CHEST Translating Basic Research Into Clinical Practice

# Pulmonary Vascular Involvement in COPD*

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**Alterations in pulmonary vessel structure and function are highly prevalent in patients with COPD. Vascular abnormalities impair gas exchange and may result in pulmonary hypertension, which is one of the principal factors associated with reduced survival in COPD patients. Changes in pulmonary circulation have been identified at initial disease stages, providing new insight into their pathogenesis. Endothelial cell damage and dysfunction produced by the effects of cigarette smoke products or inflammatory elements is now considered to be the primary alteration that initiates the sequence of events resulting in pulmonary hypertension. Cellular and molecular mechanisms involved in this process are being extensively investigated. Progress in the understanding of the pathobiology of pulmonary hypertension associated with COPD may provide the basis for a new therapeutic approach addressed to correct the imbalance between endothelium-derived vasoactive agents. The safety and efficacy of endothelium-targeted therapy in COPD-associated pulmonary hypertension warrants further investigation in randomized clinical trials.**
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**Key words:** COPD; pulmonary circulation; pulmonary hypertension

**Abbreviations:** eNOS = endothelial nitric oxide synthase; EPC = endothelial progenitor cell; ET = endothelin; NO = nitric oxide; PAH = pulmonary arterial hypertension; SMC = smooth muscle cell; VEGF = vascular endothelial growth factor

COPD is defined in terms of airflow obstruction that results from an inflammatory process affecting the airways and lung parenchyma. Despite major abnormalities taking place in the airway side, changes in pulmonary vessels represent an important component of the disease. Alterations in vessel structure are highly prevalent, and abnormalities in their function impair gas exchange and result in pulmonary hypertension, which is one of the principal factors associated with reduced survival in COPD patients.[1]

The etiopathogenic mechanisms that are responsible for pulmonary vascular abnormalities in COPD patients remain incompletely understood, but they have been extensively investigated over the past few years. Studies[2–4] conducted in patients with mild COPD that revealed significant structural and functional abnormalities in their pulmonary vessels have opened a new avenue for a better understanding of the pathogenesis of these changes, which might translate into clinical practice. In this review, we will examine the contributions of the last studies on the pathobiology of pulmonary vascular abnormalities that are associated with COPD, and will discuss the potential clinical implications in terms of diagnosis and treatment.

## Pulmonary Vascular Remodeling in COPD

Remodeling is a process that causes thickening of the arterial wall and is thought to increase resistance by causing the vessel wall to encroach into the lumen

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and reduce its diameter. In COPD patients, pulmonary vascular remodeling affects small and precapillary arteries, and has been identified at different degrees of disease severity. Intimal enlargement is the most prominent feature of pulmonary vascular remodeling. It is apparent in arteries of different sizes, although it is more pronounced in small muscular arteries (*ie*, those < 500 μm in diameter).[2,3,5] In addition, there is muscularization of arterioles that also show intimal enlargement. Changes in the tunica media are less conspicuous, and the majority of studies[2,3,5] have failed to show striking differences in the thickness of the muscular layer in COPD patients.

Remodeling of pulmonary arteries is not restricted to patients with an established diagnosis of COPD. Indeed, intimal thickening, the magnitude of which does not differ from that seen in patients with mild COPD, also occurs in heavy smokers with normal lung function.[3]

Intimal hyperplasia has the following two components: cellular and extracellular. The majority of cells proliferating in hyperplasic intimas of pulmonary muscular arteries are smooth muscle cells (SMCs), as shown by positive immunoreaction to α-smooth muscle actin.[4] Comparative analyses of serial sections show that some SMCs in the intima do not express desmin filaments, whereas all them express vimentin filaments.[4] The expression pattern of both intermediate filaments may discriminate between a synthetic phenotype for SMCs and the contractile phenotype observed in mature cells.[6,7] Accordingly, vimentin-positive, desmin-negative SMCs represent a subpopulation of less differentiated SMCs that may possess synthetic capacity and take part in an ongoing process of vascular remodeling.[8] These findings are consistent with previous observations in patients with advanced COPD showing muscle deposition in pulmonary muscular arteries and the formation of a definite muscle layer in small arterioles.[9,10] Newly formed smooth muscle bounds adopt a longitudinal disposition that differs from the circumferential disposition of normal smooth muscle.

## Inflammatory Changes

COPD is an inflammatory disease, hence, inflammatory cells might contribute to the alterations of pulmonary vessels. Indeed, the extent of pulmonary vascular remodeling correlates with the severity of inflammatory cell infiltrate in small airways.[2,11] Patients with COPD have an increased number of inflammatory cells infiltrating the adventitia of pulmonary muscular arteries, compared with nonsmokers.[12] This inflammatory infiltrate is largely constituted by activated T lymphocytes with a predominance of the CD8+ T-cell subset.[12,13] By contrast, the numbers of neutrophils, macrophages, and B lymphocytes are minimal and do not differ from those of control subjects.

In patients with mild-to-moderate COPD, the intensity of the inflammatory cell infiltrate in pulmonary arteries correlates with the degree of airflow obstruction, suggesting that, as the disease progresses, the inflammatory reaction in pulmonary arteries may become more severe.[12] Interestingly, smokers with normal lung function also show an increased number of CD8+ T cells in the arterial adventitia, with a reduction of the CD4+/CD8+ ratio, compared with nonsmokers, that does not differ from that of patients with mild-to-moderate COPD.[12]

## Endothelial Dysfunction

Endothelial cells play a crucial role in the regulation of vascular homeostasis.[14] In pulmonary vessels, endothelial cells contribute to the reduced vascular tone,[15] regulate vessel adaptation to increased flow,[16] and modulate hypoxic vasoconstriction.[17,18] Endothelial dysfunction of the pulmonary arteries has been shown with different degrees of COPD severity, as follows: patients with end-stage COPD who had undergone lung transplantation[19]; and patients with mild-to-moderate COPD.[3] The impairment of endothelial function may be associated with or result from changes in the expression or the balanced release of vasoactive mediators with vasodilator properties, such as nitric oxide (NO) or prostacyclin, and mediators with vasoconstrictive properties, such as endothelin-1 (ET-1) or angiotensin (Fig 1).

Giaid and Saleh[20] showed a significant reduction of endothelial NO synthase (eNOS) expression in pulmonary arteries in patients with severe forms of both primary and secondary pulmonary hypertension (including patients with COPD), thereby suggesting that the down-regulation of NO might contribute to the development of pulmonary hypertension. The reduced expression of eNOS has also been shown[21] in the pulmonary arteries of smokers without or with minimal airflow obstruction. More recent data[22] have demonstrated that eNOS expression in pulmonary arteries is more markedly reduced in patients with greater COPD severity. Nana-Sinkam et al[23] have recently shown that the expression of prostacyclin synthase is also reduced in the pulmonary arteries of patients with severe emphysema. Furthermore, Giaid et al[24] showed that the expression of ET-1 in pulmonary arteries was increased in both primary and secondary forms of pulmonary hypertension (including patients with COPD).