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Review Article

Physiological and miRNA phenotyping of Early Chronic Obstructive Pulmonary Disease - Two Sides of a Coin

Zheina Vlaeva Cherneva[1]*, Dinko Genchev Valev[2], Vania Milocheva Youroukova[3], Radostina Vlaeva Cherneva[3]

[1]*Medical Institute of the Ministry of Internal Affairs, Sofia, Bulgaria*

[2]*University First City Hospital, Sofia, Bulgaria*

[3]*Medical University Sofia, Department of Respiratory diseases, Clinic of University Hospital for Respiratory Diseases "St. Sophia"*

Abstract

The clinical manifestation of smoking related diseases may be associated with physiological abnormalities - abnormal values of a certain spirometry parameter with/without clinical symptoms; and/or may appear as a non-spirometry disease - the presence of certain symptoms from the lungs with/without CT data of structural abnormalities of the airways and lung parenchyma. These two forms of the disease are determined as early Chronic Obstructive Pulmonary Disease (COPD). The preclinical disease is present in smokers with recurrent respiratory symptoms, which may progress to airflow limitation according to the genetic factors and the endotype. Early COPD is detected by spirometry, but coincides with an essential functional loss of the small airways, as well with extra-pulmonary complications - cardiovascular, depression, anxiety and diminished physical activity. The contemporary genetic miRNA profiling of sputum and blood samples from mild COPD confirms the clinical heterogeneity of early disease. It raises the demand for an individualized therapeutic plan and the need of screening programmers for its timely diagnosis. The physiological profiling - the analysis of the parameters of the respiratory and the cardiovascular system during physical activity in early COPD, also validates its clinical heterogeneity and facilitates the discrimination of different functional groups even in mild stage disease.

Keywords: Early chronic obstructive pulmonary disease; Clinical heterogeneity; MiRNA profiling; Physiological profiling

***Corresponding author:** Zheina Vlaeva Cherneva, Medical Institute of the Ministry of Internal Affairs, Sofia, Bulgaria, Tel: +3589889569777; E-mail: jenicherneva@yahoo.com

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COPD Heterogeneity - COPD as a Clinical Syndrome

According to the definition of the Global Strategy for the Control and Prevention of COPD, 2017, COPD is a common disease that is treatable, preventable and is characterized by persistent pulmonary symptoms and airflow limitation. COPD is the consequence of a pathology of the airways and the alveolar sacs that is usually associated with a significant exposition to noxious particles and gases [1]. The respiratory symptoms (dyspnea, cough, sputum production), airflow limitation are not specific for COPD and may be met in other respiratory diseases. Most of the people may have such symptoms combined with normal spirometry [2]; the reverse may be also true - presence of abnormal spirometry when there are no clinical symptoms. The clinical presentation of COPD is enriched by the CT findings of emphysema or airway thickening (indication of airway pathology) in patients that have normal spirometry and no complaints [3]. COPD may be the result of various noxious agents - genetic anomalies (alpha-1 antitrypsin deficiency), smoking, exposition to biofuels, respiratory diseases in the past, history of asthma or /and inherited respiratory abnormalities. In a low percent of the patients it is not possible to say which is the exact reason for COPD pathogenesis [4]. COPD may occur alongside with the clinical presentation of another disease - asthma [5]. All the data make us assume that COPD is a clinical syndrome. It is associated with certain clinical signs and symptoms that develop alone or in combination; and may be the result of different pathological agents [6-9]. That is why the different pathological conditions that are characterized as COPD may have different evolution.

Preclinical Stage - COPD Before Spirometry Changes

Early COPD encompasses the period before the clinical manifestation (preclinical phase) [10] as well as the time during which the disease has not reached its typical clinical presentation - early disease [11]. The preclinical disease is present in smokers with recurrent respiratory symptoms, which may progress to airflow limitation according to the genetic factors and the endotype (the biological response of the individual to a certain noxious agent). This stage is traditionally associated with the definition of the Medical Research Council for the Chronic Mucous Hypersecretion (CMH) the presence of chronic cough and sputum; and /or the presence of dyspnea without airflow limitation. The early COPD is associated with minimal loss of lung function, detected by spirometry FEV1/FVC<70% and FEV1>80% (FEV1 - Forced Expiratory Volume in 1sec; FVC - forced vital capacity). They coincide with the time when COPD may be diagnosed for the first time. In some of the patients this lung function change corresponds to certain symptoms; in the rest these are not present. This the reason for the high rate of undiagnosed cases at early COPD - it varies between 12-56% in some countries and may reach the number of already diagnosed cases [11]. The symptomatic patients with early COPD are characterized by an essential functional loss of the small airways, as well with extra-pulmonary complications - cardiovascular, depression, anxiety and

diminished physical activity [12]. The physiological profiling of the respiratory and the cardiovascular system during physical activity facilitates the discrimination of different functional groups even in the early stage of the disease [13-15]. The contemporary genetic miRNA profiling of sputum and blood samples from mild COPD patients is another approach confirming the clinical heterogeneity of early COPD.

Early Detection of the Disease - Challenge and Clinical Problems

Although it is associated with a lot of health care resources, the early chronic obstructive pulmonary disease, is often unrecognized, undiagnosed and untreated [16]. A lot of patients with COPD show rapid decline of the lung function and progression of the disease to advanced clinical stages, especially if smoking cessation is not observed. Although there is much available data regarding the heterogeneity at this stage, there is still a lack of knowledge regarding the pathophysiological characteristics of the cluster groups, as well as a gap of prognostic markers for the activity of the disease [17]. The clinical significance of the early chronic obstructive pulmonary disease is determined by the fact that there is a possibility for pharmacotherapy that may slow down the lung function loss, may decrease the rate of exacerbations and may improve the quality of life at this disease stage [18]. Due to the heterogeneity in COPD the stratification of patients within the GOLD classification system that is based on the clinical, biochemical or genetic markers will enable the construction of a more precise diagnostic and treatment plan for the control of the disease [19]. The severity of the bronchial obstruction in COPD patients is just a simple model of the complexity of the disease. According to the GOLD criteria mild COPD is classified as a disease in which the forced expiratory volume to forced vital capacity ratio is under 70% and the forced expiratory volume in 1 sec is under 80% of the predicted. In the Burden of Obstructive Lung Disease, BOLD study, the COLD criteria from 2006 have been applied for the mild COPD patients. They have been 54% of all the patients and the rest of the patients were GOLD stage II-IV [20]. Consequently, the phenotypisation of COPD may be a promising approach, overcoming the clinical heterogeneity of the disease and may improve the clinical and therapeutic approach [21].

Physiological Penotypization

Gagnon et al, show the heterogeneity of GOLD I patients. There are three clusters of patients with mild COPD: 1) Patients with diminished FEV1/FVC ratio and diffusion capacity which can be misdiagnosed as healthy; 2) Patients with static pulmonary hyperinflation and normal physical activity; 3) Patients with significantly reduced physical activity, ventilatory reserve at peak load, greater dyspnea score and metabolic acidosis in comparison to the other two cluster groups of patients. Authors have investigated a cohort of symptomatic and asymptomatic patients with mild COPD [22]. Participants have been characterized by five different parameters: 1) The basic characteristic; 2) Symptoms; 3) Baseline lung function; 4) Physiological parameters during peak load; 5) Level of physical activity (steps per day, energy expenditure above 3 Metabolic Equivalents - MET (the time with physical activity above 3 MET is estimated). Having in mind the clinical heterogeneity of COPD GOLD II-IV stage the authors assume that in GOLD I there is also clinical heterogeneity. Gagnon et al, prove the clinical heterogeneity of GOLD I patients according to GOLD, 2014. They determine the presence of three different COPD groups in GOLD I applying cluster analysis. The first group is characterized by a limited diffusion capacity, low BDI score (Baseline Dyspnea Index) scale (in comparison to the control group), preserved lung function, physical capacity and physical activity; the second group is characterized by a significant static pulmonary hyperinflation, but with reserved physical activity; the third group of patients shows significantly limited physical activity, respiratory quotient at peak load and higher VE/MVV, Ve/VO2. The clinical heterogeneity of COPD is present among patients in ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) [21-23]. Gagnon et al, improve our knowledge about GOLD I - it is not a homogeneous group of patients with similar clinical presentation [22]. Some of GOLD I patients are with normal pulmonary function and functional capacity, despite the reduced values of pulmonary indicators. This can be confirmed by the fact that in 39% of the patients the ratio FEV1/FVC is more than the lower referent value. Vice versa, the decreased score of BDI scale and the reduced diffused capacity in this group of patients show that they have the pathophysiological characteristics of a pulmonary disease (COPD) [6]. The cluster analysis shows that 79% (67/85) of the patients with mild COPD differ significantly from the healthy controls, which confirms that these patients are with the characteristics of a real pulmonary disease. The patients with COPD from the second cluster group are with more pack years (>50), and have functional residual capacity and end-tidal volume more than 120%, as well as, reduced but still preserved physical capacity. Similar data is described by other authors [24]. Patients with mild COPD in the third group are characterized by reduced FEV1/FVC ratio, reduced physical capacity and activity. Although diminished physical activity has already been described in GOLD I, Gagnon et al, show that only some of the patients are with unfavorable prognosis [25]. Gagnon et al, show a dissociation between peak physical load and maximal physical activity shows that these two physiological parameters show different aspects of COPD [26]. The first group of patients demonstrate reduced ventilatory reserve at peak load in comparison to the other two groups and higher levels of dyspnea at peak load [27]. The greater values of VE/VO2 and respiratory quotient are indicators for a more severe metabolic acidosis during physical activity and muscle dysfunction, as it is also described by other authors [28].

MiRNA Profiling in Early COPD

Recent studies have led attention to miRNAs profiling in COPD. It is reported that miRNAs play a key role in inflammation - a determinant feature in many lung diseases - COPD, asthma, interstitial fibrosis. MiRNAs are a class of endogenous, short non-coding RNAs 19-25 nucleotides in length that negatively regulate gene expression via translational repression or mRNA degradation [29]. More than 2000 human miRNAs have been identified. MiRNAs have been implicated in the pathogenesis of cancer, cardiovascular, endocrine and neurological diseases. Their stability in tissue samples and biofluids, as well as, their ability to accurately detect diseases have positioned miRNA quantification as a promising approach for a wide range of diagnostic applications. MiRNAs are rapidly released from cells into the circulation with the progression of a disease. They are circulating freely in blood and can be assumed as 'biomarkers' for early diagnosis of many neurological, malignant and cardiovascular

diseases [30]. MiRNAs are usually secreted as microvesicles. Exosomes and apoptotic bodies may also be responsible for their release into the circulation [31]. Significant development has been made toward unraveling the contribution of miRNAs in pathogenesis of pulmonary diseases [32].

Inflammation and MiRNA Profiling

Wang et al, state that plasma miRNAs - miR-1229-3p, miR-145-5p, miR-338-3p, miR-3620-3p, miR-4485, miR-4707-3p and miR-636 distinguish early COPD from asthma patients and healthy smokers. These miRNAs played important role in regulating interferon-gamma inducible protein, tumor necrosis factor receptor superfamily, insulin-like growth factor-2 receptor, fibroblast growth factor binding protein 3, gammaglutamyl-transferase 6 and serine proteases [19].

Shen et al, showed the gradual down-regulation of another miRNA, responsible for inflammation [33]. Authors demonstrate down-regulation of miR-149-3 in blood samples of early COPD smokers, COPD non-smokers, non-COPD smokers and non-COPD non-smokers. They predicted a target gene of miR-149 through 3′UTR sequence analysis and performed simulated experiments in T-Helper-1 (THP-1) cells. Simulation with Cigarette Smoke Extratct (CSE) resulted in a decrease in miR-149 expression and an increase in the expression of its target gene - TLR-4 in bronchial cell lines. Furthermore, transfection of miR-149 inhibitors induced the up-regulation of TLR-4. Finally, miR-149 overexpression reversed the effect of CSE on THP-1 cells [34]. Shen et al, speculated that the miR-149 negatively regulates the inflammatory response in THP-1 cells by targeting TLR-4. Previous reports found that miR-149 might be an immune modulator for TLR/MyD88 signaling pathway in macrophages [35]. TLR-4 is regulated by members of the let-7 miRNA family. Shen et al, demonstated that the change in miR-149 expression caused alteration of TLR-4 and NF-κB p65 protein levels. Many studies have investigated the expression of TLRs on both immune and epithelial cells in COPD. Nadigel et al, described that CD8+ T cells exposed to CSE increased TLR-4 and TLR-9 levels and also increased cytokine production [36]. Another study found that acute cigarette exposure results in lipopolysaccharides-independent TLR4 activation, leading to IL-1 production and IL-1R1 signaling, which is crucial for inflammation in COPD [37]. It corresponds to increased TLR-4/NF-κB signaling pathways and elevated secretion of IL-1β and TNF-α - major triggers in COPD related inflammation.

Small Airways and miRNA Profiling

Small airway fibrosis and chronic mucus hypersecretion are also among the characteristic features in COPD pathogenesis. Cigarette smoke activates epithelial cells to release TGFβ and Fibroblast Growth Factor (FGF). They induce fibroblast proliferation and smallairway fibrosis [38]. TGFβ is a potent stimulus for myofibroblast differentiation and induction of pulmonary fibrosis. To simulate COPD in vitro, Shen et al, applied TGFβ treatment to Bronchial Epithelial cell line (BEAS2B) [39]. They demonstrated that miR4835p transfection led to TGFβmediated decrease in cell proliferation and αSMA and fibronectin expression. Authors hypothesise that, during COPD progression, low levels of miR4835p may upregulate the expression of these two proteins. This indicates that the abrogation of TGFβdecreased cell proliferation by miR4835p may be associated with the expression of αSMA and fibronectin.

Cellular Senescnece and miRNA Profiling

Fibroblasts play a role in the regulation of airway epithelial mucociliary differentiation and mucus production in COPD patients. In addition to lowered cell proliferation lung fibroblasts demonstrate increased senescence. They release a spectrum of inflammatory proteins known as the Senescence-Associated Secretory Profile (SASP) - IL-6, CXCL8, MMP2 and MMP9, Plasminogen Activator Inhibitor-1 (PAI-1). MicroRNAs play a key role in linking oxidative stress to senescence by sirtuin-1 and -6 inhibition [40]. There is an increase in miR-34a via activation of the Phosphoinositide-3 Kinase - Mammalian Target of Rapamycin (PI3K-mTOR), with parallel reduction of sirtuins-1 and -6 in COPD small airways. Specific antagomirs of these miRNAs restore sirtuins, reduce markers of senescence and secretion of SASP mediators and also restore cellular growth of lung fibroblasts (rejuvenation effect).

Chronic Mucus Hypersecretion and miRNA Profiling

Chronic Mucus Hypersecretion (CMH) is typical in COPD. Goblet cells within the airway epithelial layer together with mucous glands in the airway sub-mucosa are responsible for the secretion of mucins, the principal components of mucus [41]. The most abundant gel-forming mucins are MUC5AC and MUC5B [42]. The expression profiles of miRNA and mRNA in bronchial biopsies from 63 COPD patients were associated with chronic mucus hypersecretion CMH - 20 miRNAs and 539 mRNAs were associated with CMH in COPD. MiR-134-5p, miR-146a-5p and the let-7 family had the highest representation of CMH-associated mRNAs. They are involved in several other biological processes, including cilium development and function, neurohormonal activities, cyclic nucleotide metabolism and ion transport [43].

Ciliary dysfunction has been observed in COPD airways [44]. The movement of cilia is dependent, at least partially, on cyclic nucleotides and in particular on cAMPs [45]. Ion transport, such as $Ca^{2+,}$ Na^{+} and Cl^{-} plays an important role in regulating mucus viscosity and muco-ciliary clearance [46]. Neuro-hormonal signaling regulates Cyclic Guanosine Monophosphate (cGMP) induced mucin secretion [47]. KRAS, EDN1, PRKAR2A, GSK3B and POLR2H miRNAs are presnted as hub genes and potential regulators of CMH.

Conclusion

Clinical assessment of COPD is challenging especially in terms of early diagnosis and individualized treatment. At present there is no validated imaging, physiological, clinical or molecular approach for COPD classification and phenotypisation. Assuming the heterogeneity of this syndrome and the devastating statistics of respiratory related morbidity and mortality more sensitive physiological techniques of small airway function are demanded; new imaging methods of small airway fibrosis should be developed. The data from basic research shows that small airway fibrosis and the miRNAs responsible for them, are expected to be the new markers for COPD disease activity. A promising pharmacotherapy approach is to target cellular senescence, either by inhibiting pro-senescence signaling pathways or by induction of apoptosis. Any effect on fibrosis is expected to slow progression of COPD.

Conflict of Interests

All the authors state no conflict of interests and leave the copyright of the article if accepted.

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