

# Pulmonary hypertension associated with COPD

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**Abstract:** Although the prevalence of pulmonary hypertension (PH) in individuals with chronic obstructive pulmonary disease (COPD) is not known precisely, approximately 10%–30% of patients with moderate to severe COPD have elevated pulmonary pressures. The vast majority of PH associated with COPD is mild to moderate and severe PH occurs in <5% of patients. When COPD is associated with PH, both mortality and morbidity are increased. There are no clinical or physical examination findings that accurately identify patients with underlying PH. Radiographic imaging findings are specific but not sensitive indicators of PH. Echocardiography is the principle noninvasive diagnostic test but may be technically limited in a significant proportion of patients with COPD. Right heart catheterization is required for accurate measurement of pulmonary pressures. The combined effects of inflammation, endothelial cell dysfunction, and angiogenesis appear to contribute to the development of PH associated with COPD. Systemic vasodilators have not been found to be effective therapy. Selective pulmonary vasodilators including inhaled nitric oxide and phosphodiesterase inhibitors are promising treatments for patients with COPD associated PH but further evaluation of these medications is needed prior to their routine use.

**Keywords:** COPD, pulmonary hypertension

## Introduction

Chronic obstructive pulmonary disease (COPD) is a significant health care burden worldwide and is the only major cause of death in the United States for which both mortality and morbidity are increasing (Murray and Lopez 1997; Hurd 2000). This disease process is manifest by progressive airflow limitation, hyperinflation and air trapping, hypoxemia, hypercapnea, and elevations in pulmonary vascular pressures. Clinically, individuals with COPD develop breathlessness, cough, sputum production and disease exacerbations that impair quality of life. Factors that portend a poor prognosis include severity of airflow limitation, ventilatory capacity, hypercapnea, and pulmonary hypertension (Burrows and Earle 1969; Weitzenblum et al 1981; Anthonisen et al 1986). Survival correlates negatively with pulmonary arterial pressure and pulmonary vascular resistance and patients with COPD and PH have increased morbidity and risk for hospitalizations for acute COPD exacerbations (Burrows et al 1972; Weitzenblum et al 1984; Kessler et al 1999; Barbera et al 2003).

PH associated with COPD is increasingly recognized as a contributing factor to the clinical manifestations, morbidity, and mortality of the COPD disease process. This recognition has stimulated further research into the cellular and molecular processes contributing to the pathogenesis of PH associated with COPD and the development and testing of new therapeutic interventions. This review will examine the epidemiology of PH associated with COPD, its clinical manifestations, methods of diagnosis, pathophysiology, and treatment strategies.

## Prevalence

The prevalence of pulmonary hypertension (PH) in COPD has not been accurately measured in large epidemiologic studies because of the risks and expense of invasive

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pressure measurement by right heart catheterization. Most studies have utilized noninvasive measures to estimate pulmonary arterial pressures. Estimates of the prevalence of PH in COPD are also confounded by patient selection. Studied patients have varying severity of obstructive lung disease as well as different levels of oxygenation. Finally, over the last several decades, different groups have used various minimal pressures to define PH and severe PH (Table 1). Therefore, estimates of the prevalence of PH in patients with COPD vary widely based upon the definition of PH, the methods used to determine pulmonary pressures, and the physiologic characteristics of the studied population.

Earlier autopsy studies demonstrated anatomic evidence of right ventricular hypertrophy in patients with COPD. Two-thirds of patients with chronic bronchitis had evidence of right ventricular hypertrophy demonstrated by increased weight of the right ventricle (Millard and Reid 1974). Similarly, 71% of 20 patients dying of COPD had right ventricular hypertrophy (Scott 1976). In contrast, one-third of 104 patients with emphysema had autopsy evidence of right ventricular hypertrophy (Leopold and Gough 1957). Subsequent studies have suggested a correlation between right ventricular hypertrophy and hypoxemia in patients with COPD (Calverley et al 1992). Recent studies utilizing magnetic resonance imaging (MRI) to measure right ventricular wall thickness and volume non-invasively demonstrated a significant increase in right ventricular wall mass that was classified as concentric hypertrophy in patients with

severe COPD and either normoxemia or mild hypoxemia (Vonk-Noordegraaf et al 2005).

Several studies have determined pulmonary pressures by right heart catheterization in groups of COPD patients with varying levels of physiologic impairment. In a series of 175 patients with moderate to severe COPD ( $FEV_1\% = 40.2 \pm 11.1\%$ ) and mild hypoxemia (40.6% with  $PaO_2 < 60$  mmHg), 62 (35%) had pulmonary artery pressures  $> 20$  mmHg at right heart catheterization (Weitzenblum et al 1981). The mean pulmonary artery pressure (mPAP) in the entire cohort was  $19.8 \pm 7.6$ . Similar results were found in a study of 53 patients with severe COPD ( $FEV_1\%$ ,  $39.8 \pm 16.2$ ); the mPAP was  $19.0 \pm 4.3$  and 23 (43%) had PH (mPAP  $> 20$  mmHg) (Doi et al 2003). Seventeen of twenty-seven (63%) patients with mild to moderate hypoxemia had PH. The mPAP was slightly greater,  $26.9 \pm 8.9$  mmHg, in 215 patients with severe COPD ( $FEV_1\%$ , 24.3%) who underwent right heart catheterization prior to lung volume reduction surgery or lung transplantation (Thabut et al 2005). Approximately half of these patients had PH (mPAP  $> 25$  mmHg) (Thabut et al 2005).

In a series of 120 patients with severe emphysema ( $FEV_1\%$ , 27% and  $PaO_2$ ,  $65.9 \pm 10.0$  mmHg) who underwent right heart catheterization during evaluation for lung volume reduction surgery in the National Emphysema Treatment trial, Scharf and colleagues (Scharf et al 2002) found a mPAP of  $26.3 \pm 5.2$  mmHg. Over 90% of these patients had PH, (mPAP  $> 20$  mmHg). Although  $PaO_2$  correlated inversely with mPAP,  $PaO_2$  was not an independent predictor of mPAP based upon multiple stepwise regression analysis (Scharf et al 2002). Severe PH, (mPAP  $> 35$  mmHg) occurred in 6 patients, 5%. Thabet and colleagues (Thabut et al 2005) found severe PH (mPAP  $> 45$  mmHg) in 8 of 215 patients (3.7%) evaluated for lung volume reduction surgery or lung transplant, whereas, (in a retrospective review) only 11 (1.1%) of 998 patients with COPD had this level of PH (Chaouat et al 2005). Thus, although the measured prevalence of PH in patients with COPD ranges from approximately 20 to 50%, very few individuals have severe PH.

Measurements of pulmonary hemodynamics in patients with COPD have shown that pulmonary pressures increase significantly with exercise. Right heart catheterizations performed in 151 patients with COPD ( $FEV_1\%$ ,  $38 \pm 12\%$  and  $PaO_2$ ,  $72 \pm 11$  mmHg) by Oswald-Mammossner and colleagues (Oswald-Mammossner et al 1991) demonstrated PH (mPAP  $> 20$  mmHg) in 31 individuals, 21%. The mPAP at rest was significantly greater,  $19 \pm 4.7$  mmHg, in patients with hypoxemia ( $PaO_2 \leq 60$  mmHg) than in normoxemic patients,  $16.8 \pm 4.9$ ,  $p < 0.05$ . Further, with exercise up to 40 watts,

**Table 1** Varying thresholds defining pulmonary hypertension and severe pulmonary hypertension

Study	Pulmonary hypertension (mmHg)	Severe pulmonary hypertension (mmHg)
Weitzenblum et al 1981	mPAP $> 20$	
Oswald-Mammossner et al 1991	mPAP $\geq 20$	
Van Dijk, 1996 (149)	mPAP $> 20$ and/or PA systolic $\geq 30$	
Pilates et al 2000	mPAP $> 25$	
Kessler et al 2001	mPAP $> 20$	
Arcasoy et al 2003	PA systolic $\geq 45$	
Doi et al 2003	mPAP $> 20$	
Scharf et al 2002	mPAP $> 20$ or PA systolic $> 30$	mPAP $> 30$ or PA systolic $> 45$
Thabet et al 2005	mPAP $> 25$	mPAP $> 45$
Stevens et al 2000		mPAP $\geq 40$
Chaouat et al 2005		mPAP $\geq 40$

**Abbreviations:** mPAP, mean pulmonary artery pressure; PA, systolic pulmonary artery systolic pressure.

two-thirds, 99 of 151 patients, developed mPAP  $\geq 30$  mmHg. In the 49 patients in whom pulmonary vascular resistance could be calculated at both rest and with exercise, pulmonary vascular resistance did not change significantly with exercise. Christensen and co-workers (Christensen et al 2004) demonstrated a similar incidence of exercise induced PH, 65% in a series of 17 patients with COPD (FEV<sub>1</sub>% 35  $\pm$  10%, PaO<sub>2</sub> 10.6  $\pm$  1.1 kPa) who exercised at a work load of 25 watts. The mPAP was 19.9  $\pm$  4.5 mmHg at rest and increased to 35.0  $\pm$  2.2 mmHg with exercise. Eleven patients, 65%, had mPAP greater than 30 mmHg with exercise. Fujimoto and collaborators (Fujimoto et al 2002) studied pulmonary hemodynamics in 75 patients with mild hypoxemia (PaO<sub>2</sub> >60 mmHg) at rest and either mild (FEV<sub>1</sub>% >50%), moderate (FEV<sub>1</sub>% <50% or >35%), or severe COPD (FEV<sub>1</sub>%  $\leq$ 35%) at rest and with exercise. At rest, mPAP's were 21.5  $\pm$  2.7, 20.0  $\pm$  4.2, and 21.7  $\pm$  1.1 mmHg in the mild, moderate, and severe groups, and increased to 32.7  $\pm$  3.2, 38.1  $\pm$  2.1, and 44.4  $\pm$  2.0 mmHg, respectively, with exercise. Thus, exercise potentially elevates PA pressures in individuals with COPD.

Kessler and co-workers (Kessler et al 2001) studied the change in pulmonary hemodynamics with time in a group of 131 patients with moderate COPD (FEV<sub>1</sub>%, 34.6  $\pm$  15.7% and PaO<sub>2</sub> 67.0  $\pm$  10.4 mmHg). Upon initial right heart catheterization, no patient had a resting mPAP >20 mmHg. After a mean interval of 6.8  $\pm$  2.9 years, 33 (25%) patients had developed PH (mPAP >20) with a range of 20–32.5 mmHg. The average rate of increase in pulmonary arterial pressure was 0.4 mmHg/year. Patients who developed resting PH had higher resting and exercise mPAP and lower resting and exercise PaO<sub>2</sub>.

Thus, although numerous studies have measured pulmonary hemodynamics in patients with COPD, the prevalence of PH is not accurately known. Analysis of these studies is confounded by different sub-groups of individuals with varying severities of COPD and oxygenation and generally small numbers of patients. Nonetheless, the minimal prevalence of PH in patients with at least 1 hospitalization for COPD has been estimated to be 10%–30% (Naeije 2005) and is as high as 90% in patients undergoing evaluation for lung volume reduction surgery (Scharf et al 2002). Exercise induced PH may occur in two-thirds of patients with COPD even when pulmonary pressures are normal at rest (Oswald-Mammosser et al 1991; Christensen et al 2004).

## Diagnostic testing

### Physical examination

In a retrospective analysis of 27 patients with COPD and severe PH, Chaouat and colleagues (Chaouat et al 2005)

identified 16 individuals with other diseases or processes including appetite suppressant exposure, collagen vascular disease, portal hypertension, left ventricular disease, thromboembolic disease, restrictive lung disease, and sleep apnea syndrome that could cause or contribute to the development of PH. Therefore, a careful clinical history is required to identify or exclude recognized causes of PH in individuals with COPD. A thorough medication history including prior use of anorexigens or chemotherapeutic agents should be elicited. Potential exposures to hepatitis B and C and HIV need to be evaluated with serologies. A high prevalence of pulmonary embolism, 25%, has been detected by spiral computed tomography in patients with unexplained exacerbations of COPD (Tillie-Leblond et al 2006). Therefore, a careful evaluation to exclude chronic thromboembolic PH is warranted in all individuals with COPD. Other pulmonary processes such as concurrent interstitial lung disease should be pursued. Cottin and co-workers (Cottin et al 2005) described 61 patients with both emphysema of the upper lung zones and diffuse parenchymal lung disease with fibrosis of the lower lung zones, of whom approximately 47% had PH. A careful history of skin, joint, and muscle symptoms should be obtained to exclude connective tissue disease. Smoking is not only a leading cause of COPD, it is also a significant risk factor for the development of ischemic heart disease; therefore, a complete cardiac history and review of symptoms is also important in the evaluation of PH in patients with COPD. Both systolic and diastolic left ventricular function should be assessed.

The signs and symptoms of PH in patients with COPD are subtle and are often obscured by the clinical manifestations of the lung disease. Exertional breathlessness may be due to worsening airflow limitation and air trapping or to the development of PH (Salvaterra and Rubin 1993). Although the predictive value of specific symptoms and physical examination findings in detecting pulmonary vascular disease in a patient with COPD is not known, several signs and symptoms suggests the presence of PH (Salvaterra and Rubin 1993). Decreasing functional capacity with stable pulmonary function testing suggests pulmonary vascular involvement. Signs of right ventricle enlargement or overload such as the presence of a right ventricular lift, prominent P2, right sided S4 gallop, and the murmur of tricuspid regurgitation suggest the presence of PH (Salvaterra and Rubin 1993). Elevated jugular venous pressure, hepatojugular reflux, and a pulsatile liver are often signs of tricuspid insufficiency.

### Chest imaging

The characteristic chest radiographic findings of PH are enlargement of the central pulmonary arteries causing hilar

prominence and rapid tapering of the arteries in the lung periphery. Co-existing emphysematous changes accentuate oligemia within the lung parenchyma. The hilar thoracic index, the ratio of the distance between the start of the divisions of the right and left pulmonary arteries and the transverse diameter of the chest, has been used to quantify widening of the mediastinum (Chetty et al 1982). PH is suggested by a hilar-thoracic index  $>0.36$ . Widening of the descending right pulmonary artery to  $>16$  mm or the left descending pulmonary artery to  $>18$  mm suggest PH in patients with COPD (Matthay et al 1981). Chhabra and De (Chhabra and De 2004) confirmed the high sensitivity and positive predictive value, 100%, of the findings of increased hilar-thoracic index and width of the descending branch of the right pulmonary artery ( $>20$  mm) in 50 patients with COPD but showed that both measures were insensitive and had a low negative predictive value.

Measurement of pulmonary vessels by chest CT imaging has also been used to detect the presence of pulmonary hypertension. In a study of 36 patients with PH due to variable causes (4 had COPD), enlargement of the main pulmonary artery diameter to  $\geq 29$  mm had a sensitivity of 87%, a specificity of 89%, and a positive predictive value of 97% (Tan et al 1998). Additionally, the presence of pulmonary hypertension was predicted if the ratio of the diameters of the segmental artery to the corresponding bronchus was  $>1$  in 3 or more lobes (Tan et al 1998). Other investigators have suggested that because the diameter of the main pulmonary artery varies normally, an absolute size threshold is not useful for the diagnosis of PH (Haimovici et al 1997). Ng and co-workers (Ng et al 1999) determined the ratio of the diameter of the main pulmonary artery to the diameter of the ascending aorta in a group of 50 patients with various pulmonary and cardiovascular diseases who had undergone right heart catheterization. A ratio of the pulmonary artery to aortic diameter  $>1$  was 70% sensitive and 92% specific for PH. The positive predictive value was 96% and the negative predictive value was 52%. Thus, the presence of an enlarged main pulmonary artery with a diameter greater than that of the ascending aorta strongly suggests the presence of PH but a ratio  $<1$  does not exclude the presence of PH.

## Electrocardiogram

PH associated with COPD may cause right ventricular hypertrophy or strain. The electrocardiographic manifestations of cor pulmonale are relatively specific, 86%, but not sensitive, 51%, for PH and do not correlate with the severity of PH (Oswald-Mammosser et al 1987; Himelman et al 1988).

Features of the electrocardiogram in patients with COPD that suggest PH include: A) P pulmonale, P-wave amplitude  $>2.5$  mm in leads II, III, and/or aVF; B)  $S_1$ ,  $S_2$ ,  $S_3$  pattern; C) a  $S_1$ ,  $Q_3$  pattern; D) incomplete or complete right bundle branch block; E) evidence of RVH, R axis deviation  $\geq 100^\circ$ , dominant R wave in lead  $V_1 \geq 7$  mm in amplitude, ST segment depression and T wave inversion in leads  $V_1$  to  $V_4$ , and deep S waves in leads  $V_5$ ,  $V_6$ , I and aVL with a QRS duration  $<0.12$  s; and F) low voltage QRS (Harrigan and Jones 2002; Barbera et al 2003).

## Echocardiography

Noninvasive estimation of systolic pressures by Doppler echocardiography has been studied extensively for the detection of PH in individuals with COPD. Several techniques are used, but most frequently, tricuspid regurgitant flow is detected and the maximum jet velocity is measured by continuous wave Doppler. Using the Bernoulli principle, the peak velocity,  $v$ , is used to calculate the trans-tricuspid gradient,  $4v^2$ . The systolic PAP is considered equal to the RV systolic pressure as long as there is no evidence of RV outflow obstruction. RV systolic pressure is calculated as the sum of the trans-tricuspid gradient plus the estimated right atrial pressure (RAP). Early studies used a fixed estimation of 15 mmHg for RAP whereas subsequent studies estimate the RAP based upon the size of the inferior vena cava during inspiration: no collapse, 15 mmHg; partial collapse 10 mmHg; and complete collapse 5 mmHg (Bredikis and Liebson 1998; Arcasoy et al 2003). In addition to these estimations, determination of sPAP by Doppler echocardiography is limited by technical factors. Tricuspid insufficiency must be present to measure a maximal jet velocity. Chest wall configuration, especially the presence of air trapping and cardiac orientation, may affect the utility of this technique in patients with COPD (Arcasoy et al 2003).

Doppler echocardiographic success in estimating sPAP in patients with COPD ranges from 26%–66% (Laaban et al 1989; Tramarin et al 1991; Bach et al 1998; Arcasoy et al 2003). In a series of 374 patients undergoing evaluation for lung transplantation, Arcasoy and colleagues (Arcasoy et al 2003) were technically able to estimate sPAP in only 38% of patients with obstructive lung disease but were successful in 54% of patients with interstitial lung disease and 67% with pulmonary vascular disease. A residual volume  $>150\%$  of predicted reduced the success rate of Doppler echocardiography. In an unselected series of 73% patients with COPD seen in an outpatient clinic, sPAP could be estimated in 56, 77% (Higham et al 2001). Although there were no

differences in spirometry and diffusing capacity between the measurable and non-measurable groups, lung volumes were not determined.

Laaban and colleagues (Laaban et al 1989) compared the measurement of PAP by Doppler echocardiography with right heart catheterization in 41 patients with stable COPD. The directly measured mean sPAP was  $38.5 \pm 14.9$  mmHg and 21, 51%, had pressures  $\geq 35$  mmHg. sPAP could be estimated by Doppler echocardiography in 27 patients, 66%, and correlated significantly with the direct hemodynamic measurements,  $r = 0.65$ ,  $p < 0.001$ . In a select subgroup of patients who were undergoing evaluation for lung volume reduction surgery and had both Doppler echocardiography and right heart catheterization, Bach and co-workers (Bach et al 1998) did not find a significant correlation between the actual and estimated sPAP but suggested that this difference was due to a single outlying patient. A strong correlation between right heart catheterization and Doppler echocardiographic measurement of sPAP,  $r = 0.8$ , was seen in a group of 106 patients undergoing evaluation prior to lung transplantation, of whom 45, 42.5%, had obstructive lung disease (Ben-Dor et al 2006).

Transcutaneous jugular venous Doppler echo is another sonographic technique to estimate pulmonary pressures (Matsuyama et al 2001). During a breath hold at the end of expiration, jugular venous flow velocities are measured by Doppler echo during diastole and systole. An increasing diastolic to systolic flow ratio correlates significantly with mPAP measured during RHC (Matsuyama et al 2001). Using a diastolic to systolic flow velocity ratio of 1.0, the sensitivity of this technique was 71.4% and the specificity was 95.3%. Limitations of transcutaneous jugular venous Doppler echo include variable ratios in patients with mild PH (25–35 mmHg) and variable flow rates with tachycardias and dysrhythmias.

## Histopathology

In 1965, Hicken et al (1965) described the histopathologic changes in the pulmonary vasculature of patients with chronic bronchitis or emphysema and evidence of right ventricular hypertrophy. They noted a circular layer of smooth muscle in the media of the pulmonary arterioles that was not present in the smaller pulmonary arteries. Both the pulmonary arterioles and small pulmonary arteries had a layer of longitudinal smooth muscle beneath the internal elastic lamina but neither one of the vessels had significant intimal fibrosis. Because these vascular changes were similar to the alterations reported in PH associated with high altitude, Hicken et al (1965)

hypothesized that PH associated with hypoxic lung diseases such as COPD was caused solely by hypoxic vasoconstriction and arteriolar muscular hyperplasia. Subsequent observations that high altitude PH resolves after descent to lower altitudes (Grover et al 1996) suggested that PH associated with COPD might reverse with correction of hypoxemia. Contrary to the expected result, pulmonary pressures decreased but did not normalize in individuals with PH associated with COPD who were treated with supplemental oxygen therapy (Abraham et al 1968). Subsequent studies of acute and chronic oxygen therapy in patients with COPD also failed to show resolution of PH (Lejeune et al 1984; Timms et al 1985). These physiologic findings suggested that the PH associated with COPD that persists after correction of hypoxemia is due to fixed vascular remodeling and spurred further, more detailed histopathological studies (Wilkinson et al 1988; Peinado et al 1999; Hale et al 1980). In 1988, Wilkinson (Wilkinson et al 1988) observed similar histopathologic findings in lung tissue from 10 patients with hypoxic cor pulmonale and COPD regardless of treatment with supplemental oxygen. The media of the muscular pulmonary arteries was normal or atrophic but the intima revealed an active deposition of longitudinal muscle, fibrosis and elastosis. The media of the normally poorly muscularized arterioles revealed a circular muscular coat bounded by a new internal elastic lamina. Luminal narrowing was present with frequent recanalization of the arteriolar lumen (Wilkinson et al 1988). Subsequent studies of lung tissue from individuals with moderate to severe COPD have consistently reported similar findings (Wright et al 1983; Hale et al 1984; Wright et al 1992). Interestingly, when lung sections from smokers with COPD were compared with non-smokers, the density of the fully muscularized (0–300  $\mu$ m diameter) pulmonary arteries and the thickness of the medial muscle layer was doubled and the depth of intimal fibrosis was tripled (Hale et al 1984). This intimal thickening is due to both smooth muscle cell proliferation and increased elastin and collagen deposition (Santos et al 2002).

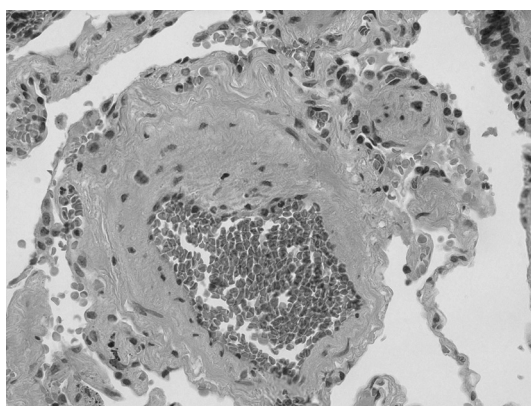
Importantly, similar findings of vascular remodeling are present in the pulmonary vasculature of smokers (Santos et al 2002; Hale et al 1980) and patients with mild COPD (Santos et al 2002). The earliest vascular changes are intimal thickening, luminal narrowing, and arteriolar muscularization (Hale et al 1980; Magee et al 1988; Barbera et al 1994; Peinado et al 1998). The degree of intimal thickening correlates with the severity of small airways disease and emphysema (Hale et al 1980). These very early histopathologic findings suggest that the morphologic changes in the

pulmonary arteries are initiated by the toxic effects of tobacco smoke and progress in parallel with the parenchymal changes of COPD (Hale et al 1980) (Figure 1).

## Pathophysiology

The pulmonary vasculature of patients with COPD associated PH is markedly abnormal and shows increased intimal and medial thickening that cause luminal narrowing and vascular obstruction of the small pulmonary arteries (Wright et al 1992). These vascular changes lead to an increase in pulmonary vascular resistance (PVR) and elevation of pulmonary artery pressures (PAP). The severity of vascular abnormalities does not correlate directly with the pulmonary pressure at rest (Wilkinson et al 1988; Wright et al 1992). However, the degree of intimal thickening is proportional to the increase in pulmonary pressure during exercise and this relationship is thought to be due in part to decreased distensibility and recruitment within the abnormal pulmonary vasculature (Kubo et al 2000).

In most cases, PH associated with COPD develops slowly over time and the pressure increases approximately 0.4 mmHg yearly (Kessler et al 2001). Moderately severe COPD is associated with PH in 10%–35% of patients (Scharf et al 2002; Eddahibi et al 2003). PH leads to pressure overload of the right ventricle (RV). RV muscular hypertrophy occurs in response to the increased pulmonary pressures (Dias et al 2002) and occurs in up to 40%–70% of patients with COPD at autopsy (11,62). Hypertrophy is followed by contractile dysfunction of the RV (Voelkel et al 2006). The contractile dysfunction leads to RV dilation, a decrease in cardiac output, and an increase in right sided filling pressures (Voelkel et al 2006). The dilation and pressure overload of



**Figure 1** Histologic evidence of vascular changes in a small pulmonary artery in a patient with COPD and associated pulmonary hypertension. Hematoxylin and eosin staining demonstrates marked medial and intimal thickening with resulting luminal narrowing (40X, original magnification). Photomicrograph was provided courtesy of Hai Bui, MD, Department of Pathology, Cincinnati VAMC, Cincinnati Ohio.

the RV causes left ventricular (LV) diastolic dysfunction (Louie et al 1995). Eventually, the ability of the RV to compensate is overwhelmed and RV failure ensues.

## Pathogenesis

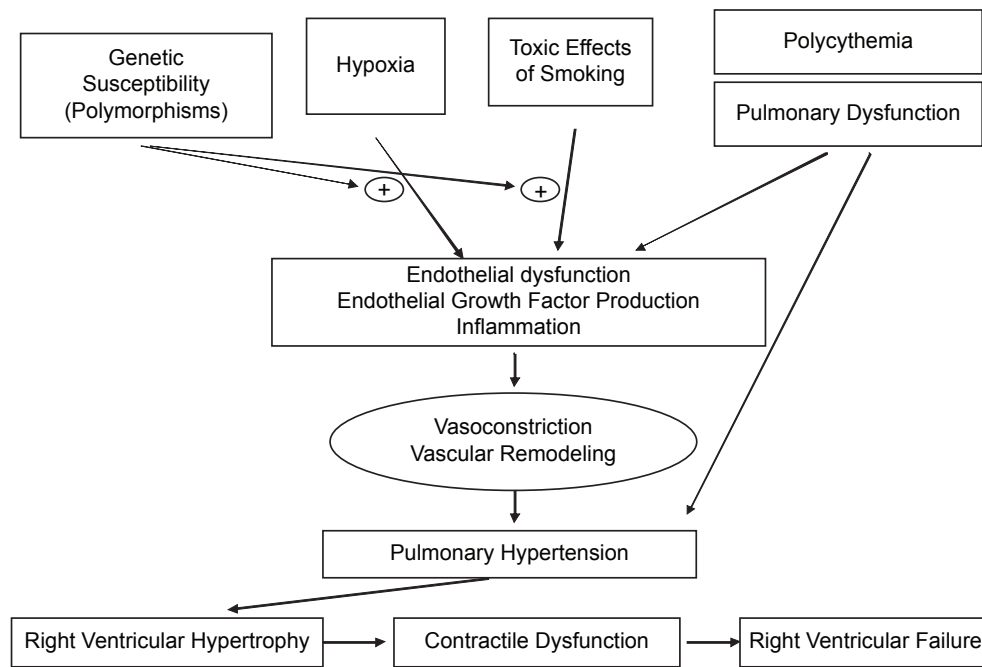
The pathogenesis of the vascular abnormalities associated with COPD have not been fully elucidated but appear to be caused by the combined effects of hypoxia (Burrows 1974), pulmonary dysfunction with air trapping (Wright 1993) and the toxic effects of smoking (Santos et al 2002; Hale et al 1980) leading to inflammation (Peinado et al 1999), endothelial dysfunction (Dinh-Xuan et al 1991; Peinado et al 1998), and angiogenesis (Santos et al 2003) (Figure 2).

## Hypoxia

Unlike the systemic circulation, acute hypoxia causes vasoconstriction in the pulmonary circulation (Von Euler and Liljestrand 1946) and a transient increase in pulmonary vascular resistance (Pease et al 1982). Although the effect of recurrent, transient episodes of hypoxia in the development of pulmonary vascular dysfunction is unclear, chronic hypoxia has been studied extensively and is a known cause of PH (Heath et al 1973; Thompson et al 1989; Vender 1994; Reeves and Grover 2005). The pathophysiologic mechanisms of hypoxic pulmonary vasoconstriction are not fully understood but are believed due to direct and indirect effects of lowered oxygen levels on the pulmonary vascular smooth muscle cells (Hida et al 2002). The direct action occurs through potassium and calcium channels (Weir and Archer 1995). In the presence of hypoxia, potassium channels within pulmonary smooth muscle cells close causing membrane depolarization and an influx of calcium, stimulating smooth muscle cell contraction (Weir and Archer 1995). Hypoxia may also act indirectly on the pulmonary vasculature by stimulating the production of transcription factors (Yan et al 1998; Mechtcheriakova et al 1999) such as hypoxia-inducible factor-1 (HIF-1) (Semenza 2000; Yu et al 1998) and the release of multiple endogenous mediators including angiotensin II (Morrell et al 1995), endothelin-1 (Chen et al 1995; DiCarlo et al 1995; Elton et al 1992; Hu et al 1998), and growth factors (Mechtcheriakova et al 1999; Santos et al 2003). These mediators trigger vasoconstriction, vascular remodeling, and angiogenesis.

## Disturbances in pulmonary function/air trapping

Animal models of smoke-induced emphysema and PH suggest that PH associated with COPD is due in some part to hyperinflation and gas trapping that compress the pulmonary



**Figure 2** Pathophysiology of PH and right ventricular dysfunction associated with COPD. The combined action of hypoxemia, toxic tobacco smoke, pulmonary dysfunction, and polycythemia lead to endothelial dysfunction, growth factor production, and inflammation in the pulmonary vasculature. These processes cause elevation of pulmonary arterial pressures. PH may cause RV hypertrophy and subsequent RV contractile dysfunction and RV failure.

vessels (Wright 1993). However, PH has not been shown to improve after lung volume reduction surgery (LVRS) despite improvement in pulmonary function and reduction in gas trapping (Haniuda et al 2003).

## Polycythemia

Secondary polycythemia occurs in COPD with hypoxia and causes an increase in blood viscosity. However, to date, there are few studies evaluating the relationship between blood viscosity, polycythemia, and PH. A retrospective analysis of 41 patients with emphysema revealed that increasing levels of hemoglobin independently correlated with increasing PVR and PAP (Nakamura et al 2000). Polycythemia also inhibits the vasodilatory effect of acetylcholine in patients with COPD. This effect is believed to be due to the inactivation of endothelial derived NO by hemoglobin (Defouilloy et al 1998).

## Toxic effects of cigarette smoke

Tobacco smoke is not only toxic to the airways and lung parenchyma but also has an effect on the pulmonary vasculature and may play a significant role in the development of PH. The small pulmonary arteries of smokers develop intimal thickening due to elastin deposition, increased collagen production, and smooth muscle proliferation regardless of the development of obstructive lung disease (Santos et al 2002; Hale et al

1980). The etiology of these changes is not fully understood; however, tobacco smoke does induce vascular inflammation (Peinado et al 1999) and impairs endothelial function (Barbera et al 2001). The number of CD8+ T-lymphocytes infiltrating the adventitia of the small muscular pulmonary arteries is increased in both smokers and patients with COPD. The degree of inflammatory infiltrate correlates positively with pulmonary arterial intimal thickness in patients with COPD (Peinado et al 1999). It is possible that this inflammatory infiltrate serves as a source of cytokines and growth factors leading to the medial hypertrophy, thickening, and luminal obstruction observed in smokers (Peinado et al 1999).

Vasoactive mediators also appear to play a role in smoking related pulmonary vascular changes. Brief exposure to tobacco smoke up-regulates gene expression of the vasoconstrictor/vasoproliferative agents endothelin-1 (ET-1) and vascular endothelial growth factor (VEGF) in Sprague-Dawley rats (Wright et al 2002). The expression of VEGF is also increased in the pulmonary arteries of smokers and correlates with the thickness of the pulmonary arteries and the degree of obstructive lung disease (Santos et al 2003). Smoke exposure also alters NO production in endothelial cells. When the lungs of smokers are compared with those of non-smokers, smokers have lower endothelial nitric oxide synthase (eNOS) levels (Barbera et al 2001). Further, in vitro exposure of pulmonary

artery endothelial cells to tobacco smoke causes irreversible inhibition of eNOS activity (Su et al 1998).

## Genetics

Multiple genetic polymorphisms within several different genes correlate with the development of pulmonary vascular disease in patients with COPD associated PH. The angiotensin converting enzyme (ACE) gene contains insertion (I) or deletion (D) polymorphisms that create three genotypes (DD, II, and DI) (Rigat et al 1992). The deletion polymorphism is associated with increases in circulating angiotensin converting enzyme (ACE) levels (Rigat et al 1990). The DI polymorphism is associated with the development of PH in Caucasians with COPD (Tkacova et al 2005). Additionally, the DI genotype may confer susceptibility to exercise induced PH in patients with COPD (Kanazawa et al 2000). Polymorphisms of the endothelial nitric oxide synthase (eNOS) gene are also present in patients with COPD. The BB polymorphism of the eNOS gene is associated with PH in patients with COPD. (Yildiz et al 2003). The serotonin transporter (5-HTT) plays a role in smooth muscle hyperplasia and vascular remodeling (Eddahibi et al 2001). L allelic polymorphisms of the 5-HTT gene promoter cause 5-HTT over-expression. LL and LS 5-HTT are more common in patients with idiopathic pulmonary arterial hypertension (IPAH) than in controls (Eddahibi et al 2001). In patients with COPD, the LL 5-HTT gene polymorphism is associated with the presence of PH in hypoxemic COPD patients and correlates with the severity of PH (Eddahibi et al 2003). The GG polymorphism of the interleukin-6 (IL-6) gene leads to increased levels of IL-6 and occurs more commonly in COPD patients with PH than in those with COPD alone (Yildiz et al 2003).

## Pathobiology

### Endothelial dysfunction

The production of vasoactive chemokines by pulmonary endothelial cells is dysregulated during hypoxic stress (Chen et al 1995; DiCarlo et al 1995; Elton et al 1992) and toxin exposure (Wright et al 2002; Wright et al 2004; Santo et al 2003). Endothelial dysfunction also occurs in patients with COPD (Dinh-Xuan et al 1991; Peinado et al 1999) and with COPD associated PH (Giaid et al 1993; Clini et al 2000).

Nitric oxide (NO) is a potent vasodilating mediator with antiproliferative effects (Murad 1997). NO is synthesized in the pulmonary vasculature by endothelial nitric oxide synthase (eNOS). eNOS expression is reduced in smokers (Barbera et al 2001) and patients with COPD (Giaid and Saleh 1995).

Fractional exhaled nitric oxide (FENO) is also reduced in patients with COPD and PH. FENO levels correlate inversely with the degree of PH and the development of cor pulmonale (Clini et al 2000). It is postulated that the reduction in FENO seen in patients with COPD, PH, and cor pulmonale is due to a decrease in endothelial production of NO.

Prostacyclin is another potent endothelial cell-derived vasodilating mediator that inhibits platelet aggregation (Gerber et al 1980) and has antiproliferative effects (Hara et al 1995). It is synthesized by prostacyclin synthase via the arachidonic acid pathway (Alhenc-Gelas et al 1982). Prostacyclin synthase is reduced in patients with IPAH (Tuder et al 1999) and in patients with emphysema (Lee et al 2005; Nana-Sinkam et al 2006). However, little is known about the role that prostacyclin plays in COPD associated PH.

Endothelin (ET-1) is a potent vasoconstricting (LeDouceur et al 1993) and mitogenic mediator produced by the endothelium (Dubin et al 1989; Boscoe et al 2000; Wedgewood et al 2001). Endothelin levels are increased in patients with COPD (Spiropoulos et al 2003), and rise further during COPD exacerbations (Roland et al 2001). Endothelin levels are increased in patients with pulmonary arterial hypertension (PAH) and PH associated with COPD, interstitial lung disease (ILD) and congestive heart failure (CHF) (Giaid et al 1993).

### Growth factors

It is currently unclear what role growth factors play in the development and maintenance of the pulmonary vascular abnormalities observed in COPD and PH (Papaioannou et al 2006). VEGF is an endothelial growth factor that stimulates angiogenesis and permeability (Papaioannou et al 2006). VEGF expression is increased in the pulmonary arteries of patients with COPD (Santos et al 2003). Hypoxia also stimulates VEGF production via the transcription factor Hypoxia-Inducible Factor-1 (HIF-1) (Carmeliet et al 1998; Iyer et al 1998; Semenza 2000). Although VEGF is a potent endothelial cell mitogen and is increased in smokers and patients with COPD and hypoxia, VEGF may also have a protective role in the pulmonary vasculature. When animals treated with a VEGF inhibitor are exposed to hypoxic conditions, severe PH develops (Taraseviciene-Stewart et al 2001). Additional studies are needed to understand VEGF's potential protective role in the development of pulmonary vascular changes in patients with COPD.

Platelet derived growth factor (PDGF) is another mediator of angiogenesis that may be involved in vascular remodeling in hypoxia and COPD. PDGF is a potent mitogen for



smooth muscle cells (Hannink and Donoghue 1989). Indirect evidence that PDGF is important in the development of PH comes from rat models of hypoxic and monocrotaline induced PH that demonstrate reversal of PH after inhibition of PDGF (Schermyly et al 2005).

## Inflammation

The role of inflammation in the pathogenesis of COPD associated PH is uncertain. The degree of inflammatory infiltrate within the pulmonary vascular adventitia of patients with COPD correlates with the severity of the intimal thickening in the pulmonary arteries (Peinado et al 1999). Additionally, systemic inflammatory markers, C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-alpha), are increased in COPD patients with PH (Joppa et al 2006) when compared with COPD patients without PH. However, the significance of these findings is unclear and additional investigations are needed to determine the etiologic significance of inflammation in the vascular remodeling that occurs with smoking, COPD, and COPD associated PH.

## Management

The treatment of patients with COPD associated PH requires a multifaceted approach that includes smoking cessation, optimization of COPD management, and correction of hypoxemia. Additionally, recent advances in the understanding of the pathogenesis of COPD associated PH provide several potential biologic targets for future therapies.

## Smoking cessation

Toxic effects of tobacco smoke (Santos et al 2002; Hale et al 1980) play a role in the development of the pulmonary vascular disease that occurs in COPD associated PH. Smoking cessation is the single most important intervention to slow progression of COPD (Anthonisen et al 1994; Anthonisen et al 2002) and thus likely decreases the risk of developing COPD associated PH. Once an individual quits smoking, resumption of cigarettes should be continually discouraged as there is a steeper rate of decline in FEV1 in patients who restart smoking than in those who smoke without interruption (Sherrill et al 1996).

## Supplemental oxygen

Correction of hypoxemia with supplemental oxygen is also recommended therapy for patients with COPD and PH. Long term oxygen therapy is recommended for patients with COPD whose resting PaO<sub>2</sub> is <55 mmHg or is between 56 and 59 mmHg during rest, sleep, or exertion and who have clinical

evidence of cor pulmonale or polycythemia (Celli et al 2004). Long term oxygen therapy (LTOT) improves survival in hypoxic COPD patients and is associated with a mild improvement in pulmonary hemodynamics (Medical Research Council Working Party 1981; Nocturnal Oxygen Therapy Group 1980). Additionally, supplemental oxygen during exercise decreases PAP (Burrows et al 1972; Fujimoto et al 2002), increases exercise tolerance (Fujimoto et al 2002) and improves RV function (Olvey et al 1980). Pulmonary pressures are known to increase with sleep in patients with COPD associated PH (Raeside et al 2002). Acutely, oxygen therapy abolishes this nocturnal rise in pulmonary pressures (Raeside et al 2002). Long term nocturnal oxygen decreases pulmonary pressures in patients with moderate to severe COPD, PH, and daytime PaO<sub>2</sub> >60 mmHg but who experience nocturnal desaturation (Fletcher et al 1992). A 3 year randomized trial involving 51 patients with moderate to severe COPD and PH demonstrated that patients with nocturnal desaturation treated with supplemental oxygen experienced a 3.7 mm Hg decrease in PAP whereas those patients with nocturnal desaturation who were treated with room air experienced a 3.9 mm Hg increase in PAP (Fletcher et al 1992). LTOT also ameliorates the progression of COPD associated PH. In 1985, Weitzenblum and colleagues (Weitzenblum et al 1985) evaluated the progression of COPD associated PH before and after 2–4 years of LTOT. Prior to LTOT, the PAP increased by approximately 1.47 ± 2.3 mmHg per year whereas the PAP decreased by 2.15 ± 4.4 mmHg per year with oxygen therapy. Despite the beneficial effects of oxygen therapy in patients with hypoxemia and COPD, LTOT does not lead to the normalization of pulmonary pressures (Abraham et al 1968) or the reversal of morphologic derangements in the pulmonary vasculature (Wilkinson et al 1988). Therefore, additional interventions are needed to treat the fixed vascular remodeling in COPD associated PH.

## Systemic vasodilators

Calcium channel blockers (CCB) have been studied extensively in COPD associated PH. Acutely, the administration of a short acting CCB (nifedipine) decreases the PAP, increases cardiac index (CI) (3.7 ± 0.2 to 4.6 ± 0.3 L/min/m<sup>2</sup>) and decreases PVR (426 ± 52 to 294 ± 28 dyne•s<sup>-1</sup>•cm<sup>-5</sup>) (Sturani et al 1983). The acute improvement in hemodynamics with CCB has been reproduced by several other investigators (Garzaniti et al 1985; Muramoto et al 1985). Despite the acute beneficial effects of CCB's, they are ineffective long term pulmonary vasodilators (Agostoni et al 1989) and do not effect progression of COPD associated PH (Sturani et al

1983). Additionally, CCB's can alter ventilation perfusion (VQ) matching deleteriously and worsen hypoxemia (Melot et al 1984). Due to these negative side effects, CCB's are not recommended in the routine management of COPD associated PH.

Hydralazine has been tested in stable patients with PH secondary to COPD. Acutely, hydralazine improved pulmonary hemodynamics and oxygenation in a small group of hypoxemic COPD patients (Keller et al 1984). However, nearly one quarter of the patients (3/14) could not tolerate hydralazine due to tachycardia. Hydralazine neither improves pulmonary hemodynamics in patients during COPD exacerbations nor increases exercise capacity in patients with severe COPD and associated PH (Cerda et al 1985; Dal Nogare and Rubin 1986).

Modulation of the renin-angiotensin systems has also been studied in COPD associated PH. Animal studies suggested that angiotensin converting enzyme (ACE) inhibition may be beneficial in the treatment of COPD associated PH (Nong et al 1996); however the intravenous administration of captopril did not result in an acute change on pulmonary hemodynamics in patients with COPD (Patakas et al 1988). Furthermore, chronic treatment of patients with COPD associated PH with losartan did not result in a statistically significant change in echocardiography, exercise capacity, or respiratory symptoms (Morrell et al 2005).

## Theophylline

Theophylline is a phosphodiesterase inhibitor used in the treatment of COPD. In a small study, it has been shown to reduce pulmonary artery pressures acutely with intravenous bolus administration (Liu et al 1992). Further studies are needed to validate this finding and to assess the effect of chronic theophylline therapy on COPD associated PH.

## Future therapeutic targets

The most likely targets of future therapies in COPD associated PH are the endothelium and pulmonary vascular remodeling. Interventions aimed at these targets include nitric oxide (NO), phosphodiesterase inhibitors (PDEI) and statins.

NO is a selective pulmonary vasodilator that does not cause systemic hypotension (Pepke-Zaba et al 1991) and is effective treatment for idiopathic PH (Pepke-Zaba et al 1991). In patients with COPD associated PH, 3 months of therapy with inhaled pulsed NO via nasal cannula improved pulmonary hemodynamics. The mean pulmonary artery pressure (mPAP) decreased from 27.6 to 20.6 mmHg,

PVR decreased from 276.9 to 173  $\text{dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$  and no worsening of hypoxemia occurred (Vonbank et al 2003). However, when Barbera and colleagues (Barbera et al 1996) administered inhaled NO (40 ppm) to patients with COPD, VQ matching worsened.

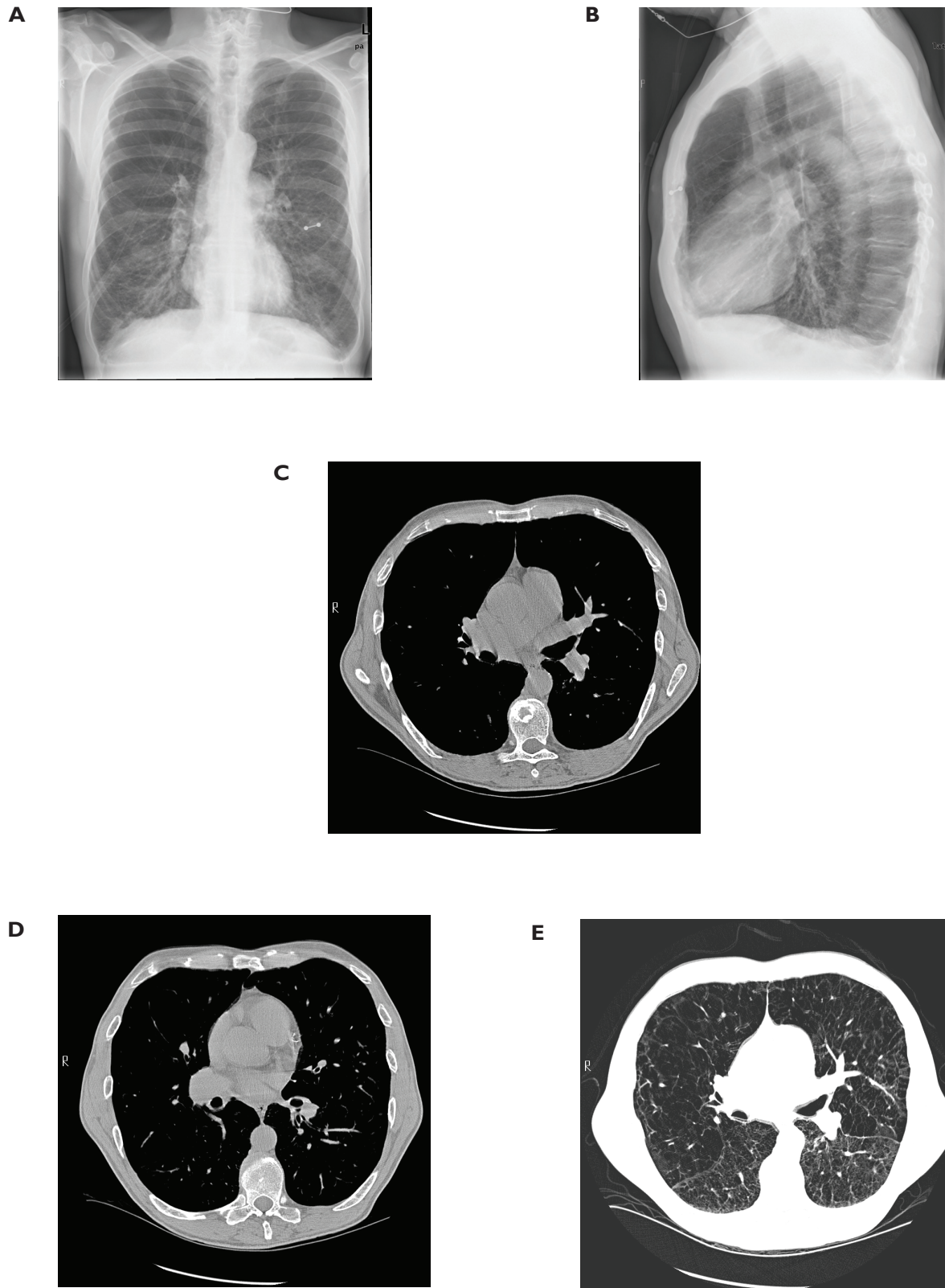
Phosphodiesterase inhibitors (PDEI) have been tested in small numbers of patients with COPD associated PH. PDEI prolong the effect of NO by inhibiting the degradation of NO's second messenger (cGMP) and promoting smooth muscle relaxation (Rabe et al 1994). In 6 patients with COPD associated PH, pulmonary hemodynamics improved after the initial dose of intravenous sildenafil and, after 3 months of oral therapy with sildenafil 50mg twice daily, the mPAP decreased from  $30.2 \pm 5.5$  to  $24.6 \pm 4.2$  mmHg, PVR declined from  $401 \pm 108$  to  $264 \pm 52$   $\text{dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$  and the six minute walk distance increased from  $351 \pm 49$  to  $433 \pm 52$  m (Alp et al 2006).

Despite these promising, preliminary results demonstrating beneficial effects of NO and PDEI in COPD associated PH, larger studies are needed to determine their safety and efficacy in COPD associated PH. Prostacyclin and endothelin antagonists are also potential targets for therapy; however, very limited information exists on the use of these agents in COPD associated PH.

3-hydroxy-3-methyl-glutaryl – coenzyme-A (HMG-CoA) reductase inhibitors (statins) have anti-inflammatory, antioxidant, and antithrombotic effects, restore endothelial function (Bonetti et al 2003), and may ameliorate the deleterious effects of tobacco smoking on the lung parenchyma and vasculature (Lee et al 2005). In rats exposed to 16 weeks of tobacco smoke with or without concomitant statin treatment, parenchymal destruction, vascular changes, and inflammation were attenuated by statin administration (Lee et al 2005). Further studies of statins are needed to determine if they promote vascular remodeling in COPD and PH.

## Summary

Pulmonary hypertension is a common feature of advanced COPD and is estimated to affect  $\geq 20\%$  of patients with advanced COPD (Weitzenblum et al 1981; Scharf et al 2002; Oswald-Mammosser et al 1991). The vast majority of PH associated with COPD is mild to moderate (mPAP 20–35 mmHg). Severe PH (mPAP  $\geq 40$  mmHg) occurs in  $< 5\%$  of patients with COPD (Chaouat et al 2005). Severe PH in patients with COPD reduces median survival by approximately 40 months (Chaouat et al 2005). The pathogenesis of PH associated with COPD has not been clearly elucidated but is likely due to the combined effects of inflammation



**Figure 3** **A.** Posterior-anterior chest X-ray and **B.** Lateral chest X-ray demonstrating enlarged pulmonary arteries and severe hyperinflation. The metallic opacification is a left nipple ring. **C.** Chest CT scan at the level of the pulmonary outflow tract demonstrating a main pulmonary artery diameter greater than the adjacent aorta. **D.** Chest CT scan at the level of the lower lobes demonstrating segmental pulmonary arteries that are larger than the accompanying bronchi. **E.** Chest CT at the same level as **Figure 3C** using parenchymal windows to demonstrate severe emphysematous changes throughout the lung parenchyma.

(Peinado et al 1999), endothelial cell dysfunction (Dinh-Xuan et al 1991; Peinado et al 1998), and angiogenesis (Santos et al 2003) that lead to intimal thickening, luminal narrowing, and arteriolar muscularization (Barbera et al 1994; Peinado et al 1998; Magee et al 1988; Hale et al 1980). Long-term oxygen therapy is a proven therapy for COPD associated PH (Medical Research Council Working Party 1981; Nocturnal Oxygen Therapy Group 1980). Systemic vasodilators have not been found to be effective therapy in COPD related pulmonary hypertension (Sturani et al 1983). Selective pulmonary vasodilators are currently being evaluated. Inhaled NO (Vonbank et al 2003) and PDEI (Alp et al 2006) are promising treatments for patients with COPD associated PH. However, further evaluation of the safety, efficacy, and optimal dosing of these medications is needed prior to routine use of these therapies in the management of PH associated with COPD.

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## Case study

This 54 year old man smoked up to 3 to 4 packs per day for the past 36 years and continues to smoke occasional cigarettes. He is breathless walking down the hallway and has dyspnea with most daily activities. He has no cough or sputum production. His medications include: a long acting beta agonist, short acting beta agonist, short acting anticholinergic, and an inhaled corticosteroid. The alpha-1 antitrypsin level was 218. Physical examination revealed a resting SaO<sub>2</sub> of 85%. The chest was hyperresonant with markedly reduced breath sounds with a prolonged expiratory phase but no wheezes. The left ventricular impulse was subxiphoid and the second heart sound was increased. There was no clubbing or peripheral edema.

### Pulmonary function studies:

TLC	8.35	110%		
FRC	6.48	177%		
RV	4.41	190%		
FEV <sub>1</sub>	1.34	32% (Prebronchodilator)	1.35	32% (Postbronchodilator)
FVC	3.84	73% (Prebronchodilator)	4.62	88% (Postbronchodilator)
DLCO	3.30	8.6%		

Echocardiogram showed normal left ventricular size and function with a left ventricular ejection fraction of 50%. The left ventricular wall thickness was normal and there were no regional wall motion abnormalities. Systolic and diastolic ventricular septal flattening was present suggesting right

ventricular (RV) pressure overload. The RV was mildly dilated and systolic function was mildly to moderately reduced. The systolic pulmonary artery pressure was calculated to be 51–56 mmHg assuming a right atrial pressure of 5–10 mmHg. Agitated saline contrast study did not reveal an intracardiac shunt (Figure 3).

Assessment for coexisting etiologies of pulmonary hypertension was performed. Connective tissue disease serologies and HIV testing were negative. Ventilation perfusion scanning was interpreted as low probability for pulmonary embolism. Arterial blood gas sampling confirmed resting hypoxemia but did not show hypercarbia. Liver function testing was normal and there was no clinical evidence of hepatic dysfunction.

Treatment with long acting beta agonist, short acting beta agonist, short acting anticholinergic, and an inhaled corticosteroid was continued. Supplemental oxygen was instituted for resting hypoxemia. Smoking cessation was strongly encouraged and interventions were successful.

The patient's dyspnea improved with smoking cessation, supplemental oxygen and inhaled therapies for COPD. He completed pulmonary rehabilitation and is now enrolled in a pulmonary rehabilitation maintenance program.

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