Pathophysiology Updates for Chronic Obstructive Pulmonary Disease

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Abstract New insights into cellular and molecular mechanisms have recently emerged, leading respiratory physicians to re-examine and even revise current phenotype classifications of COPD. Studying mechanisms of COPD must now go beyond mere enumeration of separate pathophysiological features, for example airflow limitation, air trapping, and inhomogeneity of ventilation distribution. Rather, how to precisely define various phenotypes of COPD patients should become the main objective for all respiratory physicians, because accurate phenotypes will lead to better cures and, hence, better prognosis for COPD patients. During the last decade respiratory physicians have gained much insight into COPD pathophysiology. Yet we are still far from mastering effective biological tools, including genetic and molecular fingerprints readily available for all patients for easy diagnosis and effective prevention of worsening of COPD.

Keywords Airway inflammation · Chronic obstructive pulmonary disease (COPD) · Small airways · Emphysema · Oxidative stress · Protease · Phenotype · Imaging · Depression · Diabetes · Ischemic heart disease · Lung cancer · Osteoporosis · Mortality · Prognosis · Phosphodiesterase 4 inhibitor · Airflow limitation · Exacerbation · Hyperinflation · Chronic bronchitis · Quantitative CT · Bronchodilator responsiveness · Genetics · Impulse oscillometry

Introduction

Although chronic obstructive pulmonary disease (COPD) is an insidious and distressing condition that affects an

increasing number of individuals worldwide [1•, 2–4], early diagnosis, individual treatment, and effective prevention of COPD remain largely unsatisfactory. This is a cause of major concern for the international community of respiratory scientists and physicians. Recent breakthroughs in cellular and molecular mechanisms, clinical descriptions, and physiological features have provided new information about the pathogenesis of COPD [5–11]. New drugs targeting both inflammation and bronchial smooth muscle contraction, e.g. phosphodiesterase-4 inhibitors, have recently been added to the range of drugs used to treat COPD [12–14]. Clinical trials have also revealed that COPD patients remain largely heterogeneous, and prediction of individual responses to new therapy is often fraught with difficulties [14–16]. In other words, pathophysiological studies of COPD in 2013 should not merely enumerate clinical, physiological, or radiological features of this condition but must attempt to better define clusters of patients sharing the same patterns of clinical and biological characteristics and, hence, the same pattern of responses to conventional and new therapy [17]. In this way, not only will we be able to reduce symptoms as recommended by the latest GOLD guidelines [1•] but prediction of occurrence and prevention of worsening of COPD will also be achieved. In this paper we review some of the most recent and significant findings on the pathophysiology of COPD. We also stress the heterogeneity of this complex disease and, finally, indicate the need to group patients according to their clinical phenotypes and molecular profiles [5].

Pulmonary Pathophysiological Disturbances in COPD

Airflow Limitation and Air Trapping

There is increasing evidence to suggest that abnormality of the small airways—those less than 2 mm in internal diameter—is critical in COPD [18, 19]. Underlying mechanisms include widespread inflammation, airway wall fibrosis, and luminal exudates [20, 21], that ultimately reduce

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FEV₁ and FEV₁/FVC ratio and accelerate the rate of decline of FEV₁ over time among COPD patients [22].

Assessing airway patency is of particular importance for COPD patients whose forced expiration is usually associated with dynamic collapse of small airways impeding complete exhalation and causing air trapping and hyperinflation. Pulmonary function tests assessing small airway patency, including spirometry, enable measurement of airflow, airway resistance, ventilation distribution, and airway closure [19]. Spirometry can evaluate flow from small airways by means of measurement of the forced expiratory flow at 50 % of vital capacity (FEF50 %) and at 25 % to 75 % of vital capacity (FEF25 %–75 %), but the validity of the latter for accurate reflection of flow limitation in the small airways is still a matter of debate [23]. Resistance in the small airways can be assessed by impulse oscillometry (IOS) [24]—measurement at low frequency (5 Hz) can reveal increased resistance, owing to obstruction of small and peripheral airways even when resistance measured at higher frequency (20 Hz) remains normal. IOS is probably the preferred method for elderly or severe COPD patients because it is non-invasive and can be easily performed during quiet ventilation. Furthermore, IOS can, in some instances, be more sensitive than FEV₁ for assessment of bronchial reversibility of COPD patients [25].

In COPD patients, reduced airflow resulting from small airways obstruction, in the presence of normal pulmonary blood, leads to ventilation/perfusion mismatch (or inhomogeneity). The latter can be assessed by noninvasive methods which assess nitrogen washout by use of multiple and single breaths after inhalation of 100 % oxygen [26]. For COPD patients air trapping occurs as a result of dynamic collapses of the distal airways at the end of forced expiration. Accumulated air trapping leads to lung hyperinflation that will, in turn, perturb COPD patients' energy expenditure. Assessing air trapping through lung volume measurements is, therefore, mandatory. Because residual volume and the ratio residual volume/total lung capacity correlate with changes in resistance of peripheral airways, it is conceivable that changes in lung volumes are closely related to obstruction of distal airways of COPD patients. In this respect, bronchodilator compounds that can reach the distal airways will reduce air trapping through bronchodilation, thereby reducing residual volume and dyspnea and improving exercise capacity. Air trapping can also be seen in emphysematous lungs of patients with severe COPD because of disruption of alveolar attachments to small airways inducing collapse of the latter. Lung hyperinflation because of air trapping is associated with increased functional residual capacity, especially during exercise (a phenomenon known as dynamic hyperinflation), and leads to exertional dyspnea [27]. A link between lung mechanics abnormality and inflammation has recently been suggested, because hyperinflated lungs not

only contribute to impairing the contractility of respiratory muscles but are also associated with increased production of local pro-inflammatory cytokines [1•]. Assessment of small airways patency and the extent of emphysema can be achieved by use of high-resolution computed tomography (HRCT) [28]. This technique is, however, expensive, especially for low-income countries; it also requires the presence of trained professionals, and, last but not least, it exposes patients to radiation. Alveolar concentration of nitric oxide (NO) has been suggested as a marker of distal lung inflammation in COPD [29]. It will, however, be necessary to provide evidence showing a direct relationship between increased alveolar concentration of NO and alveolar inflammation in COPD patients, as has recently been shown for patients with scleroderma-associated alveolitis [30].

Gas-exchange Abnormalities

In advanced-stage COPD, ventilation/perfusion mismatch usually occurs as a result of obstruction of the small airways which impairs ventilation, and alveolar wall destruction, i.e. emphysema, which reduces perfusion [31, 32]. By increasing the work of breathing, severe bronchial obstruction also reduces ventilatory drive, hence alveolar ventilation [1•]. Perturbed lung gas exchange is reflected by hypoxemia in most patients with advanced COPD and the combination of hypoxemia and hypercapnia in COPD patients with end-stage lung disease. Hypoxemia is diagnosed by blood gas measurement by use of a blood gas analyzer. Measurement of oxygen saturation during exercise is a noninvasive and elegant way of assessing the capability of the lungs to cope with augmented oxygen demands in practical conditions characterized by increases of both ventilatory and circulatory drives. Excessive oxygen desaturation during exercise is also indicative of perturbed lung gas exchange in patients who might soon need oxygen therapy.

Mucus Hypersecretion

Chronic productive cough is a clinical characteristic of COPD. Excessive sputum production is the clinical expression of chronic bronchitis; it is usually located in the large airways, although not all chronic bronchitis patients develop obstructive airway and not all COPD patients constantly have chronic bronchitis. Airway inflammation results from chronic irritation of the airways caused by cigarette smoke, noxious gas, toxic fumes, and dust. The underlying histological damage leads to an increased number of goblet cells and enlarged submucosal glands. A variety of mediators, including proteases and cytokines, are released from resident lung cells, and inflammatory circulatory cells, during inflammation. These mediators, in turn, stimulate mucus hypersecretion by activating the epidermal growth factor lung receptor [7]. The

neurotransmitter acetylcholine released by vagus nerve endings during inflammation also induces submucosal gland secretion, thus providing logical grounds for use of anticholinergic compounds to treat COPD patients with excessive mucus secretion. Cough and sputum production are risk factors for poor outcomes among patients with COPD [33].

Pulmonary Hypertension

Inflammatory processes in COPD are not restricted to the bronchial tree—they also crucially affect the pulmonary vasculature. Remarkably, inflammatory mechanisms are very similar in both airways and pulmonary vessels from COPD patients. Pulmonary vascular structural changes include intimal hyperplasia and vascular smooth muscle hypertrophy and/or hyperplasia in the late stage [34]. Different mechanisms may cause pulmonary hypertension in COPD patients [35, 36]. Endothelial dysfunction is one of the main mechanisms leading to increased pulmonary vasomotor tone in COPD [37]. In dysfunctional endothelial cells, production of vasoconstrictors is increased and synthesis of endothelial-derived nitric oxide (NO) is impaired. Losses of pulmonary vascular bed associated with alveolar wall destruction with hypoxic pulmonary vasoconstriction are the two main causes of pulmonary hypertension in patients with emphysema. Because elevated pressure in the pulmonary circulation increases right heart afterload and, subsequently, the work of the right ventricle, this will invariably result in right ventricular hypertrophy and right-heart cardiac failure [1••].

Exacerbation

According to GOLD recommendations, exacerbation of COPD is defined as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication” [1••]. Exacerbation is serious and may occur in all COPD patients; not only may this be life-threatening at the time of the acute exacerbation but it can also negatively affect the course of the disease. Many studies have shown that exacerbation is costly, accelerates lung function decline, worsens quality of life, and increases mortality, especially among hospitalized patients [38]. Exacerbation of COPD is usually initiated by bacterial or viral infection or pollutants. However, the cause of one third of cases of exacerbation is unknown. Lung hyperinflation and gas trapping worsen during exacerbation. The results are reduced expiratory flow and increased dyspnea [38]. Ventilation/perfusion mismatch increases thereby augmenting dead space, perturbing lung gas exchange, and, hence, causing hypoxemia [39]. Other conditions, for example pneumonia, thromboembolism, and acute cardiac failure often coexist. There have been many attempts to predict the occurrence of COPD exacerbation.

The most reliable of risk factor is a preexisting episode of exacerbation that has required hospitalization in the previous year. Multivariate analysis has shown that the increase in bronchial wall thickness or greater total emphysema measured by quantitative CT will increase the annual incidence of exacerbation.

Systemic Features

COPD is not only a disease restricted to the lungs—systemic comorbidities being now increasingly recognized [40, 41•]. Inflammatory mediators are not secluded in the respiratory system but are also present in the whole body circulation thereby initiating or worsening comorbidity symptoms [1••]. The abnormalities of lung function, especially airflow limitation and hyperinflation negatively affect cardiac function and gas exchange [31]. Because lung perfusion involves all the blood coming from the heart that will subsequently be distributed to the whole body, systemic cardiovascular diseases are, naturally, the most frequent and most important comorbidities among COPD patients. Osteoporosis and depression are associated with poor health status and prognosis but often are underdiagnosed. Lung cancer is the most frequent cause of death of patients with mild COPD. Other comorbidity conditions, for example skeletal muscle wasting, cachexia, normocytic anemia, diabetes, and metabolic syndrome, are related to circulating inflammatory mediators.

Phenotyping in COPD

Grouping COPD with similar features will probably make diagnosis, treatment, and prognosis simpler [42]. The earliest way of phenotyping COPD patients was based on simple clinical observation individualizing blue bloater in chronic bronchitis subtype from pink puffer in emphysema subtype. The dominant symptom of blue bloater is productive cough whereas that of pink puffer is dyspnea. The blue bloater patient has a stocky build whereas the other is usually thin. The blue bloater is wheezing whereas the pink puffer is not. On clinical examination, the blue bloater usually has right heart failure whereas the pink puffer has hyperinflated lung and quiet chest. On chest X ray, both could have a normal image or increased markings in blue bloater patients only and hyperinflation, reduced marking, and bullae in pink puffer patients. The other phenotyping is the classic Venn diagram describing the underlying diseases: asthma, chronic bronchitis, and emphysema in COPD. Many subtypes of COPD have emerged from this illustration [43].

Those traditional clinical phenotypes are, however, insufficient to categorize all COPD patients. While revising, in 2007, the Venn diagram taking into account the expanded heterogeneity of COPD [44••], Friedlander et al. suggested

there are three phenotypes of COPD: clinical, physiologic, and radiologic. The clinical phenotype is based on a variety of information, including dyspnea [45], exacerbations rates, BMI spanning from pulmonary cachexia to obesity, ICS responsiveness, depression and/or anxiety, and tobacco smoke status. The physiologic phenotype includes airflow limitation, rate of lung function decline, bronchodilator reversibility, airway hyper-responsiveness, hypercapnia, exercise tolerance, hyperinflation, low DLCO, and pulmonary hypertension. The radiologic phenotypes are subdivided into emphysema and airways disease.

Recently, composite indexes, for example BODE, have been introduced to classify and phenotype COPD patients differently [46, 47]. The response to treatment with salmeterol/fluticasone in COPD varies depending on different phenotypes [48, 49]. Genetic association analysis of COPD candidate genes with bronchodilator responsiveness has been investigated [50]. For some phenotypes, for example the rapid decliner, the potential susceptibility genes are listed [44•]. Finally, adhering to the notion that different phenotypes should have distinct clinical outcomes, Friedlander et al. have listed only five phenotypes: frequent exacerbator, pulmonary cachetic, ICS responders, and emphysema/airways disease phenotypes. Differentiating COPD into small subgroups with homogeneous phenotypes has also been suggested by Rennard and Vestbo in an attempt to increase awareness that COPD might be a collection of orphan diseases [51]. By doing so, these authors hoped that the orphan status could facilitate the development of treatments for phenotypic subsets of COPD patients, especially drugs designed to change the natural history of the disease. They stated that COPD is heterogeneous and some phenotypes are relatively rare. Han et al. recognized the complexity of phenotypes, because there are, and will be, many phenotypes based on any observable characteristic of an organism [52]. With the development of biology, COPD phenotypes will not only include symptoms and radiography and physiology information. Cellular and molecular fingerprints will also have their place, making the picture more complex. Han et al. also acknowledged that any phenotype may have a different etiology, and that one COPD patient may have multiple phenotypes. With the vision that too many phenotypes might lead to confusion, Han et al. have proposed a definition of COPD phenotypes which relate only to clinically meaningful outcomes: symptoms, exacerbation, response to therapy, rate of disease progression, or death. The authors also suggested that an iterative validation process will be needed for any COPD phenotype before its relevance to clinical outcomes is confirmed. The validation of COPD phenotype requires longitudinal study. There are now already several studies of this type: longitudinally to identify predictive surrogate endpoints (ECLIPSE) [53], spiromics, and COPD gene [54].

Last, the concept of “diseasome” linking cellular networks and phenotypic manifestations is emerging. Combined with advanced statistical techniques, the identification of relevant phenotypes and specific therapy are highly expected.

Conclusions

We have just started to understand the mechanisms underlying the symptoms and signs of COPD, for example airflow limitation, air trapping, gas exchange abnormalities, mucus hypersecretion, pulmonary hypertension, exacerbation, and its comorbidities, but the pathophysiology of COPD in the future should not be restricted to symptomatic, physiologic, and radiologic characterization, because biologic or molecular characterization should also be included. Furthermore, phenotyping COPD will help to diagnose the disease in an early stage, to find effective treatment, to predict and even to change its outcome. Hopefully, this will progressively reduce the burden of this disease and reverse its current trend making it one of the three worst diseases worldwide during the next decade.

Compliance with Ethics Guidelines

Conflict of Interest Le Thi Tuyet Lan has served on boards for GlaxoSmithKline and Boehringer, has received grants from GlaxoSmithKline, AstraZeneca, and MSD, and has served on speakers' bureaus for GlaxoSmithKline, Boehringer, MSD, and AstraZeneca. Anh Tuan Dinh-Xuan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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