Defining COPD: from simplistic approach to multilateral assessment of COPD

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Abstract Chronic obstructive pulmonary disease (COPD) is a multisystemic pathology, which cannot be characterized, diagnosed or assessed only by the severity of airflow limitation. Thus, it appears there is urgent unmet need of new approach in COPD. In this article we review the most recent multidimensional classification of COPD, based on analysis of functional and physiologic parameters, health status, and risk of exacerbations. A, B, C, D system will permit a more accurate risk stratification of patients. In addition, new trends are presented in assessment of COPD: from phenotypes, multidimensional indices, scale-free networks and diseasome to radical concept of P4 medicine (Personalized, Predictive, Preventive, and Participatory elements).

Keywords COPD · Comorbidity · Exacerbation · CAT · Systemic effects · Assessment · GOLD classification · Severity · Phenotypes · Scale-free networks · Diseasome

Introduction

Chronic obstructive pulmonary disease (COPD) represents a major problem for public health worldwide, an important cause of morbidity and mortality at the global level and its

burden is expected to increase in the next decade. COPD is one of the major non-communicable diseases (NCDs), which will be the predominant health problem of the 21st century. COPD is actually the 4th leading cause of chronic morbidity and mortality worldwide. Mortality from COPD is expected to increase further and to rank at the 3 position in 2020, after coronary artery disease and stroke [1]. Unfortunately, COPD remains largely under-perceived by patients and underdiagnosed by doctors, and as a result undertreated.

Definition

In 2001 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) was launched and suggested the definition: COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [2].

In the last GOLD 2011 report [3••], the scientific committee suggested the following definition of COPD: a common preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

If we will compare old definition with new, then we can state that the complexity of COPD and its heterogeneous and systemic character was finally recognized by respiratory medicine specialists in the last decade. In addition, the word “abnormal” inflammatory response has been replaced by the “enhanced chronic” inflammatory response after the suggestions of Siafakas et al. [4].

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Systemic effects and comorbidities

There are two different theories relating the observed associations between COPD and systemic manifestations and comorbidities [5•]. The first theory considers that COPD is the result of a systemic “spill-over” of the inflammatory and reparatory events occurring in the lungs of patients with COPD, with the disease remaining primarily in the lungs [6]. The second theory states that pulmonary manifestations of COPD are one more form of expression of a “systemic” inflammatory state with multiple manifestations [7•].

The best studied risk factor for COPD is cigarette smoking; it is also one of the major risk factors of all chronic diseases [8]. It is well known that the cigarette smoking induces not only local inflammation (airway and lung), but also systemic inflammation (cellular and humoral), systemic oxidative stress, marked changes of vasomotor and endothelial function, and enhanced circulating concentrations of several procoagulant factors [9].

A number of patients with COPD have evidence of systemic inflammation [5•, 10••], measured either as increased circulating cytokines (leukotriene B₄, interleukins-1, 6 and 8 and tumor necrosis factor alpha), chemokines and acute phase proteins (C-reactive protein, fibrinogen, serum amyloid A, surfactant D), and abnormalities in circulating cells (neutrophils, macrophages, and T lymphocytes).

One-half of all people aged ≥ 65 years have at least three chronic medical conditions, and one-fifth have five or more [11]. It can be explained by the concept of inflammaging, in fact, process of aging is associated with a chronic low-grade inflammatory status as a consequence of lifelong antigenic exposure leading to some genetic modifications.

These systemic effects of cigarette smoking or age or some another unknown factors or sum of them could contribute substantially to the development not only of the COPD, but also of comorbidities. Thus systemic inflammation is potentially the common pathway leading to multiple chronic diseases and might explain the high prevalence of comorbidities in the same patient.

The most common comorbidities [12, 13] described in association with COPD are skeletal muscle dysfunction [14], cachexia [15], cardiovascular disease (hypertension, coronary artery disease, heart failure, pulmonary vascular disease) [16], pulmonary infections [17], osteoporosis [18], lung cancer [19], and diabetes [20]. Comorbidities widely affect health outcomes in COPD: mortality of COPD patients caused by nonrespiratory diseases, such as cardiovascular diseases and cancer [21].

Any COPD patient should be carefully evaluated for comorbidities and the systemic effects of COPD since they not only influence the prognosis, but also have an impact on disease management [7•].

Classic COPD classification

All classic classifications of COPD were based exclusively on the single parameter post-bronchodilator forced expiratory volume in 1 s (FEV₁) as an expression of airflow obstruction [2, 22]. Also FEV₁ was considered as “golden standard” and used widely for diagnosis, treatment of COPD, and was one of the most of important outcomes in large studies.

After appearance in literature of the first serious evidences that COPD is a complex disease with multiple pulmonary and extrapulmonary manifestations, it became evident that old COPD classifications cannot reflect complexity of disease. COPD patients cannot be described by only using the severity of airflow limitation.

Multidimensional indices

First attempts in facilitation of risk assessment were made by development and validation of new staging systems which permit categorization of the heterogeneous population with COPD. There were developed a lot of multidimensional indices, in which widely was used different clinical, functional, or quality of life variables. There were proposed more than 15 multilateral indices: BODE index which included body mass index (BMI), FEV₁, dyspnea and exercise capacity [23], the ADO index which included age, dyspnea, FEV₁ [24], the DOSE index which included dyspnea, FEV₁, smoking status, and exacerbation frequency [25], the HADO which included health-related quality of life, activity, dyspnea and degree of airflow obstruction [26], etc.

The most cited in literature is BODE index, which was proposed by Celli and Cote in 2004. In BODE were incorporated three variables which are better predictors of mortality than FEV₁ (BMI, dyspnea assessed by Medical Research Council scale, and exercise capacity evaluated by 6-min walking test). The BODE index was shown to be better than FEV₁ in predicting the risk of death among patients with COPD [23]. Also, the BODE index is responsive to exacerbations [27], and more importantly acts as a surrogate marker of future outcome after interventions such as lung volume reduction surgery or pulmonary rehabilitation [28]. The BODE index as adequate expression of comprehensive severity of disease was proposed for new approach in the management and treatment of COPD patients [29].

The majority of multidimensional indices were developed for clinical use, but unfortunately they all lack sufficient evidence for implementation. Impact studies are required to establish if the use of prognostic indices improves or not COPD disease management and patient outcome [30•].

COPD phenotypes

Another important step in reflection of heterogeneity of clinical presentation and progression of COPD was introduction of phenotyping. Specific definition of COPD phenotype was proposed [31••]: a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death).

Clinical COPD phenotype must have predictive value, need validation in prospective studies for each of the outcomes to which they may relate, and must be able to classify patients into distinct subgroups that allow physicians to better determine the most appropriate therapy to improve clinically meaningful outcomes [31••].

Phenotypic characterization of COPD subjects may rely on clinical and physiological manifestations, imaging, assessment of patient-related outcomes (health related quality of life), COPD comorbidities, COPD exacerbations, and systemic inflammation [32].

In recent years, it has been proposed that cluster analysis can be applied for examining COPD phenotypic heterogeneity. In multiple studies it was demonstrated that COPD patients with similar airflow limitation had very different clinical characteristics, including symptoms, comorbidities, and predicted mortality [33].

In recent studies [34, 35] it was shown that roflumilast improved lung function and reduced the frequency of exacerbations in patients with specific clinical COPD phenotype (bronchitic symptoms and severe airflow limitation). This is the first proven personalized treatment based on phenotypic characteristics of COPD [35]. It suggests that multiple phenotypic subgroups of patients exist within the broad range of COPD, and that specific therapies might improve disease management.

Thus, the exact clinical, functional, imaging, and molecular characterization of clinical COPD phenotypes presents great clinical value because it would allow its early identification, with eventual using of more targeted therapy and as a result improved management of COPD patients.

Scale-free networks in COPD

The key components of the pathology of COPD are well studied (oxidant-mediated tissue damage, especially the oxidative damage of the cell DNA [36•, 37], protease/antiprotease imbalance, and leucocyte-driven inflammation). It is immediately apparent that these three central processes are intrinsically linked [38]. For describing of network of innate and adaptive immunity and inflammation, which coexist in continual dialogue and as self-modifying systems, the term

contiguous immunity was proposed [39]. To better define COPD, Sabroe and colleagues suggest that we should think in terms of complex systems with a scale-free topology.

Consideration of COPD as a chronic network of inflammatory processes may allow new approaches to its modeling in vitro and potential development of new drugs.

Diseasome

Diseasome is combined set of all known disorder/disease gene associations that results from linking the Human Disease Network (a scale-free network whose nodes are connected if there is at least one gene that has been implicated in both) and the Disease Gene Network (a scale-free network whose nodes are connected if they are involved in the same disease) [40, 41••].

This absolutely new concept of a “diseasome” may link cellular networks and phenotypic manifestations of the disease and this concept may be applied with success in COPD.

P4 medicine

The P4 medicine is a proposed new form of medical practice that combines Personalized, Predictive, Preventive, and Participatory elements [41••]. The P4 medicine is a medicine of the future and will be very useful in the management of COPD patients.

What does P4 medicine mean for COPD? It will be “personalized” because it will be based on the genome of each person; it will be “predictive” because this personalized information will be able to determine the risk for COPD in each individual; it will be “preventive” because, given the prediction of risk of COPD, prophylactic measures will be able to be taken to decrease risk; and it will be “participative” because many of these prophylactic interventions will require the participation of the COPD patient [41••].

New COPD classification: the A, B, C, D system

In the GOLD 2011 report [3••], the scientific committee suggested new combined approach with assessment of symptoms, airflow limitation severity, health-related quality of life, and risk of exacerbations.

Functional domain: it is well known that dyspnea is a cardinal symptom of COPD. For assessment of dyspnea, new GOLD proposes to use the five-point Medical Research Council (MRC) scale developed by Fletcher and colleagues. The MRC dyspnea scale is a set of five statements about dyspnea. The subject is asked to select the statement that most closely applies.

The MRC dyspnea scale considers a single dimension and has proven to be an excellent discriminative instrument for categorizing patients according to the severity of their breathlessness [42]. Also, it has been shown that the MRC dyspnea scale can predict survival in patients with COPD [43].

Physiologic domain: spirometry is the most reproducible, discriminatory, and objective measurement of airflow limitation available [3•, 44]. The FEV1 remains essential for the diagnosis and quantification of the respiratory impairment resulting from COPD [1, 2, 3•]. In addition, the rate of decline in FEV1 is a good marker of disease progression and mortality.

Exacerbation domain: an 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 [3•]. Acute exacerbations can be measured in many ways: time to first exacerbation, number of exacerbations, number of unscheduled and emergency department visits for COPD, number of hospitalizations for COPD, and number of intensive care unit admissions for COPD [45]. Due to seasonal variation, an evaluation of exacerbation frequency requires a period of ≥ 1 year [46]. The rate of exacerbations varies greatly between COPD patients [47]. The best predictor of having frequent exacerbations is a history of previous treated events [48]. In addition, it has been proven that worsening airflow limitation is linked with an increasing prevalence of exacerbations, risk of hospitalizations, and risk of death [48–50].

Health status domain: health status measurement provides a standardized method of assessing the impact of disease on patients' daily lives, activity, and well-being [51]. The COPD Assessment Test (CAT) is a short, simple patient-completed questionnaire for COPD with very good measurement properties [52]. CAT covers a broad range of effects of COPD on patients' health, despite the small number of component items [52]. The CAT is an easy-to-use questionnaire that distinguishes between patients of different degrees of COPD severity and appears to behave the same way across countries [53].

New approach for COPD finally becomes more complex, but simultaneously can be used easily by respiratory doctors at the global level. This new approach potentially will facilitate a more accurate risk stratification of COPD patients and a better understanding of disease pathophysiology, and eventually develop more targeted therapy and improved management of patients with COPD.

Following the development of the current GOLD classification, the next step for COPD researchers must be performing of the impact studies. These studies should establish both the applicability and the impact on healthcare of implementation of this new approach in daily clinical practice.

Complex assessment of COPD

As we mentioned earlier, there is a new complex approach with assessment of four domains: functional (symptoms), physiologic (airflow limitation severity), health status (health related quality of life), and exacerbation (risk of exacerbations), which comes to facilitate deeper understanding of the impact of COPD on an individual patient. New A, B, C, D system is more comprehensive than the old GOLD classification.

In everyday practice this approach can be applied very easily. There are two simple steps in complex COPD evaluation: assessment of symptoms and risk evaluation. For assessing of symptoms MRC scale or CAT test can be used: LOW level of symptoms is indicated by MRC grade ≤ 1 or a CAT score < 10 points, HIGH level of symptoms can be characterized by MRC grade ≥ 2 or a CAT score ≥ 10 points [3•]. For the next step of risk evaluation two methods can be applied.

Spirometric assessment of the grade of airflow limitation: LOW risk will have patients with GOLD 1 and 2 stage and HIGH risk will have patients with GOLD 3 and 4 stage.

Another option that can be used is assessment of the history of COPD exacerbations in the preceding year: 0 or 1 exacerbation indicates LOW risk, while ≥ 2 exacerbations indicates HIGH risk. In case of different level of risk by these two systems, the risk should be determined by the method indicating highest risk [3•].

For example, we have a patient with an MRC score of 2 points and CAT test score of 9 points, FEV1 of 55 % predicted and a history of 2 exacerbations per year. Assessment of symptoms by MRC and CAT score demonstrates that patient has LOW level of symptoms.

Assessment of risk by spirometry shows LOW risk because patient is GOLD 2 (moderate severity of obstruction), but patient had 2 COPD exacerbations per year this indicates HIGH risk. In this situation risk must be determined by the method indicating highest risk, thus our patient will be included in group C.

COPD exacerbations assessment

Exacerbations of COPD are the most important adverse events in the progression of COPD. It is a common cause of mortality, hospital admission, increased healthcare costs, diminished lung function and worsening of health-related quality of life in COPD patients. The assessment of COPD exacerbations remains a provocation for physicians at the global level, because little systemic research has been done. The most popular stage system for COPD exacerbations is clinical staging based exclusively on clinical symptoms: increase in sputum volume, increase in sputum purulence, and increase of

dyspnea [54]. Aaron et al. recently described two distinct patterns of exacerbation onset: sudden and gradual [55]. Sudden onset COPD exacerbation is associated with increased respiratory symptoms but shorter recovery times; it can be useful for better clinical management of COPD exacerbations.

Unfortunately, there are currently no known biomarkers of COPD exacerbations with wide acceptance [56], but some biomarkers can provide clinically relevant information (C-reactive protein for the detection of a COPD exacerbation and procalcitonin for antibiotic guidance).

Recently Hurst et al. demonstrated that the major determinant of frequent exacerbations in all stages of COPD severity may be a history of COPD exacerbations [48]. COPD frequent exacerbator represents distinct phenotype in moderate and severe stage of COPD and the incidence of frequent exacerbations increases with increasing of severity of obstruction, that is can be easily used for targeting of the exacerbation prevention and treatment strategies.

Conclusions

COPD is multilevel disease from clinical, cellular, and molecular point of view. This review summarized the evolution of our knowledge from the simplistic classical approach, based on degree of airflow limitation to the new GOLD assessment, which combines the functional, physiologic, exacerbation, and health status domains. New GOLD classification will facilitate understanding of the impact of COPD on an individual patient.

In anticipation of progressive changes in our knowledge about complexity of COPD new tools were reviewed (phenotypes, scale-free networks, diseaseome) which will help the medical community to develop and apply the new concept of participatory medicine (P4) in the management of COPD.

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- Of importance
- Of major importance

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