Pulmonary hypertension (PH) is a clinically relevant problem in chronic obstructive pulmonary disease (COPD) due to its high prevalence and the impact that it exerts on morbidity and mortality. Pulmonary hypertension is present in more than 25% and 50% of patients with COPD GOLD 3 and 4 stages, respectively. Five year survival of patients suffering PH is almost half of patients without PH (36% and 62%, respectively). Furthermore, signs of elevated pulmonary artery pressure (PAP) are associated with more frequent exacerbation episodes.

Pulmonary hypertension in COPD is usually of mild-to-moderate severity and progresses slowly. Nevertheless, a reduced group of patients (3-5%) may present severe PH, which is associated with markedly reduced survival. COPD patients which present severe PH depict some clinical features that resemble more aggressive forms of PH, such as idiopathic pulmonary arterial hypertension (PAH).

Different factors may account for the development of PH in COPD: vessel remodeling, loss of capillary bed, hypoxic vasoconstriction, thrombosis and hyperviscosity. Currently, there is substantial evidence showing that pulmonary vascular remodeling in COPD is strongly associated with cigarette smoking, acting through endothelial cell damage. Endothelial damage is associated with an imbalance between endothelium-derived vasoactive mediators that favor a vasoconstrictive and proliferative phenotype that provides the basis for the development of pulmonary vascular remodeling and the eventual progression to PH when additional factors, such as hypoxia or emphysema, concur.

Endothelial damage and dysfunction in the lungs of COPD patients is associated with endothelial dysfunction in systemic arteries, reduced numbers of circulating angiogenic progenitor cells and increased numbers of circulating endothelial microparticles (EMPs). These changes might explain the frequent association between COPD and cardiovascular disease. Interestingly, an increased number of circulating EMPs originated by apoptosis is also associated with the presence of emphysema. In fact, studies in experimental models exposed to cigarette smoke have shown a connection between PH and emphysema through nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) dependent mechanisms and there is evidence that patients with severe emphysema may also develop severe PH.

Studies providing evidence on the critical role of the endothelial cell and its derived mediators in the pathogenesis of COPD-associated PH have provided the rationale for the potential use of agents that modulate endothelial function in the treatment of this condition, as is currently done in idiopathic PAH. Nevertheless, randomized controlled trials with drugs used to treat PAH in COPD –most commonly phosphodiesterase-5 inhibitors or endothelin-1 receptor antagonists– have failed to substantiate any clinical benefit of these treatments in COPD patients with mild-to-moderate PH. Furthermore, the use of targeted pulmonary vasodilators may impair gas exchange in COPD due to the inhibition of hypoxic pulmonary vasoconstriction.

However, recent studies in experimental models have revealed that a new generation of agents used to treat PAH, soluble guanylate cyclase (sGC) stimulators, not only diminished PAP and restricted the remodeling of pulmonary vessels, but also prevented the development of pulmonary emphysema. These findings suggest a critical role of the NO–cGMP axis in the preservation of lung structure integrity and open the opportunity to explore the NO–cGMP axis as a new therapeutic target in COPD.
Bibliography


