REVIEW

Chronic Obstructive Pulmonary Disease in a new concept

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. Although COPD is a nonspecific term referring to a set of conditions that develops progressively because of a number of different disease processes, it most commonly refers to patients with chronic bronchitis and emphysema and to a subset of patients with asthma. Several different definitions were proposed for COPD in time. COPD is not asthma but can coexist with asthma, the other major airways obstructive disease caused by airway inflammation. Inflammation underlying in asthma has characteristic features, distinct of that from COPD. Longitudinal studies revealed the heterogeneous character of COPD. The pathological hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema). International guidelines stress the importance of accurately discriminating between asthma and chronic obstructive pulmonary disease. Although characteristic pathological features have been described for both conditions, their discriminatory power has never been systematically assessed. This might be rectified by improving pathological definitions.

***Keywords*:** COPD, asthma, inflammation, remodeling, apoptosis.

COPD represents a pathological status characterized by airflow limitation and manifested through chronic cough, effort dyspnea, expectoration and wheezing, symptoms that appears in context of airways hyper-responsiveness and may be partially reversible. Although COPD is a nonspecific term referring to a set of conditions that develops progressively because of a number of different disease processes, it most commonly refers to patients with chronic bronchitis and emphysema and to a subset of patients with asthma [1].

Several different definitions were proposed for COPD in time. The American Thoracic Society (ATS) has defined COPD as "a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible" [2].

The European Respiratory Society (ERS) defined COPD as "reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment" [3].

In 1998, in an effort to bring more attention to COPD, its management, and its prevention, a committed group of scientists encouraged the US National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Based on current knowledge, a working definition is Chronic Obstructive Pulmonary Disease (COPD), a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [4].

For these three different definitions, however, the precise classification of airflow limitation, reversibility, and severity of disease varies. In addition, the definitions and diagnoses of chronic bronchitis, emphysema, and asthma also can vary [1].

Despite the simplicity of the definition, COPD is a complex disease that is based on inflammation. A mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person, causes the chronic airflow limitation characteristic of COPD.

Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration.

Emphysema, or destruction of the gas exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD. Chronic bronchitis, or the presence of cough and sputum production for at least three months in each of two consecutive years, remains a clinically and epidemiologically useful term. However, it does not reflect the major impact of airflow limitation on morbidity and mortality in COPD patients. It is also important to recognize that cough and sputum production may precede the development of airflow limitation. On the other hand, some patients develop significant airflow limitation without chronic cough and sputum production [5].

Airflow limitation is the slowing of a patient's expiratory airflow, as measured by spirometry, with a persistently low FEV1 and a low FEV1/FVC ratio despite treatment. The ATS definition of COPD did not list a specific level of the FEV1/FVC ratio for airflow limitation, while the ERS definition for airflow limitation is an FEV1/slow vital capacity ratio of 88% of the predicted value for men and a ratio of 89% of the predicted value for women [2, 3].

The GOLD definition for airflow limitation is an FEV1/FVC ratio of 70% [5].

Airflow limitation reversibility can be acute, in response to an inhaled bronchodilator, or in response to oral or inhaled corticosteroids [5]. The ATS definition of COPD did not specifically define reversibility, although a previous ATS statement classified reversibility as an FEV1 increase of 200 mL and 12% above baseline FEV1 for treatment with inhaled bronchodilators [6].

The ERS definition of COPD classifies reversibility as a >10% improvement in predicted FEV1 after a patient receives a bronchodilator [3]. The GOLD definition of COPD classifies reversibility as an FEV1 increase of 200 mL and a 12% improvement from baseline FEV1 for treatment with either inhaled corticosteroids or bronchodilators [5].

The term "partial reversibility" is frequently mentioned but has not been fully defined. In the context of the definitions, this term probably defines patients who in fact have "reversibility" in response to therapy with either corticosteroids or a bronchodilator (as defined above), yet their best FEV1 and FEV1/FVC ratio classifies them as having airflow limitation [1].

Disease severity has typically been determined using the degree of lung function impairment, although the wisdom of this approach has been questioned, with the suggestion that factors such as arterial blood gas levels, time and distance walked, sensation of dyspnea, and body mass index be included in this determination [7].

The ATS criteria classify COPD into the following three stages: stage 1 (FEV1, ≥50% of predicted), stage 2 (FEV1, 35 to 49% of predicted), and stage 3 (FEV1, <35% predicted) [2].

The ERS criteria classify COPD into the following three stages: mild (FEV1, ≥70% of predicted), moderate (FEV1, 50% to >80% of predicted), and severe (FEV1, <50% of predicted) [3].

The GOLD criteria classify COPD into the following three stages [5]:

- *Stage I – Mild COPD*, characterized by mild airflow limitation (FEV1/FVC <0.70; FEV1 ≥80% predicted);
- *Stage II – Moderate COPD*, characterized by worsening airflow limitation (FEV1/FVC <0.70; 50%≤ FEV1 <80% predicted);
- *Stage III – Severe COPD*, characterized by further worsening of airflow limitation (FEV1/FVC <0.70; 30%≤ FEV1 <50% predicted);
- *Stage IV – Very Severe COPD*, characterized by severe airflow limitation (FEV1/FVC <0.70; FEV1 <30% predicted *or* FEV1 <50% predicted plus the presence of chronic respiratory failure);
- *Stage IV – Very Severe COPD*, even if the FEV1 is >30% predicted, whenever these complications are present.

Chronic bronchitis, which is defined in clinical terms, is the presence of a chronic productive cough for three months in each of two successive years, if other causes of chronic cough have been ruled out [2].

Airway obstruction occurs because of varying degrees of inflammation and nonspecific bronchial hyper-reactivity associated with chronic bronchitis. Unfortunately, many surveillance systems that attempt to estimate the burden of chronic bronchitis do not have this specific definition and only estimate "physician-diagnosed" chronic bronchitis or recurrent episodes of bronchitis (typically, three episodes) in the previous year [1].

Emphysema, which is defined in anatomic terms, is defined as the destruction of alveolar walls and the permanent enlargement of the airspaces distal to the terminal bronchioles [2]. The ensuing loss of lung elastic recoil and intralumenal pressure in the terminal airways causes small airways to lose their potency, especially during forced expiratory maneuvers.

The collapse of these airways furthermore results in airflow limitation that is independent of exertion. Clinically, the patient experiences progressive dyspnea and variable cough. It is not clear how most clinicians diagnose emphysema. While the use of imaging such as a CT-scan would be optimal in the diagnosis of emphysema, it is likely that the majority of cases are diagnosed using different criteria.

COPD is not asthma. COPD can coexist with asthma, the other major airways obstructive disease caused by airway inflammation. Anyway, inflammation underlying in asthma has characteristic features, distinct of that from COPD [5].

Asthma, which is defined in physiologic terms, is defined as reversible smooth muscle contraction that narrows the airway lumen, limiting expiratory airflow and resulting in symptoms including wheeze, cough, and exertion dyspnea [8].

The distinguishing feature of asthma is the reversibility of symptoms in response to treatment with inhaled bronchodilators (anticholinergic agents, methyl-xanthines, and corticosteroids).

Histopathological studies of COPD show a predominant involvement of peripheral airways

(bronchioles) and lung parenchyma, whereas asthma involves inflammation in all airways but usually without involvement of the lung parenchyma.

There is obstruction of bronchioles, with fibrosis and infiltration with macrophages and T-lymphocytes. There is destruction of lung parenchyma and an increased number of macrophages and T-lymphocytes, with a greater increase in CD8+ (cytotoxic) than CD4+ (helper) cells.

Bronchial biopsies show similar changes with an infiltration of macrophages and CD8+ cells and an increased number of neutrophils in patients with severe COPD. Broncho-alveolar lavage (BAL) fluid and induced sputum demonstrate a marked increase in macrophages and neutrophils. In contrast to asthma, eosinophils are not prominent (Table 1) [9].

Table 1 – ***Remodeling and inflammation in COPD and asthma (Jeffery PK, 2001 [48])***

	COPD	Asthma
Epithelium	metaplastic	fragile
Reticular basement membrane	not thickened	thickened
Fibrosis	present	unlikely
Vessels	likely	angiogenesis
Bronchial smooth muscle	increased (small airways)	increased (large airways)
Glands	hypertrophy	hypertrophy
Inflammation	CD8+ and CD68+	CD4/Th2
Emphysema	yes	no

COPD has been long recognized as a heterogeneous disorder or group of disorders, with components of asthma, chronic bronchitis, emphysema, and airflow obstruction all being important parts of the final disease process. The different components of disease heterogeneity in COPD include different mechanisms in development, presentation, and course. Disease heterogeneity in COPD may ultimately provide opportunities for targeted interventions in COPD patients [1].

Smoking is the dominant risk factor for the development and progression of COPD; 25% of smokers develop COPD. The fact that 15% of COPD-related mortality occurs in never-smokers, suggests that other factors are important. Smoking cessation is the single most important intervention in COPD management, although the best reported cessation rates are still fewer than 30%, indicating that better treatments are needed as Rennard SI and Daughton DM study sustains [10].

There are involved also, α1-antiprotease deficiency, in a very small percentage of cases, undefined genetic factors, infections, especially adenoviral infections and occupational and environmental exposures to various pollutants [11–14].

COPD is also heterogeneous in its presentation. Based on data from NHANES III [15] a significant proportion of patients with severe airflow limitation (FEV1, <50% of predicted) may not report symptoms. The symptoms reported most frequently include wheezing and shortness of breath in 64% of subjects, respectively, with FEV1 values <50% of predicted. COPD has become increasingly recognized as a systemic illness, with effects on nutritional status, muscle wasting, and depression [16, 17].

A large proportion of patients probably have components of chronic bronchitis, asthma, and emphysema occurring together. While some of this overlap may be related to misdiagnosis, some of it may be a measure of the presence of reversibility. A better definition of the individuals comprising these groups ultimately may help to tailor better interventions.

An indication of disease heterogeneity and reversibility in COPD patients can be obtained by looking at respiratory symptoms, lung function, and activity limitation in subjects who report COPD alone, asthma alone, COPD and asthma together, and neither COPD or asthma. Longitudinal studies revealed the heterogeneous character of COPD and concluded that the correct appreciation of the reversibility of the symptoms improves the survival rates in certain patients with COPD [1].

It has become apparent that airway abnormalities and emphysema interact in a complex fashion, rather than simply additively in the development of airflow limitation and COPD. The type of emphysema that smokers develop seems to determine, largely, the quantity and possibly type of inflammation and airway remodeling found, suggesting that different pathogenesis mechanisms might be at play in the development of COPD [18].

The pathological hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema).

Peripheral airways include small bronchi and bronchioles with internal diameter smaller than 2 mm. It is obvious that the early decline of the pulmonary function in COPD is positive correlated with inflammatory changes in peripheral airways (similar to those that occur in central airways): inflammatory exudates in the airways lumen, inflammatory infiltrate in the walls, goblet cell and/or squamous cell metaplasia of the respiratory epithelium, mucosal edema due to the inflammation and excess mucus because of the goblet cell hyperplasia, respectively bronchiolo-alveolar attachment destruction [5].

In COPD, inflammation is characterized by increased macrophages, CD8+ T-cells and neutrophils and is largely driven by IL-8, tumor necrosis factor-a, leukotriene (LT) B4 and TGF-b [19–26].

Macrophages appear to play a pivotal role in the pathophysiology of COPD and can account for most of the known features of the disease [27, 28].

There is a marked increase (5–10 fold) in the numbers of macrophages in airways, lung parenchyma, BAL fluid and sputum in patients with COPD. A careful morphometric analysis of macrophage numbers in the parenchyma of patients with emphysema showed a 25-fold increase in the numbers of macrophages in the tissue and alveolar space compared with normal smokers. Macrophages are localized to sites of alveolar wall destruction in patients with emphysema [28–30].

There is a correlation between macrophage numbers in the airways and the severity of COPD [31].

Macrophages may be activated by cigarette smoke extract to release inflammatory mediators, including tumour necrosis factor (TNF)-a, IL-8, other CXC chemokines, monocyte chemotactic peptide (MCP)-1, LTB4 and reactive oxygen species, providing a cellular mechanism that links smoking with inflammation in COPD.

Alveolar macrophages also secrete elastolytic enzymes, including MMP-2, MMP-9, MMP-12, cathepsins K, L, S, and neutrophil elastase taken up from neutrophils. Alveolar macrophages from patients with COPD secrete more inflammatory proteins and have a greater elastolytic activity at baseline than those from normal smokers and this is further increased by exposure to cigarette smoke [32–35].

There is an increase in the total numbers of T-lymphocytes in lung parenchyma, peripheral and central airways of patients with COPD, with the greater increase in CD8+ than CD4+ cells. There is a correlation between the numbers of T-cells and the amount of alveolar destruction and the severity of airflow obstruction. There is also an increase in the absolute number of CD4zT-cells, but the ratio of CD4+: CD8+ cells are reversed in COPD [29, 30, 36–38].

The increase in number of T lymphocyte CD8+ is reported in both central and peripheral airways, lung parenchyma, pulmonary arteries and lymph nodes that drain the lymph from the territory in COPD patients. This aspect sustains the hypothesis that the inflammatory process is homogenous distributed in the tracheo-bronchial tree and pulmonary tissue.

Neutrophils are an important component of the airway inflammation. Increased numbers of activated neutrophils are found in sputum and BAL fluid of patients with COPD. There are only relatively small increases in the airways or lung parenchyma. This may reflect their rapid transit through the airways and parenchyma [22, 30].

The major inflammatory cell density is in the submucosa (between smooth muscle and epithelial basal membrane) comparative with the adventitia (between smooth muscle and lung parenchyma). There is a positive correlation between the submucosal cellular density and the bronchial obstruction grade. These data suggest that submucosal prevalent inflammation is a COPD characteristic that amplifies the smooth muscle contraction effect resulting in airways caliber reduction [39].

Inflammation initiated by cigarette smoking and the other risk factors leads to repeated cycles of outrage and repair of the peripheral airways walls [5]. Airway remodeling includes subepithelial fibrosis, increased smooth muscle mass, enlargement of glands, neovascularisation and epithelial alterations. Remodeling is observed in almost every injured tissue, particularly in tissues that undergo repeated chronic injury [40].

Airways of patients with chronic obstructive pulmonary disease are characterized by squamous cell metaplasia, loss of epithelial cilia, goblet cell hyperplasia, mucus gland enlargement and smooth muscle hypertrophy [19, 41–43], with increases in smooth muscle mass more predominant in smaller than larger airways [44].

Airway wall fibrosis and stenotic lesions are also observed in the small airways [45].

Normally, basement membrane thickening is not characteristic of airway remodeling in COPD patients, although it has been reported in a subgroup of COPD patients who have a predominant eosinophilic inflammatory profile [46]. Angiogenesis is also observed in COPD airways [47].

Cigarette smoking may impair lung repair mechanisms, thereby further contributing to altered lung structure. Normal lung repair mechanisms can lead to airway remodeling because tissue repair in the airways, like elsewhere in the body, may involve scar tissue formation. This injury and repair process, results in airway wall structural remodeling, with increasing in collagen content and scar tissue formation that narrows the lumen and produces fixed airways obstruction.

Fibrosis in the peripheral airways, as elsewhere in the body, is characterized by the accumulation of mesenchymal cells (fibroblasts and myofibroblasts) and extracellular connective tissue matrix. Mediators secreted by mononuclear phagocytes and epithelial cells drive this process [5].

Goblet cells are normally absent or sparse in airways less than 2 mm in diameter (i.e., small bronchi and bronchiole), but they appear and increase in number in these peripheral airways in COPD, a process referred to as mucous metaplasia [48].

Increase in number of the goblet cells may determine increased mucus secretion and decreased bronchiolar surfactant secretion due to Clara cells substitution resulting in high superficial tension and airways obstruction. Goblet cell hyperplasia in the cigarette smoking patients peripheral airways epithelium is accompanied by increased neutrophils. *In vitro*, neutrophilic elastasis exerts intense secretagogue activity on the glandular cells [39].

The airway epithelium in chronic bronchitis and COPD often shows squamous metaplasia, which may result from increased proliferation of airway epithelial cells. Proliferation in basal airway epithelial cells, measured by PCNA is increased in some normal smokers, but is markedly increased in patients with chronic bronchitis and correlates with the degree of squamous metaplasia. Epithelial growth factor receptors show increased expression in airway epithelial cells of smokers and may contribute to basal cell proliferation, resulting in squamous metaplasia and an increased risk of bronchial carcinoma [9].

The changes in airway smooth muscle are more prominent in the small airways than in the large airways. In the large airways, alterations in smooth muscle mass were not observed, and the amount of airway smooth muscle did not correlate with airflow limitation, although the wall internal to the muscle was significantly thickened and was associated with a reduction in the ratio of FEV1 to forced vital capacity.

Although the airway smooth muscle mass is increased, it is unknown whether this process is caused by an increased number of airway smooth muscle cells, an increase in airway smooth muscle size, or both [49].

The lung parenchyma includes the gas-exchanging surface of the lung (respiratory bronchioles and alveoli) and the pulmonary capillary system. The most common type of parenchimal destruction in COPD patients is the centrilobular form of emphysema, which involves dilatation, and destruction of the respiratory bronchioles.

Emphysematous lesions occur more frequently in the upper lung regions in milder cases, but in advanced disease, they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed. Panacinar emphysema, which extends throughout the acinus, is the characteristic lesion seen in alpha-1antitrypsin deficiency and involves dilatation and destruction of the alveolar ducts and sacs as well as the respiratory bronchioles. It tends to affect the lower more than upper lung regions. Because this process usually affects all the acini in the secondary lobule, it is also referred to as panlobular emphysema [5].

Morphological changes in emphysema consist of destruction and enlargement of the aerial spaces distal from the terminal bronchioles without fibrosis. Fibrosis absence is a controversial affirmation because some studies demonstrated that in emphysema may be an increase in collagen corresponding to a fibrosis degree [39].

It is demonstrated that in cigarette smokers there is major destruction bronchiolo-alveolar attachment degree that positive correlates with the peripheral airways inflammation intensity. It is possible that the inflammatory mediators secreted by the bronchiolar inflammatory cells to interact with alveolar tissue mainly at the point of junction between the bronchiole and the alveolar wall where the mechanic stress is probably maximum. It is a major aspect of the airflow limitation mechanism sustained by the observation that the alveolar attachment loss degree correlates with peripheral airways inflammation and mainly with lung elastic recoil decrease and bronchial obstruction degree in cigarette smokers.

It should be noted in this regard that a major signal for cellular apoptosis is loss of extracellular matrix contact. Most cells seem ready to commit to programmed cell death (apoptosis) when faced with an unsolvable loss of matrix attachment. Indeed, cellular survival may depend on signals from the integrin family of adhesion receptors continuously sensing the extracellular milieu. Thus, it is likely that the development of emphysema involves apoptosis of cells of the alveolar wall following focal proteolytic damage to their underlying matrix (or the cells themselves) (Table 2) [50].

Examination of lung tissue from patients suffering from chronic obstructive pulmonary disease (COPD) reveals the presence of apoptotic cells in greater numbers than in control lungs or those from smokers without COPD. Apoptotic cells include alveolar and bronchial epithelial cells as well as endothelial cells in the parenchyma. Importantly, the apoptosis persists in patients with COPD after smoking has ceased. In rodents, deliberate induction of endothelial or epithelial apoptosis is accompanied by loss of pulmonary alveoli and pathologic evidence of emphysematous changes. These different types of observation raise the important question of a possible causal relationship between apoptosis (or response to this) and COPD.

Simplistically, this could be no more than an indication of cell damage in the lung that would be expected within the hypothesis that emphysema is a consequence alveolar destruction. The similar pathologic changes seen after targeting either the endothelium or epithelium could be readily reconciled by the demonstration that there is significant interaction between the two cell layers of the alveolus so that severe damage to one could reasonably lead to disruption of the other, and presumably the matrix and interstitium as well.

An alternative direction of effect in COPD could be induction of apoptosis subsequent to destruction of the supporting alveolar matrix. The finding of more detectable apoptosis in smokers with COPD than non-COPD smokers suggests that cigarette smoke itself is not the sole agent causing the apoptosis, or its ability to be detected, although COPD-prone individuals could conceivably be more susceptible to smoke induced cell damage and apoptosis [51].

Table 2 – ***Cellular and structural changes in COPD cigarette smokers (adapted from Saetta M et al., 2001 [42])***

Central airways wall	
Lumen	▪ Increase in macrophages and T-lymphocytes (particularly CD8+ T-lymphocytes); ▪ Neutrophils in severe disease; ▪ Neutrophils.
Peripheral airways	▪ Goblet cell metaplasia and mucous plugging; ▪ Smooth muscle hypertrophy; ▪ Fibrosis; ▪ Inflammation (particularly CD8+ T-lymphocytes); ▪ All inflammatory cells including neutrophils in severe disease.
Parenchyma	▪ Inflammation (particularly CD8+ T-lymphocytes); ▪ Destruction (centriacinar and panacinar emphysema); ▪ Fibrosis.
Pulmonary arteries	▪ Endothelial dysfunction; ▪ Intimal thickening; ▪ Medial thickening (less frequently); ▪ Adventitial inflammation (particularly CD8+ T-lymphocytes).

Pulmonary vascular changes begin early in the natural history of the disease, when lung function is well maintained and vascular pressures are normal and are characterized by a thickening of the vessel wall. Endothelial dysfunction of the pulmonary arteries, which is may be caused directly by cigarette smoke products or indirectly by inflammatory mediators, occurs early in COPD.

Since endothelium plays an important role in regulating vascular tone and cell proliferation, it is likely that endothelial dysfunction might initiate the sequence of events that results ultimately in structural changes.

Thickening of the intima is the first structural change, followed by an increase in vascular smooth muscle and the infiltration of the vessel wall by inflammatory cells, including macrophages and CD8+ T-lymphocytes. These structural changes are correlated with an increase in pulmonary vascular pressure that develops first with exercise and then at rest. As COPD worsens, greater amounts of smooth muscle, proteoglycans and collagen further thicken the vessel wall [5].

Small (<500 μm) pulmonary vessels in airway-obstructed smokers show intimal thickening as compared with those of non-obstructed nonsmokers: in severely obstructed smokers, there is medial hypertrophy also. Such structural changes likely contribute to the narrower lumens and vascular obstruction of these vessels. Interestingly, there is infiltration of the pulmonary arterial wall by CD8+ T lymphocytes that are increased in both nonobstructed smokers and smokers with COPD compared with nonsmokers. The intensity of the inflammatory infiltrate has been shown to correlate with both endothelium-dependent relaxation and intimal thickness [48].

Kranenburg AR *et al.* [47] examined by immunohistochemistry the cellular expression pattern of VEGF, Flt-1, and KDR/Flk-1 in central and peripheral lung tissues obtained from ex-smokers with COPD. VEGF, Flt-1, and KDR/Flk-1 immunostaining was localized in vascular and airway smooth muscle cells, bronchial, bronchiolar and alveolar epithelium, and macrophages. Pulmonary endothelial cells expressed Flt-1 and KDR/Flk-1 abundantly but not VEGF. That indicates that endothelial cells are effectors cells under the VEGF action rather that an autocrine source.

Someone could ask whether the endobronchial biopsy could make the routine differential diagnosis between asthma and COPD. Bourdin A *et al.* [52] sustained in their study that specific histopathological features of asthma and COPD probably exist, but current routine analysis procedures to assess endobronchial biopsies specimens are not discriminatory. They have analyzed endobronchial biopsies specimens from patients having a clear clinical diagnosis of asthma respectively COPD.

Eosinophils strongly biased the pathological diagnoses in favor of asthma, whereas their estimated prevalence was similar (11–37% in asthma and 13–41% in COPD). Metaplasia (11–39% in COPD, 1–18% in asthma) and epithelial inflammation (28–61% in COPD, 11–38% in asthma) tended to be specific to COPD, whereas epithelial desquamation (80–98% in asthma, 61–88% in COPD) and basement membrane thickening (71–94% in asthma, 53–88% in COPD) tended to be associated with asthma.

International guidelines stress the importance of accurately discriminating between asthma and chronic obstructive pulmonary disease. Although characteristic pathological features have been described for both conditions, their discriminatory power has never been systematically assessed. This might be rectified by improving pathological definitions.

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