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Pulmonary vascular involvement in chronic obstructive pulmonary disease

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ABSTRACT: Chronic obstructive lung disease affects the entire lung, not just the airways. Although pulmonary hypertension (PH) has long been recognised in a subset of patients with COLD, the important pathophysiological questions remain unanswered. Oxygen supplementation, however, has been shown to blunt the exercise-induced PH in these patients. Hypercoagulability has also been described in patients with COLD. This may, in part, be due to the inflammatory aspects of COLD exacerbation events. In addition to perivascular inflammation, the pathology of vessels in COLD includes intimal thickening, muscularisation of arterioles, *in situ* thrombosis, loss of capillaries and precapillary arterioles, and vascular congestion and stasis. Recent work describes apoptosis of septal endothelial cells and decreased expression of vascular endothelial growth factor (VEGF) and one of its receptors, VEGFRII, in lungs from patients with emphysema. Based on this work, a rat model was developed that shows chronic blockade of VEGF receptors leads to septal cell apoptosis and results in emphysema and PH. This animal model has led to prevention trials using 1) a broad-spectrum caspase inhibitor, 2) a superoxide dismutase mimetic, and 3) α_1-antitrypsin.

These findings highlight the importance of vascular endothelial growth factor, apoptosis, oxidative stress and protease activity in the pathogenesis of emphysema. They also underscore the importance of the vasculature in what is traditionally thought of as an airways disease. Future treatment strategies need to address the vascular components of chronic obstructive lung disease.

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The syndrome of chronic obstructive lung disease or chronic obstructive pulmonary disease (COPD) evokes the image of sick airways, of nonasthmatic airway disease, although it is conceded that the overlap with typical asthma may be important for a number patients with smoking-induced COPD. Yet COPD is more than an airway disease, as is true for most chronic diffuse lung diseases where the disease process transgresses compartment borders. Certainly the alveolar septal structures are affected and so are the lung microvessels and the precapillary arterioles [1–4]. Broadly, in COPD varying degrees of inflammation are found in the airways, in the parenchyma, even in the pleura and tissue destruction and fibrosis are found. The chronic smoker thoroughly smokes their lungs! Because vascular endothelial cells are next to the liver cells the most metabolically active cells when it comes to detoxifying xenobiotics, whether they arrive *via* the blood stream or the smoke of the cigarette, the large lung vascular endothelial cell surface area is affected by the disease and gradually reduced as the disease progresses. Thus, all the lung cells are working overtime, they become dysfunctional, undergo apoptosis, inflammation, ischaemia, proteolysis and fibrosis, eventually remodelling of the lung tissue, airways, and vessels occurs.

Pulmonary hypertension in chronic obstructive pulmonary disease

In the early days of COPD research it had been recognised that not all patients with COPD look alike and the clearly distinguishable phenotypes, of the "blue bloater" and the "pink puffer" were described [5]. It was also recognised that some patients had pulmonary hypertension whereas others did not. In a landmark article BURROWS *et al.* [6] showed how varied the pulmonary artery pressure really was in the patients with COPD at rest, and in particular during exercise [6].

BURROWS *et al.* [6] also showed that the exercise-induced pulmonary hypertension was blunted considerably by treatment of the patients with supplemental oxygen, more in some, less in others [6]. These findings were later confirmed in studies that also demonstrated a wide spectrum of pulmonary hypertensive responses to exercise in their cohorts of COPD patients [7–9]. Interestingly, now 30 yrs after the description of the haemodynamics in patients with COPD by BURROWS *et al.* [6] many of the important pathophysiological questions remain unanswered. The intricate relationships between the mechanical and biochemical aspects of lung function, pulmonary vasomotor tone regulation, the cardiac performance in the setting of the hyper-inflated lung, the influence of hypoxia and hypercarbia and the various forms and degrees of lung vascular remodelling (see below) are still not understood. A more detailed discussion of these issues can be found in recent reviews and other publications [10–13]. Briefly, most patients with COPD have mild or moderate pulmonary hypertension at rest (table 1), yet their pulmonary hypertension may be latent and can easily be unmasked by exercise (fig. 1). Unfortunately the severely hyperinflated lung tissue make the echocardiographic evaluation of pulmonary hypertension

Table 1. – Factors, which affect pulmonary artery pressure at rest

Vasoconstriction (hypoxic and nonhypoxic) [14–17]
Lung vessel loss [18, 19]
In situ thrombosis [20]
Polycythaemia

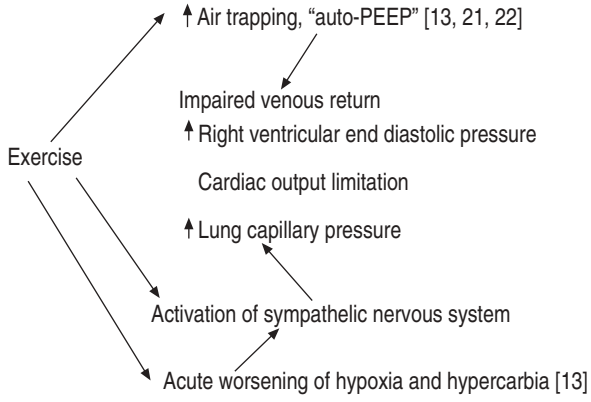

Fig. 1. – Factors which affect pulmonary artery pressure with exercise. PEEP: positive end-expiratory pressure.

technically very difficult and the current authors are not aware of any echocardiographic data obtained in patients with COPD during exercise. One can postulate a number of different pulmonary hypertensive phenotypes depending on the vigor of the (perhaps genetically determined) hypoxic pressure response and the factors involved in pulmonary vascular remodeling, which likewise may have a genetic basis.

Oxygen supplementation may act on a number of different levels reducing the exercise-induced pulmonary hypertension: oxygen likely decreases dyspnoea perhaps decreasing the respiratory rate during exercise allowing for a better emptying of the lung and less auto-positive end-expiratory pressure, and it may decrease the sympathetic tone (fig. 1).

Clotting and thrombosis in chronic obstructive pulmonary disease

As already stated the pulmonary arteries in COPD are characterised by endothelial cell dysfunction; cytokines like interleukin (IL)-1, and IL-6 have been shown to be increased in the plasma of patients with COPD. These, and in addition oxidative stress and C-reactive protein may affect endothelial cell function and render the endothelium a more thrombogenic surface. In fact a hypercoagulable state has been described in patients with COPD [23, 24]. There appears to be an increased frequency of deep venous thrombosis and pulmonary embolism in acute exacerbations of COPD [24, 25], and histopathologically thrombotic lesions were detected in lung tissue from patients with severe emphysema undergoing lung-volume reduction surgery [26]. Apparently, the frequency of venous thrombosis is increased during exacerbations of COPD. Clearly the clotting and embolism aspects of COPD, especially during an exacerbation, require further focused investigations. The inflammatory aspects of the so-called COPD exacerbation may trigger a hypercoagulable state and increase the risk of thrombosis. Some *post mortem* studies indicate that a considerable number of patients dying with COPD have pulmonary embolic events. Should indeed a hypercoagulable state, or pulmonary embolism or *in situ* thrombosis be frequent events in patients with severe COPD, perhaps associated with the so-called exacerbations of COPD, then anti-coagulation of patients with COPD could be an important therapeutic modality.

Pathohistology

Figure 2 lists the most frequently encountered lung vascular alterations in COPD. It is very important to point out that vascular abnormalities are not a late, end stage finding, but as demonstrated by BARBERA *et al.* [2], accompany even mild obstructive lung disease. Muscular arteries are infiltrated by inflammatory cells including lymphocytes [27] and when examined *ex vivo* display a decreased expression of their endothelial cell nitric oxide synthase [28] and impaired endothelial cell-dependent vasodilation [29, 30, 31]. T-cell cytokines may activate proteolytic pathways; lymphocytes may attach to endothelial cells and destroy them. Inflammation may be driven by activation of the nuclear factor (NF)-κB since it has been shown that cigarette smoke condensate activates NF-κB, destroys an inhibitor of NF-κB called IκBα and increases cycloxygenase 2 gene expression [32], of interest, surfactant protein D regulates NF-κB and matrix metalloproteinase production in alveolar microphysiology [33]. Whereas a better description of the pathology of the small airways and small vessels in COPD is still needed, the dissection of disease mechanism requires the study of animal models.

Vascular changes in animal models of hypoxia-induced pulmonary hypertension

"To understand pulmonary hypertension we must understand the structural remodeling caused by the original injury, by adaptation to this injury and to established pulmonary hypertension," REID and DAVIES [34].

In the twentieth century pulmonary hypertension was based on contemporary concepts pathophysiologically explained by vasoconstriction. Pathologists saw the crenated elastic laminae of the pulmonary arteries and concluded that vasoconstriction of the lung vessels must indeed have been severe and caused the structural changes. However, eventually mitogenesis and cell proliferation became recognised "Proliferation of vascular cells is a feature of all types of pulmonary hypertension. Proliferation can occur as part of the original injury – that is, mitogens are released as part of the acute damage – it may be part of the repair process or of the adaptation that occurs when pulmonary hypertension is established" [34]. For many decades investigators have used

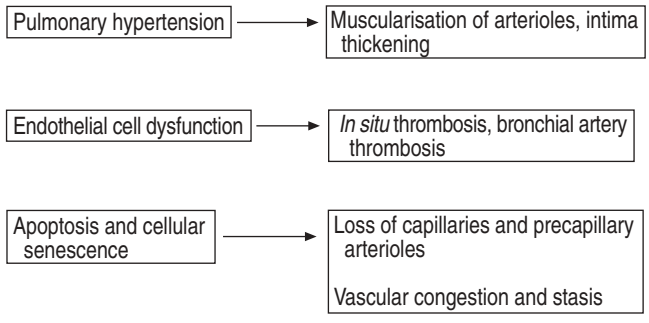

Fig. 2. – Lung vascular abnormalities in chronic obstructive pulmonary disease.

animals exposed to chronic hypoxia, hypobaric or not, to investigate the mechanisms of pulmonary vascular remodelling. Because patients with COPD are frequently hypoxic and hypoxaemic, chronic hypoxia exposure animal models continue to be used with the assumption that the information gathered can be translated to the human condition of COPD. But it must be asked which human disease or what aspects of human disease are being modelled [35]. Indeed muscularisation of precapillary arterioles and loss of pulmonary capillaries, as shown by a loss of the "background haze" by angiography occurs in rat models of chronic hypoxic pulmonary hypertension [34, 35]. The thickening of the media of precapillary arterioles in chronic hypoxia exposure models has originally been attributed to vasoconstriction resulting in a form of work hypertrophy. Muscularisation of precapillary arterioles, normally not endowed with thick layers of muscle cells and therefore normally not contractile, was explained by migration of smooth muscle cells. An alternative view is that the immediate adaptive response of the stressed precapillary arterioles is really a response of endothelial cells which transdifferentiate into smooth muscle cells [36–37]. Although the hypoxia-exposure animal models lack the airway disease component of COPD and the inflammatory cells, which are present in the COPD lungs, hypoxia activates cytokines and generates features of inflammation in the lung parenchyma [38, 39].

Vascular changes in animal models of emphysema

Vascularisation of arterioles has been described in chronic cigarette smoke exposed guinea pigs [40] yet little attention to the vascular morphology has been paid in the description of many of the recently developed mouse emphysema models [41, 42]. KASAHARA *et al.* [43] recently described apoptosis of alveolar septae and vascular endothelial cells in the lungs from patients with emphysema and also decreased expression of the vascular endothelial growth factor vascular endothelial growth factor (VEGF) and the VEGF receptor II KDR. To explore the hypothesis that impaired VEGF signalling causes alveolar septal cell apoptosis and emphysema, a rat model had been developed [44] and indeed it could be shown that chronic blockade of VEGF receptors causes septal cell apoptosis, results in emphysema and lung capillary loss and causes some degree of pulmonary hypertension [44].

The current authors believe that important insights can be gathered from this model and new hypotheses can be developed. This non-inflammatory model of emphysema supports the concept that VEGF is an obligatory survival factor [45] for lung micro-vascular endothelial cells, and perhaps other lung cells [46]. The current authors also believe that the abundance of expression of VEGF in the lung [39, 47] is to a large measure explained by the immense number of capillary endothelial cells, which generate and secrete VEGF, which they need to survive. This makes VEGF a strong player in a team of lung structure maintenance factors [43, 44].

This model of VEGF receptor blockade-triggered emphysema has now been subjected to three different prevention trials. First the present authors showed that a broad-spectrum caspase inhibitor prevented the VEGF receptor blockade-induced emphysema indicating that indeed apoptosis of alveolar septal cells caused emphysema [44]; second it was shown that chronic treatment with a superoxide dismutase mimetic prevented emphysema in this model [48] and more recently that *i.v.* injection of VEGF receptor blocked animals with α-antitrypsin prevented emphysema development [49]. This indicates that oxidative stress and protease(s) activity [49, 50] become unbalanced when effective VEGF signal transduction is impaired. Caspases are cysteinyl aspartate-specific proteases and are activated by proteolytic processing of aspartic residues, and caspases can do double duty as elastases. Finally, the fact that apoptotic cells can be observed at all in the emphysematous lungs may indicate that on a cellular level there is also a phagocytosis failure, *i.e.* impairment of engulfing and removing of dead cells [51, 52]. VEGF may also be involved in effective phagocytosis and apoptotic cell clearance.

The current authors take the view that VEGF receptor signalling which results in endothelial cell prostacyclin and nitric oxide production [53] is critically involved in the structure maintenance of the lung microvessels. If so, then emphysema is also a vascular disease [18, 54], VEGF is abundantly expressed in the lung tissue [55] in vascular smooth muscle cells [56], its expression is induced by IL-1 [57] and IL-6 [47], VEGF increases the expression of superoxide dismutase in endothelial cells [58] and protects them against oxidative stress, perhaps also the endothelial cells of the systemic vasculature. It is of interest that α_1-antitrypsin treatment of adult rats prevents the development of VEGF-receptor blockade-induced lung capillary loss [50]. The current authors also believe that endothelial cells and vascular smooth muscle cells form a "functional" syncytium [36], yet the intricate interactions on a molecular level between growth factors [59–63], haemodynamic variables, vascular injury [64], hypoxia [36, 65, 66] proteases [49, 67] and control of apoptosis [43, 49], and how they affect the so-called vascular remodelling, are still largely unclear.

Therapeutic considerations and recommendations

What is it about the vascular component in chronic obstructive pulmonary disease that may require treatment? This question is posed in the context of D. Flenley's provocative statement that "COPD patients die *with* cor pulmonale but not of cor pulmonale" [68] and the observation of many clinicians that long-term oxygen treatment has dramatically decreased the incidence of cor pulmonale [7, 69, 70]. Indeed the emphasis and focus of treatment strategies may shift towards prevention of exacerbations of chronic obstructive pulmonary disease, and address anticoagulation in order to prevent embolism and *in situ* thrombosis [63]. New strategies need to be developed; those should be designed and directed to break the cycle of inflammation, proteolysis, oxidative stress and apoptosis, [71] since it is this vicious cycle, which plays out in the small airways and adjacent lung vessels. Prevention of chronic obstructive pulmonary disease progression also entails prevention of the ongoing loss of lung capillaries. Perhaps protease- and apoptosis-inhibiting drugs may accomplish this.

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