Medical Hypotheses 91 (2016) 20–23

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Asthma-COPD Overlap Syndrome (ACOS): Single disease entity or not? Could exhaled nitric oxide be a useful biomarker for the differentiation of ACOS, asthma and COPD?

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ARTICLE INFO

Article history:
Received 3 March 2016
Accepted 7 April 2016

Keywords:
Asthma
Chronic obstructive pulmonary disease
Asthma-COPD overlap syndrome
Fractional exhaled nitric oxide

ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) represent two major public health problems. However, there is a significant proportion of patients with a mixed asthma-COPD phenotype. This condition is defined as asthma-COPD overlap syndrome (ACOS). Since there are no internationally accepted criteria for the diagnosis of that syndrome, its management remains difficult. Given the fact that patients with ACOS have an increased risk of exacerbation and hospitalization, there is a pressing need for a more targeted approach and better management. We propose that fractional exhaled nitric oxide (FeNO), a marker of eosinophilic inflammation, could help clinicians differentiate ACOS from asthma and COPD. We evaluate this hypothesis, using data derived from the existing literature.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) represent two different disease entities, which share some common features. Asthma is a chronic inflammatory disease of the airways, typically presenting in childhood and is characterized by bronchial hyperresponsiveness, bouts of breathlessness, cough and wheezing. Symptoms vary over time and airflow limitation is reversible [1]. COPD is also an inflammatory disease, particularly affecting small airways, characterized by persistent airflow limitation that is usually progressive. COPD is subdivided into two diseases: emphysema and chronic bronchitis [2]. However, a significant proportion of patients present with clinical features of both asthma and COPD [2]. This condition is called asthma-COPD overlap syndrome (ACOS), its prevalence is approximately 20% in patients with COPD and is characterized by increased rates of exacerbations [3].

The debate over that syndrome has started since 1961, when Orie and his colleagues at the University of Groningen, Netherlands, proposed that asthma and COPD might be different expressions of one disease entity, as they frequently found difficulties in the differentiation between asthma and COPD [4]. This theory was later revised and named " the Dutch Hypothesis" by Fletcher and his colleagues [4]. More specifically, this theory suggests that there is one disease-entity named "chronic non-specific lung disease" and the clinical phenotype depends on genetic and environmental factors, as well as, on the presence of complications and the adequacy of treatment [4]. Therefore, one patient could present with symptoms of bronchitis in youth, with a more asthmatic profile as an adult and finally with the phenotype of COPD [4]. Nowadays, even though data describing the overlap between asthma and COPD have been widely promulgated, GINA and GOLD have not given a specific definition of that syndrome, stating the need for more evidence on "clinical phenotypes and underlying mechanisms". Therefore, the diagnosis of ACOS is based on questionnaires and doctor's personal opinion [2].

Based on the above data, it is more than evident that there is a pressing need for a biomarker that differentiates ACOS from asthma and COPD. Fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic inflammation and is measured via a fast, non-invasive and easy way [5]. It is mainly used in patients with asthma, as spirometry cannot directly measure the level of inflammation [5]. In this article, we investigate the presence of ACOS and examine a new perspective concerning the potential role of FeNO as a biomarker of the syndrome.

2. Hypothesis

Despite an exponential increase of our knowledge, the field remains puzzling. In an attempt to elucidate this issue, we opted to investigate whether ACOS should be considered as a separate disease entity or not and we hypothesized that FeNO could repre-

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http://dx.doi.org/10.1016/j.mehy.2016.04.008
0306-9877/

sent an important tool for the diagnosis of the syndrome. The association of elevated FeNO values with eosinophilic inflammation could help us discriminate patients with COPD characterized by predominant neutrophilic inflammation from patients with COPD characterized by co-presence of eosinophilic inflammation and therefore define ACOS. Patients with COPD that have increased FeNO levels during exacerbation or during everyday life might be patients with ACOS, as the majority of patients with COPD do not have increased FeNO. The confirmation of that hypothesis would be extremely beneficial for that specific category of patients. It would contribute to the proper use of corticosteroids and would reduce exacerbations and hospitalizations. Furthermore, given the fact that ACOS is a common condition, the confirmation of that hypothesis would be beneficial not only for the patients, but also for the financial management of the syndrome in the era of austerity.

3. Evaluation of the hypothesis

3.1. The background

We extracted data from the literature concerning the presence of ACOS and the role of exhaled nitric oxide as a potential biomarker in order to evaluate our hypothesis. Data presented are the essential background for the support of our hypothesis.

3.2. Asthma-COPD overlap syndrome (ACOS)

The diagnostic label "Asthma-COPD overlap syndrome" has been applied to define the condition in which a patient shares clinical characteristics of both asthma and COPD [3]. Although they are two different disease entities, the clinical presentation of asthma and COPD may converge and mimic each other, especially in elderly patients [2].

Therefore, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) presented a joint project. They recommended that clinicians should compare the number of features that are in favor of each diagnosis and if there are three or more features of either asthma or COPD, the patient is likely to have that disease. The main features are: age at onset, pattern and time course of respiratory symptoms, past history or family history, type of airflow limitation, lung function between symptoms, chest X-ray pattern and type of airway inflammation. In case there is a similar number of features for asthma and COPD, the diagnosis of ACOS should be considered. However, this is not a definition, as GINA and GOLD have stated the need for more evidence on "clinical phenotypes and underlying mechanisms" [6]. The only definition available originates from a Spanish Consensus of experts in the field that defined ACOS in patients with COPD. According to that, there are three major criteria ((1) very positive bronchodilator test defined as an increase in FEV1 > 15% and >400 mL (2) eosinophilia in sputum (3) personal history of asthma) and 3 minor criteria ((1) high levels of total IgE (2) personal history of atopy (3) positive bronchodilator test on at least two occasions defined as an increase of FEV1 > 12% and >200 mL). Two major criteria or one major and two minor criteria are needed for the diagnosis of ACOS [7].

Due to the fact that the need for a specific, established and internationally acceptable definition is still unmet, the reported prevalence of ACOS in patients with obstructive airway disease ranges between 15% and 45% [2]. However, the majority of recent studies agree that approximately one out of five patients with obstructive airway disease have ACOS [3,8].

Recently many fruitful studies, which compare features of patients with ACOS and COPD, have been conducted. Patients with ACOS are younger than patients with COPD, older than patients with asthma, have higher Body Mass Index (BMI) and maybe fewer pack-years [9–13]. Studies yielded controversial results concerning the pulmonary function tests (PFTs). There are both studies that reported worse PFTs for patients with ACOS [14,15] and studies that reported the opposite [9,16]. However, all studies did not report a significant difference. Studies which measured 6 Minute Walk Distance did not also find any significant difference between the two groups [10,11]. Regarding CT findings, lower Emphysema Index and emphysema more predominant to the upper zone was attributed to patients with ACOS, while the variation in Air Trapping and expiratory Mean Lung Density after bronchodilation was greater in subjects with ACOS than in subjects with COPD [17]. Furthermore, three studies, which used Airway Questionnaire 20 (AQ20) and St. George's Respiratory Questionnaire (SGRQ), mentioned the worse health-related quality of life of subjects with ACOS compared to subjects with COPD [9–11]. In line with this notion, ACOS was attributed to higher rates of exacerbations, hospitalizations and visits to the emergency department [10,13,14]. Finally, it is extremely important to admit that the cost for medications for patients with ACOS was reported much higher than the cost for patients with COPD [13]. Collectively, there is abundant evidence showing that ACOS is a different phenotype that should be managed with a different approach. The role of a biomarker would be invaluable in this direction.

3.3. Fractional exhaled nitric oxide (FeNO)

Asthma: Chronic airway inflammation is a hallmark of asthma. However, the management of the disease is based on spirometry and symptoms [1]. As spirometry represents a flow-marker, there was a pressing need for an inflammometer [18]. Fractional exhaled nitric oxide is a marker of eosinophilic inflammation and is measured via a fast and easy method [19]. Therefore, it is a relatively newly established tool for the management of asthma in combination with spirometry [18]. It is extremely useful for the measurement of corticosteroid responsiveness [18]. Furthermore, the available separate measurement of bronchial (J_{NO}) and alveolar (C_{alv}) nitric oxide enables the clinician to detect more detailed information. More specifically, although bronchial (J_{NO}) is closely correlated with FeNO50, alveolar (C_{alv}) is a marker of distal airway inflammation and its elevated values are associated with more severe disease [18]. All these prove the established and pivotal role of FeNO for the management of patients with asthma.

COPD: Chronic inflammation of the airways is also a main feature of COPD [20]. However, due to the fact that neutrophilic inflammation is predominant, FeNO values do not differ significantly between patients with COPD and healthy volunteers and FeNO measurement is less robustly associated with the management of the disease [20]. FeNO values are increased only in a subgroup of patients with COPD [20]. Another factor that limits the role of FeNO in COPD is the smoking history of the patients, as there is compelling evidence that smoking reduces FeNO values [19]. Endothelial NO synthetase is reduced owing to the alveolar wall destruction caused from emphysema, especially in severe disease [21]. FeNO values are reported lower in more severe disease [22]. Based on the above data, FeNO might be useful for the management of a specific subgroup of patients with COPD, if used appropriately, in order to avoid erroneous interpretations.

Asthma-COPD overlap syndrome (ACOS): Studies reporting the role of FeNO in the management of that syndrome are still limited. However, during the last few years there is progress in the field. Recently, Donohue et al. reported that FeNO values were elevated in a specific category of patients with COPD, those with mixed asthma/COPD airway obstruction [20]. FeNO values were not linearly associated with GOLD classification [20]. Most recently, Tamada et al. tried to estimate ACOS prevalence via FeNO measure-