Smoking: Is it a risk factor for pulmonary vascular diseases?

Chronic obstructive pulmonary disease (COPD) summarizes chronic bronchitis and lung emphysema. A major trigger for this disease is cigarette smoking. However, the occurrence and role of pulmonary vascular remodeling and pulmonary hypertension (PH) in COPD is not clarified yet. Although PH and lung vascular remodeling were thought to be infrequent events in COPD, recent clinical data estimate that 30-70% of patients with COPD also have PH.[1] In 50% of COPD patients evaluated for lung transplantation, mean pulmonary arterial pressure was above 25 mmHg.[2] In addition, a much larger portion of COPD patients may be affected by morphological changes of the lung vessels and/or borderline PH.[3-5] In this regard it has recently been stated that "moderate-to-severe PH is not a rare event" in COPD[2] and "numerous studies have shown that the presence of even mild PH is of prognostic relevance in patients with COPD."[3]

Without doubt, late-stage COPD can result in a lack of oxygen, which can trigger pulmonary vascular remodeling, similar to chronic alveolar hypoxia. However, recently it has been proposed that pulmonary vascular alterations are not secondary to lung emphysema development but can even be the driving force of COPD. Indeed, there is increasing evidence that cigarette smoke may have a major direct impact on the pulmonary vasculature, suggesting that PH and subsequent cor pulmonale are not necessarily secondary to hypoxia in patients with COPD.[6-8] This field of research was largely driven by investigations from Joan Barbera's group, who documented that pulmonary vascular remodeling (resembling pulmonary vascular remodeling occurring in PH patients) occurs in smokers who have not yet developed COPD.[5]

For detailed investigations of the time course of possible tobacco-smoke induced pulmonary vascular remodeling processes and emphysema development, animal experiments can be helpful. They may decipher 1) whether lung vascular remodeling generally occurs during tobacco smoke exposure, 2) whether it leads to PH, and 3) whether it precedes lung emphysema development. Early studies already clearly showed that tobacco smoke causes vascular remodeling with thickening of the vessel wall, and studies in guinea pigs and recently in mice described that pulmonary vascular remodeling may be observed prior to lung emphysema development.[9-12] An investigation from our group showed that pulmonary vascular remodeling and PH induced by tobacco smoke occur in the absence of hypoxia

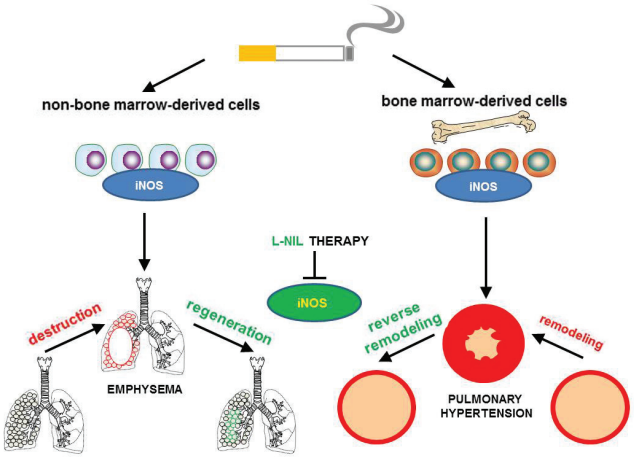

Figure 1: Smoke-induced vascular alterations and emphysema development. A recent study in mice revealed that tobacco smoke-induced vascular remodeling and PH is dependent on iNOS activity in bone marrow-derived cells, whereas lung emphysema development was dependent on iNOS activity in non-bone marrow-derived cells. iNOS inhibition with L-N^6-(1-iminoethyl)-lysine (L-NIL) could not only prevent but also reversed established PH and emphysema in mice.[15]

and precede the development of alveolar destruction and emphysema formation. This study furthermore revealed that emphysema and PH development are not essentially linked but can occur independently—at least in mice. Whereas emphysema development was dependent on the inducible NO synthase (iNOS) in non-bone marrow derived cells, PH was dependent on iNOS in bone marrow-derived cells (Fig. 1).[12] Nevertheless, this study proposed that a vascular iNOS upregulation induced by tobacco smoke, even in the absence of vascular remodeling, can trigger emphysema.

Provided that such animal studies also apply to the human situation—which is supported by studies in smokers that have not yet developed COPD, but display pulmonary vascular remodeling—[5,13] it is clear that tobacco smoke can trigger vascular alterations even without signs of COPD. Such alterations, which can affect biochemical pathways, vascular function, as well as the morphology of the pulmonary vessels,[14] may also—going beyond pulmonary vascular disease—drive emphysema development.

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