasting hypoxic vasoconstriction [2,3]. In fact, as illustrated in Fig. 1, all layers of the vessel wall appear to be involved, with intimal changes being the most prominent. This peculiar pathological picture could be explained by the combined effects of hypoxia, mechanical stress and/or inflammatory reaction due to repeated stretching of hyperinflated lungs [2], and, very importantly, the toxic effects of cigarette smoke [3]. Chronic hypoxia at high altitudes induces isolated medial hypertrophy (with, sometimes, longitudinal deposition of a few smooth muscle fibers in the intima) and is associated with complete reversal of pulmonary hypertension a few weeks after return to sea level [4]. Pulmonary hypertension in COPD often is not, or is only minimially, reversible by supplemental oxygen, acutely [5] or chronically [6].

Pulmonary hypertension in COPD is generally limited to an increase in mean pulmonary artery pressure (Ppa) to 25–35 mmHg in the face of a normal cardiac output (Q) [7]. However, as illustrated in Table 1, mean pulmonary artery

COPD = chronic obstructive pulmonary disease; PaO_2 = arterial partial pressure of oxygen; Pla = left atrial pressure; Ppa = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; Q = cardiac output.

Figure 1



Optic-microscopic view of a pulmonary artery from a patient with pulmonary hypertension secondary to COPD. All three vessel wall layers are remodeled, with prominent intimal thickening.

Table 1

Hemodynamics at rest in 74 patients with advanced chronic obstructive pulmonary disease (from [7])

Variable	COPD	Range	Limits of normal
Q (l/min per m^2)	3.8 ± 0.8	2.2–5.2	2.6–4.6
Pra (mmHg)	4 ± 4	0–8	2–9
Pla (mmHg)	6 ± 4	2–10	4–14
Ppa (mmHg)	35 ± 12	11–59	8–20
PVR (dyne·s·cm^{-5} per m^2)	660 ± 284	91–1228	40–200

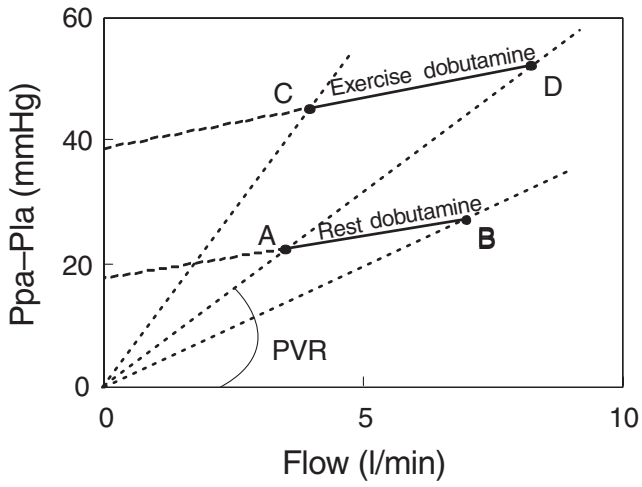
Values are mean ± SD. Pla = left atrial pressure (estimated from a pulmonary artery occluded pressure); Ppa = mean pulmonary artery pressure; Pra = right atrial pressure; PVR = pulmonary vascular resistance; Q = cardiac output.

pressures higher than 40 mmHg are not uncommon, especially in patients with at least one previous episode of acute respiratory failure [7]. The experience of patients with primary pulmonary hypertension, in whom the disease process is limited to the pulmonary vasculature, shows that pulmonary artery pressures higher than 35–40 mmHg are associated with clinical right ventricular failure and limited exercise capacity [8].

Dobutamine versus exercise stress tests

How to detect COPD patients prone to the development of severe pulmonary hypertension? One could imagine a dobutamine stress test would be revealing, with the rationale that an increase in flow would be associated with an abnormal increase in Ppa because of a restricted pulmonary vascular bed. However, in most patients with COPD, the increase in Ppa with blood flow is less than predicted by the pulmonary

Figure 2



Relations between mean pulmonary artery pressure (Ppa) minus left atrial pressure (Pla) and pulmonary blood flow in a representative patient with COPD at rest (A) and at exercise (C), redrawn from reference 9. Dobutamine is supposed to induce a passive increase in flow. Pulmonary vascular resistance (PVR) is the slope of the (Ppa – Pla)/Q relation. Passive increases in flow (A to B and C to D) increase pressure less than predicted by the PVR equation. Exercise (A to C and B to D) increases pressure more than predicted by the PVR equation.

vascular resistance (PVR) equation. Unilateral balloon occlusion studies have shown that the passive Ppa:Q curve in COPD is shifted to higher pressures with a decreased slope and an increased extrapolated pressure intercept [9], suggesting vascular closure [10]. The same phenomenon was observed with dobutamine in Vizza's study [1], which is not surprising, because a low dose of dobutamine increases flow without having an intrinsic effect on pulmonary vascular tone [11]. Vascular closure in COPD can be explained by high pulmonary volume-induced stretching of alveolar vessels and dynamic hyperinflation, as well as by remodeling of the pulmonary arteries. As illustrated in Fig. 2, a Ppa:Q relationship with decreased slope makes calculated PVR unreliable for the estimation of changes in the functional state of pulmonary resistive vessels at variable flow. In other words, a decrease in PVR brought about by dobutamine should not be interpreted as a pulmonary vasodilation.

Exercise has been used to detect familial susceptibility to pulmonary hypertension [12]. Exercise in COPD may be associated with marked increases in Ppa, especially when there is pre-existing pulmonary hypertension at rest [13]. Patients with exercise-induced pulmonary hypertension are particularly prone to develop resting pulmonary hypertension in the long term [14]. As illustrated in Fig. 2, the increase in Ppa in exercising COPD patients is greater than predicted by the PVR equation, indicating pulmonary vasoconstriction [15]. This unexpectedly large increase may be due to enhancement of hypoxic pulmonary vasoconstriction by

decreased mixed venous partial pressure of oxygen, increased tone of the sympathetic nervous system, and decreased arterial pH due to aggravated hypercapnia or lactic acidosis or both. Changes in intrathoracic pressures may also play a role. An exercise-induced increase in ventilation may aggravate dynamic hyperinflation and thereby increase alveolar pressure at expiration. Increased ventilation in the presence of obstructed airways is associated with markedly negative inspiratory pleural pressures. Negative pleural pressures are associated with decreased ventricular pressures relative to alveolar pressure and therefore correspond to an increase in right ventricular afterload.

Right ventricular failure and its treatment

Severe pulmonary hypertension increases right ventricular afterload and eventually leads to the clinical syndrome of right-sided 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) [16]. This apparent paradox has stimulated speculation that edema in COPD might be a renal rather than a right ventricular problem [17]. However, edema in COPD is probably explained by repeated stretching of the right atrium because of increased right ventricular diastolic pressures at exercise or conceivably during sleep apneas, causing increased tone of the sympathetic nervous system and activation of the renin–angiotensin–aldosterone system, with resultant renal retention of salt and water [18]. Such retention may be aggravated by hypercapnia [17,18].

What could be done to relieve the overloaded right ventricle in COPD? In addition to optimal bronchodilation to limit dynamic hyperinflation and negative pleural pressure swings, oxygen to correct hypoxemia, and diuretics to limit salt and water retention, it might be possible to limit pulmonary vascular remodeling by pharmacological interventions. Pulmonary arteries from patients who have COPD show impaired endothelium-dependent vasorelaxation [19,20]. Pulmonary arteries from heavy smokers present show a reduction in expression of endothelial nitric oxide synthase [21]. Altered endothelial function, with a vasodilator–vasoconstrictor imbalance, appears to play a role in the progression of primary pulmonary hypertension [8]. Accordingly, prostacyclin derivatives, given intravenously [22], subcutaneously [23], by inhalation [24] or even orally [25], and endothelin-receptor antagonists [26], have been reported to improve the condition of patients with primary pulmonary hypertension. Inhaled nitric oxide, given as pulses together with supplemental oxygen, might also be effective [27]. It thus appears possible to restore the endothelial vasoconstrictor–dilator imbalance.

Conclusions

At this stage, a randomized, controlled trial with one of these agents might be justified in patients with advanced COPD and clinically significant right-sided heart failure. There could be concern that vasodilators might aggravate hypoxemia by increasing ventilation/perfusion mismatching through an inhibition of hypoxic vasoconstriction or/and an increase in blood flow [15,28,29]. However, since most of the hypoxemia in COPD is caused by low ventilation/perfusion ratios, rather than by an intrapulmonary shunt, this can be easily corrected by a slight increase in supplemental oxygen [30].

Competing interests

None declared.

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