Airflow obstruction: is it asthma or is it COPD?

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Abstract: Despite the availability of guideline recommendations, diagnostic confusion between COPD and asthma appears common, and often it is very difficult to decide whether the obstruction is caused by asthma or COPD in a patient with airway obstruction. However, there are well-defined features that help in differentiating asthma from COPD in the presence of fixed airflow obstruction. Nonetheless, the presentations of asthma and COPD can converge and mimic each other, making it difficult to give these patients a diagnosis of either condition. The association of asthma and COPD in the same patient has been designated mixed asthma–COPD phenotype or overlap syndrome. However, since the absence of a clear definition and the inclusion of patients with different characteristics under this umbrella term, it may not facilitate treatment decisions, especially in the absence of clinical trials addressing this heterogeneous population. We are realizing that neither asthma nor COPD are single diseases, but rather syndromes consisting of several endotypes and phenotypes, consequently comprising a spectrum of diseases that must be recognized and adequately treated with targeted therapy. Therefore, we must treat patients by personalizing therapy on the basis of those treatable traits present in each subject.

Keywords: airway obstruction, asthma, ACOS, chronic obstructive pulmonary disease

Introduction

For many years, there has been controversy between the “Dutch hypothesis” proposing that asthma and COPD are manifestations of the same basic disease and the “British hypothesis” that conversely suggests that both diseases are distinct entities generated by different mechanisms. Undoubtedly, asthma and COPD can differ in their extremes. Specifically, an atopic individual who wheezes, is a never-smoker or ex-smoker with less than 10-pack-year exposure, with significant bronchodilator reversibility at the time of clinical evaluation, and an average age around 35 years can be considered a pure asthmatic patient, whereas a current or ex-smoker with fixed airway obstruction, generally with an age greater than 55 years is the pure COPD subject. These findings give strength to the fundamental concept that COPD is not asthma and asthma is not COPD. Actually, these two illnesses have different etiology, symptoms, type of airway inflammation, inflammatory cells, mediators, consequences of inflammation, response to therapy, and course.

Nevertheless, despite the availability of guideline recommendations, diagnostic confusion between COPD and asthma appears common, and often it is very difficult in a patient with airway obstruction to decide whether the obstruction is caused by asthma or COPD.

How to differentiate asthma from COPD

Examining the two fundamental studies of Fabbri et al and Contoli et al, we have described features that are useful to differentiate asthma from COPD in the presence of...
Patterns of airway inflammation
The patterns of airway inflammation in asthma and COPD are markedly different. Asthma is characterized by mast-cell activation and infiltration of eosinophils, driven by activation of T-helper type 2 (T_{h2}) cells and type 2 innate lymphoid cells. In COPD, there is infiltration of neutrophils and macrophages driven by T_{h1}, T_{h17}, and CD8^+ T cells, and typically no mast-cell activation, which accounts for the lack of reversibility. Nevertheless, eosinophil might play an important role in 10%–40% of patients with COPD. Furthermore, patients with severe asthma may have prominent neutrophilia in biopsy specimens, although these patients are steroid-dependent and demonstrate more severe disease when compared to patients in whom bronchoalveolar lavage eosinophilia is evident.

There is no doubt that evaluation of bronchial biopsy specimens adds value to help differentiate asthma from COPD, but bronchial biopsy specimens are not a routine approach in everyday practice, and their use is limited. In any case, peripheral blood eosinophil count is a surrogate marker for airway eosinophilia in stable COPD, with a reasonable degree of accuracy.

Pulmonary function
The distinction between asthma and COPD based simply on spirometric parameters is difficult; therefore, there is a need for more discriminatory tests, such as lung volumes and DL_{CO} measurements in terms of lung function. Postma et al reviewed the literature and concluded that the most peripherally located small-airway disease contributes to COPD, and the more proximally located contributes to asthma. This is the likely explanation of the fact that COPD is typically associated with more severe increases in resting lung volume that are greatest during exertion, whereas asthma is conventionally thought to be associated with resting hyperinflation only during attacks. It is well known that FEV₁ does not fully capture patients’ severity or function. Furthermore, generally, lung volumes do not allow distinction of whether their increases are caused by COPD versus asthma, mainly when the illnesses have progressed to moderate or severe airflow obstruction. However, there is agreement on the variability in residual volume (RV)/total lung capacity (TLC), particularly around the lower limit of normal for FEV₁. Although RV or RV/TLC may not help make a diagnosis as to whether the patient has asthma or COPD, to know how much “hyperinflation” is present is rather important if reducing it is a therapeutic goal.

Although DL_{CO} is considered a distinguishing factor between COPD and asthma, because in COPD patients it is typically decreased due to the loss of alveolar–capillary surface area that is associated with emphysema, there is some evidence that it has a poor predictive value. A DL_{CO} of 80% is merely 77% sensitive and 71% specific in discriminating COPD from asthma. When lung mechanics are normal (normal spirometry and lung volumes), “isolated” reduction in DL_{CO} does suggest emphysema, but normal DL_{CO} does not rule it out. In any case, the combination of FEV₁, TLC, and DL_{CO} correlates better with severity of emphysema.

Airway hyperresponsiveness and bronchial reversibility
High degree of airway hyperresponsiveness in response to such stimuli as methacholine is usually associated with asthma, and remains a useful measure in distinguishing asthma from COPD. In COPD, airway hyperresponsiveness is typically limited to direct stimuli, such as histamine, suggesting that the airway response in this illness is largely determined by airway caliber, rather than an inflammatory bronchoconstriction. However, we have known for a long time that the presence of airway hyperresponsiveness, which is influenced by baseline lung function, is more common in smokers, with an association that becomes stronger with increasing age.

In any case, using reversibility as a key diagnostic criterion to distinguish between asthma and COPD is neither specific nor sensitive, also because in COPD the administration of high doses of bronchodilators has been associated with an unpredictable variability in airflow obstruction. While reversible airflow obstruction is the hallmark of asthma and mainly irreversible airflow obstruction the hallmark of COPD, many patients with asthma have persistent obstruction, while many with COPD have a reversible component. A 15% improvement in FEV₁, used as the threshold to distinguish between asthma and COPD affords only 44% sensitivity for detecting asthma, and a quite modest 72% specificity in distinguishing asthma from COPD.
It has been shown that after 400 μg salbutamol inhalation, both asthmatic and COPD patients show an increase in all flow-volume curve parameters, although in asthma most patients show an increase in FEV\textsubscript{1} alone or in both forced vital capacity (FVC) and FEV\textsubscript{1} and usually mean responses are significantly greater than in COPD for all FEV\textsubscript{1} criteria,\textsuperscript{29} whereas in COPD an FVC response alone is most common.\textsuperscript{29} Rarely in COPD is an isolated FEV\textsubscript{1} increase noted. Absolute changes in FVC after bronchodilator administration are significantly greater in asthma subjects in comparison to COPD patients. The forced expiratory flow when 50% of FVC has been exhaled (FEF\textsubscript{50}) shows a significant response to salbutamol in asthma patients, but not in those with COPD.\textsuperscript{29} Pre- and postbronchodilator FEV\textsubscript{1}/FVC ratios remain almost the same in the COPD group, whereas in comparison the ratio increases significantly in the asthma group postbronchodilator.\textsuperscript{30}

**Fractional exhaled nitric oxide**

Although F\textsubscript{ENO} is one of the most sensitive and specific markers of eosinophilic inflammation,\textsuperscript{31} there is evidence that it is higher in ex-smokers with COPD than in healthy nonsmokers or current smokers with COPD,\textsuperscript{32} higher in COPD than in smokers with chronic bronchitis,\textsuperscript{33} and higher in COPD patients with reversible airflow limitation than in those with no reversibility.\textsuperscript{34} Nevertheless, F\textsubscript{ENO} is highest in asthma and lowest in COPD.\textsuperscript{35} Intriguingly, it has been reported that there are patients with asthma-like airway inflammation, as represented by the high F\textsubscript{ENO} values among COPD patients with a prevalence rate of 16% when 35 ppb is used as the cutoff value of F\textsubscript{ENO}.\textsuperscript{36} It was shown that a baseline F\textsubscript{ENO} level >35 ppb yielded 80% sensitivity and 66.7% specificity for identifying subjects with significant improvement in FEV\textsubscript{1} (greater than 200 mL).\textsuperscript{37} In cigarette smokers, a low F\textsubscript{ENO} level also argues against asthmatic/eosinophilic inflammation.\textsuperscript{38}

**High-resolution computed tomography findings**

COPD patients have more prominent HRCT findings, such as parenchymal abnormalities, compared with asthmatics, whereas walls are thicker in asthmatics than in patients with COPD.\textsuperscript{39,40} In the asthmatics, abnormal HRCT findings are more prominent, with increased severity.\textsuperscript{41} Actually, it seems that airway-wall thickness and lumen diameter are related to disease severity, decreased FEV\textsubscript{1} values, and duration of asthma.\textsuperscript{39,41} There is no such relationship in COPD patients.\textsuperscript{39} The pattern of radiographic change from whole-lung HRCT differs between neutrophilic asthma and COPD.\textsuperscript{40} In fact, neutrophilic asthma is a dominant airway (and not parenchymal) disease, where there is an intense neutrophilic bronchitis and probably bronchiolitis. This indicates that although the neutrophilic inflammatory pattern may be similar in these airway conditions, neutrophilic asthma is a distinct inflammatory subtype of asthma with a different pathogenesis to COPD.\textsuperscript{42}

**Comorbidities**

COPD and asthma are disorders associated with many comorbidities, albeit asthma to a lesser extent than COPD.\textsuperscript{43} Compared to those patients that do not suffer from COPD, COPD patients are at increased risk for cardiovascular events (ischemic heart disease, cardiac arrhythmia, heart failure, and other forms of heart disease), nonpsychotic mental disorders, including depression, diabetes mellitus, osteoporosis, with a higher impact of COPD on women aged <75 years, and malignant pulmonary neoplasms.\textsuperscript{44} Asthma appears to be weakly associated with cardiovascular and hypertensive diseases, depression, diabetes mellitus, dyslipidemia, osteoporosis, and rhinosinusitis.\textsuperscript{45} In contrast, it is strongly associated with gastroesophageal reflux disease and particularly allergic rhinitis. A specific study focused on the prevalence of cardiovascular diseases in asthma and COPD\textsuperscript{46} has confirmed that the diagnosis of COPD is significantly associated with an increased likelihood of diagnosis of cardiovascular and hypertensive diseases, whereas although cardiovascular and hypertensive diseases are more prevalent in patients with a diagnosis of asthma than in the general population, apparently asthma has a weak association with these diseases.

**Mixed asthma–COPD phenotype or overlap syndrome**

The description of the possible differences between asthma and COPD proves why often it is very difficult to determine whether a patient is suffering from asthma or COPD, and this happens also and mainly because “pure” forms of asthma and COPD may represent the extremes of the same disease.\textsuperscript{47} Actually, there is a large group of asthmatic patients, commonly smokers with severe asthma, who have fixed airway obstruction, primarily as a result of airway remodeling in addition to a neutrophilic pattern, and in this manner resemble those with COPD, and on the other side many COPD patients with good reversibility of airway obstruction and increased eosinophil counts, and consequently they can be confused with asthmatic patients.\textsuperscript{48} Furthermore, it is widely recognized that there are patients, especially those who are elderly, who
present with features of both illnesses. The presentations of asthma and COPD can converge and mimic each other, making it difficult to give these patients a diagnosis of either condition.\(^4\) The association of asthma and COPD in the same patient has been designated mixed phenotype asthma–COPD or asthma–COPD overlap syndrome (ACOS).

In recent years, there has been enormous interest in describing ACOS. The interest was so great that the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) jointly decided to publish a separate report on ACOS defined as a clinical condition characterized by persistent airflow limitation with several features usually associated with asthma and other features typically associated with COPD.\(^49\) However, they also highlighted that a specific definition for ACOS is still impossible, because evidence about its clinical phenotypes and underlying mechanisms is still too scarce.

The lack of a precise definition of ACOS makes it difficult to categorize the contrasting distinctive features of this syndrome. Consequently, we cast doubts about the existence of ACOS, mainly because it does not identify a clearly independent disease entity.\(^6\) However, there are many physicians and also researchers who claim the existence of ACOS as a specific syndrome.

For example, it was reported that compared to “pure” COPD patients, patients with ACOS exhibit lower cumulative smoking, suffer more from obesity and atopic diseases, and use more asthma treatments.\(^50\) Disease severity (dyspnea, quality of life, exacerbations, comorbidities) and prognosis (mortality) are not different from “pure” COPD patients. In our opinion, it seems more appropriate to define these patients as chronic asthmatics who smoke or have smoked, also considering the presence of atopy. On the contrary, the presence of obesity is not a qualifying factor. We conducted a large population-based cross-sectional epidemiologic study to explore the association between body mass index (BMI) and COPD or asthma among nonsmokers, smokers, and ex-smokers.\(^51\) The increase in BMI was frequently associated with the diagnosis of COPD or asthma, suggesting that the probability of suffering from COPD or asthma increases with increased body weight regardless of smoking status or illness.

Kitaguchi et al\(^52\) observed significant differences in several parameters of pulmonary function tests between a COPD group and an asthma with airflow limitation group and between an ACOS group and an asthma with airflow limitation group. The fundamental question in accepting these findings is that the authors categorized into the ACOS group patients with COPD who had experienced asthmatic symptoms, such as episodic breathlessness, wheezing, cough, and chest tightness worsening at night or in the early morning. Nighttime and early morning symptoms among patients with COPD are very common.\(^53\) More than 75% of patients with COPD may experience nocturnal symptoms.\(^54\) Moreover, the morning has been reported as the worst time of day by COPD patients, especially among those with severe COPD.\(^55\)

A study that analyzed 10,192 subjects (COPDGene) reported that bronchodilator responsiveness and degree of emphysema could help define ACOS.\(^56\) Clinical features that were used to identify subjects with ACOS with bronchodilator response were: 1) a history of asthma or hay fever, evidence of obstructive lung disease noted on spirometry (FEV\(_1\)/FVC < 0.7) with improvement in FEV\(_1\) >200 mL and FEV\(_1\) >12% following bronchodilator administration, and <15% emphysema on HRCT; or 2) evidence of obstructive lung disease noted on spirometry with improvement in FEV\(_1\) >400 mL and FEV\(_1\) >15% following bronchodilator administration regardless of history of asthma or hay fever, and <15% emphysema on HRCT. Subjects were categorized as having COPD with emphysema if they had obstructive lung disease noted on spirometry with a postbronchodilator improvement in FEV\(_1\) <400 mL and FEV\(_1\) <15% with no history of asthma or hay fever, and >15% emphysema on HRCT. Subjects with ACOS were younger, African-American, current smokers, with higher BMI, less emphysema, and more small-airway disease noted on HRCT compared to those with COPD with emphysema. What we have previously described on bronchodilator-induced reversibility and HRCT findings when used for differentiating asthma from COPD questions these conclusions. Considering that many patients with asthma have persistent obstruction, while many with COPD have a reversible component,\(^27\) and there is considerable overlap in bronchodilator responsiveness in health and disease and between asthma and COPD,\(^57\) in the absence of more information on patient characteristics it is conceivable that the first criterion recognized asthmatic patients with partially reversible airway obstruction and the second one COPD patients with good reversibility, whose existence has been confirmed by the results of the ECLIPSE study.\(^58\) We must mention that CT-defined emphysema is weakly related to absolute change in FEV\(_1\) postbronchodilator.\(^58\)

In another study that aimed to identify the prevalence of comorbidities in patients with ACOS treated in primary care, allergic rhinitis, anxiety, gastroesophageal reflux disease, and osteoporosis were more frequent in ACOS than COPD.\(^59\) In contrast, chronic kidney disease and ischemic heart disease...
were less frequent. It must be mentioned that patients who had received a primary care physician-confirmed diagnosis of both asthma and COPD were identified as ACOS cases. It is well known that a previous clinical diagnosis of asthma, COPD, chronic bronchitis, or emphysema is not fully reliable, particularly in family practice, where the diagnostic process is primarily based on symptoms and signs presented by the patient.\textsuperscript{60} In a confirmatory, restrictive, but more clinically valid subpopulation analysis, the authors considered only those patients who were 1) \( \geq 40 \) years of age, 2) had physician-diagnosed COPD plus spirometry-confirmed airflow limitation (FEV\(_1\)/FVC < 0.7), 3) had a registered smoking history (current or former smoker status), and 4) were using respiratory medication (Anatomical Therapeutic Chemical code R03). Apart from the fact that (as already mentioned) all these characteristics are not peculiar to differentiate asthma from COPD, we must highlight that the identified comorbidities were the same as those that we described in a large population of patients with asthma,\textsuperscript{46} which we have already discussed herein. Therefore, it is likely that the cases of ACOS identified by van Boven et al\textsuperscript{90} were cases of chronic asthma in smokers.

**The reason why it is difficult to differentiate asthma from COPD**

In 1995, the American Thoracic Society stated:

... it may be impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema with partially reversible airflow obstruction and bronchial hyperresponsiveness.\textsuperscript{61}

The real issue is that both asthma and COPD are not single diseases, but rather syndromes consisting of several endotypes and phenotypes, which implies the possibility of a spectrum of different specific conditions that might also be relatively rare.\textsuperscript{52,63} Accordingly, the current definitions of asthma and COPD do not reflect the heterogeneity of disorders characterized by airway obstruction in the community, which may have differing pathophysiological processes, clinical features, or response to medical treatment. It is becoming increasingly obvious that these different endotypes and phenotypes must be recognized, in order to be properly treated with targeted therapy.

Interestingly, the analysis of 1,059 subjects with asthma from the US National Health and Nutrition Examination Survey 2007–2012 showed that the weighted proportion of asthma with obesity, eosinophilia, \( T_{\text{h}}{\text{2}} \)-low and \( T_{\text{h}}{\text{2}} \)-high asthma, and ACOS were 50\%, 43\%, 30\%, 16\%, and 11\%, respectively. However, the Venn diagram showed 12 overlap categories and an unclassified subgroup (6\%). A substantial overlap was observed, with patients having two (48\%), three (8\%), and four (0.6\%) phenotypes.\textsuperscript{64} Furthermore, there is suggestive but not firm evidence that there is overlap in the genetics of asthma and COPD.\textsuperscript{85}

As elegantly pointed out by Reddel,\textsuperscript{66} even ACOS cannot be understood as a single disease or a single phenotype. In fact, it includes different phenotypes, such as patients with COPD and eosinophilic inflammation, patients with asthma and severe disease or who smoke in whom there is predominantly neutrophilic inflammation, and patients with asthma who have largely irreversible airway obstruction due to structural changes.\textsuperscript{56}

As we have already highlighted in the past,\textsuperscript{9} the frequent use of the umbrella term “ACOS” is the easiest way to avoid further diagnostic investigations and apparently simplify the therapeutic approach. However, due to the absence of a clear definition and the inclusion of patients with different characteristics under this umbrella term, it may not facilitate treatment decisions, especially in the absence of clinical trials addressing this heterogenic population.\textsuperscript{67} Therefore, we strongly believe that the term “ACOS” must be abandoned, because it does not identify a clearly independent disease entity.\textsuperscript{9}

**What to do to overcome these problems in future**

Our opinion is that “asthma” and “COPD” are obsolete terms that do not fully recognize the molecular and clinical heterogeneity of these pathological conditions. This heterogeneity indicates a wide range of disease mechanisms.\textsuperscript{68} Furthermore, as elegantly highlighted by Hizawa,\textsuperscript{69} asthma and COPD are not only heterogeneous diseases but also associated with complex medical conditions; therefore, different molecular characteristics associated with different endotypes may occur in varying proportions in any given patient. For this reason, it would be useful to abandon both the Dutch and the British hypotheses in favor of the paradigm that diseases of airway obstruction are a collection of endotypes, driven by unique biological/genetic mechanisms.

Hizawa\textsuperscript{68} has also proposed that endotypes of asthma or COPD may be primarily characterized by increased susceptibility to type 2 inflammation, increased susceptibility to viral infections, bacterial colonization, or impaired lung development. This proposal could be an oversimplification, but at least it has the merit of inducing thought about asthma and COPD in a different way from the classic one.
In the meantime, we could test the four-step algorithmic approach proposed by Kostikas et al. for patients with airway obstruction but not “pure” asthma or COPD. This approach suggests identifying patients with airway disease, and then evaluating the presence of eosinophilic airway inflammation (eg, increased sputum eosinophils or FENO) or other asthma characteristics (eg, positive bronchodilator reversibility); as a step third, assessing persistent airflow obstruction (as expressed by the absence of complete reversibility after bronchodilator reversibility testing and/or treatment); and finally, evaluating exacerbation history. This type of approach could allow a more rational therapeutic approach than that used until now. It fits perfectly with the view of Agusti et al., according to which patients with airway disease must be managed based on those treatable traits present in each subject.

Disclosure
The authors report no conflicts of interest in this work.

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