FEATURES OF ASTHMA AMONG SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Astman ja keuhkoahtaumataudin esiintyminen samanaikaisesti tietyillä potilailla on noussut tutkimuksen kohteeksi vasta hiljattain. Niin sanottu “asthma COPD overlap” (ACO) on suhteellisen uusi termi eikä yhdenmukaista diagnostista kriteeristöä tai hoitosuositusta ole vielä pystytty laatimaan. On myös epäselvää, mitä ja kuinka paljon astmaan liittyviä ominaisuuksia keuhkoahtaumatautipotilallla esiintyy.

Tähän tutkimukseen otettiin mukaan 64 potilasta, joilla kaikilla oli vähintään kymmenen askivuoden tupakointihistoria, spirometriassa FEV_1/FVC keuhkoputkia laajentavan lääkkeen jälkeen alle 0,70 sekä radiologisesti todettu keuhkoemfyseema. Yhdelläkään potilaista ei ollut aiempaa astmadiagnoosia. Tämän tutkimuksen tarkoituksena oli selvittää erilaisten astmaan liittyvien piirteiden esiintyvyyttä potilailla, joilla on entuudestaan varma keuhkoahtaumatautidiagnoosi.

Uloshengityksestä mitattu typpioksidipitoisuus > 50 ppb sekä merkittävä vuorokausivaihtelu kahden viikon PEF-seurannassa esiintyivät aineistossamme 4,7 % potilaista. Veren seerumista mitattu IgE > 100 IU/l esiintyi jopa 47,4 % potilaista. Muiden mitattujen ominaisuuksien esiintyvyydet jakautuivat näiden kahden arvon välille. Aineiston potilaista 44 % sai merkittävän FEV_1-vasteen hengitettävästä β_2-agonistista. Heidän sekuntikapasiteettinsa ennen keuhkoputkia laajentavaa lääkitystä oli merkittävästi matalampi (48.9 (12.9) vs 57.4 (15.7) % pred, p=0.023) ja he saivat vasteen hengitettävästä kortikosteroidilääkityksestä useammin (37.0 vs. 6.3 %, p = 0.003) kuin potilaat, jotka eivät reagoineet merkittävästi keuhkoputkia avaavaan lääkitykseen. Veren eosinofiilisillä valkosoluilla ei ollut yhteyttä vasteeseen hengitettävälle β_2-agonistille.

Astmaan liittyviä ominaisuuksia esiintyy keuhkoahtaumatautia saiarastavilla potilailla hyvin paljon. Tästä syystä diagnostiikan ja hoitosuositusten taustalla ei tulisi kyttää yksittäisiä kriteereitä, vaan perustaa päätökset useisiin löydöksiin ja suhtautua potilaaseen ja tämän oireisiin kokonaisuutena.

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FEATURES OF ASTHMA AMONG SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Asthma-COPD overlap (ACO) is a relatively new entity without uniform diagnostic protocol. Different criteria of ACO have been presented, but it is not known how prevalent these features are and how they are related to each other among subjects with COPD.

We recruited 64 subjects with COPD (smoking history ≥ 10 pack-years, post-bronchodilator $FEV_1/FVC<0.70$, emphysema of the lung, no previous diagnosis of asthma) and studied the prevalence of different features of ACO or asthma among these subjects.

The prevalence of asthma-like features among the subjects with COPD varied between 4.7 % (FeNO > 50 ppb and significant diurnal variation in peak flow monitoring) and 47.4 % (serum IgE > 100 IU/l). Forty-four % of the subjects had significant response to β_2-agonists in FEV_1 and they had lower baseline pre-bronchodilator FEV_1 (48.9 (12.9) vs 57.4 (15.7) % pred, p=0.023) but more often significant response to inhaled fluticasone treatment (37.0 vs. 6.3 %, p = 0.003). Blood eosinophil count was not associated with response to β_2-agonists.

Different criteria of ACO, especially those concerning responsiveness to β_2-agonists, are frequently fulfilled among subjects with COPD and therefore diagnosis of ACO or asthma in these subjects should not be based on any single feature.

Keywords

Chronic obstructive pulmonary disease, asthma, asthma-COPD overlap, eosinophil, salbutamol, fluticasone, spirometry, FEV_1, FVC, FeNO, Immunoglobulin E

Conflicts of Interest

The authors declare no conflicts of interest regarding the study

Introduction

Both chronic obstructive pulmonary disease (COPD) and asthma are very common diseases among general population. Globally about 175 and 360 million people are estimated to have COPD and asthma, respectively (1). Prevalence of COPD is about 10 % among adults aged 40 years or more (2) while the prevalence of asthma is even higher in many western countries (3).

Approximately 20 % of the patients with COPD also have symptoms associated with asthma (4, 5). This asthma-COPD overlap (ACO) is a relatively new term and it is not clear whether it is a combination of the two diseases or a separate condition. A key feature of ACO is a chronic bronchial obstruction as in COPD with asthma-like features such as partial reversibility and some degree of responsiveness to inhaled corticosteroid (ICS) treatment (4, 6). Patients with ACO have poorer quality of life, higher mortality rate and greater risk of hospitalisation when compared to patients with only COPD or asthma (4-8). Due to its very heterogeneous nature, knowledge of various pharmacological interventions for treating ACO is very limited (9). Also, COPD patients with features of asthma and asthma patients with features of COPD are usually excluded from pharmacological studies further diminishing our knowledge on treatment responses in subjects with ACO.

Different criteria for diagnosing ACO have been presented but still there is no uniform consensus. The Global Initiatives for Asthma (GINA) and COPD (GOLD) have a joint project to provide guidelines for diagnosing patients with ACO (10, 11). This GINA/GOLD guideline presents ACO as a condition featuring persistent bronchial obstruction with several properties usually associated with asthma and several properties usually associated with COPD. These properties include, for example, patient's history of respiratory diseases and smoking, respiratory symptoms as well as characteristic lung function for either asthma or COPD in spirometry.

Some national guidelines on asthma or COPD have presented their own somewhat divergent criteria for ACO (12-15). Different criteria used to define ACO in clinical studies or guidelines were reviewed recently (16) showing considerable variation. A recent consensus published by Sin et al. introduces a series of major and minor criteria to identify patients with ACO from those with asthma or COPD. (17) According to the committee a diagnosis of ACO requires fulfilment of all of the three major criteria (significant persistent airway obstruction in patient aged 40 years or older, a history of smoking at least 10 pack-years or an equivalent exposure to air pollution, a history of asthma before the age of 40 or a significant response in FEV_1 to inhaled β_2-agonists) and at least one of the three minor criteria (documented history of atopy, a bronchodilator response in $FEV_1 \geq 200$ ml and 12 %, elevated blood eosinophil count).

None of the guidelines for diagnosing ACO are based on solid scientific evidence and it is not known how large proportion of subjects with COPD fulfils different individual criteria of ACO. The aim of this study was to compare among subjects with definite COPD the prevalence of different features proposed as criteria for ACO and to study how these features differ in subjects with or without responsiveness to β_2-agonists or according to blood eosinophil count.

Material and methods

Subjects

We recruited 64 patients with suspected COPD who were referred from primary care to the Department of Respiratory Diseases at Tampere University Hospital (18). The inclusion criteria were a smoking history of at least 15 pack-years, symptoms compatible with COPD, post bronchodilation $FEV_1/FVC < 0.70$ and emphysema visible on high resolution CT of lungs. Exclusion criteria were a previous diagnosis of asthma, COPD or any other chronic lung disease, and arterial oxygen tension less than 8.0 kPa. Only reliever medication with short-acting β_2–agonists was allowed during the measurements. Possible previous treatments with inhaled corticosteroids (ICS), leukotriene antagonists, long-acting bronchodilators or theophylline were withdrawn for at least 4 weeks before the first measurements. The study was approved by the Ethics Committee of Tampere University Hospital and all subjects gave their written informed consent.

Study protocol

Spirometry (Vmax 20C, SensorMedics, Yorba Linda, CA, USA) was measured and a two-week home peak expiratory flow (PEF) monitoring was conducted. Exhaled nitric oxide at flow rate of 50 ml/s (FeNO) was measured (Sievers NOA280, Boulder, Colorado) (19). Blood eosinophil count and serum level of IgE were analysed. While the subjects were lying in supine position and performing full inspiration, high resolution computed tomography (HRCT) of the lungs was scanned (Siemens Somatom Plus 4, Siemens Medical, Erlangen, Germany; a section thickness of 1 mm was used with a 10 mm inter-slice spacing at 140 kV and 206 mAs) to assess the presence of emphysema. The same measurements excluding PEF-monitoring and HRCT were repeated after 4 weeks of treatment with inhaled fluticasone propionate (Flixotide Diskus 500 µg b.i.d., GlaxoSmithKline, Ware, UK).

Statistics

All the data were analyzed using SPSS statistics version 23 (IBM, USA). Data is presented as percentages, mean (SD) or as median [inter-quartile range]. Comparisons between groups were analyzed with independent sample T-test or median test for continuous variables. Chi^2-test or Fischer's exact test were used to compare differences between groups in categorical variables.

Results

The basic characteristics of our sample of patients can be found in table 1. The subjects were mostly male and mostly active smokers with an average smoking history of 42.3 pack-years. Majority of the subjects had a GOLD stage 2 or 3 obstruction. Only 11 % of the subjects were on regular ICS treatment at enrollment and this was stopped four weeks before the measurements.

The prevalence of different features regarded as criteria for asthma or ACO in different guidelines are shown in table 2. Prevalence of asthma-like features varied between 4.7 % (FeNO > 50 ppb and significant diurnal variation in 2 weeks PEF-monitoring) and 47.4 % (serum IgE > 100 IU/l). The prevalence of reversibility to β_2-agonists varied from 15.6 to 43.8 % depending on the criterion. Approximately 10 % of the subjects had blood eosinophil count higher than 0.45 x 10^9/l.

Table 3 presents the results by dividing the subjects to those with and without significant β_2-agonist induced change in FEV_1. Those with significant partial reversibility had poorer baseline lung function and the proportion of ex-smokers was higher. As expected, those with significant reversibility in spirometry had also higher mean response to β_2-agonists during PEF monitoring, but interestingly there was no difference in spontaneous diurnal variation in PEF between the groups. The subjects with significant response to β_2-agonists were also more often responsive to inhaled fluticasone (defined as improvement in pre-bronchodilator FEV_1 at least 12 % and 200 ml).

In table 4 we divided the subjects into two groups using a 0.20 x 10^9/l cut point for blood eosinophils. Subjects with blood eosinophil over this cut-point had a higher median value of serum total IgE level (33. 0 vs 23.5 IU/l, p = 0.027) and they more often fulfilled the criterion of having IgE level higher than 100 IU/l (vs. 16 (61.5 %) vs. 9 (30 %), p = 0.023) as compared to subjects with blood eosinophil below 0.20 x 10^9/l. The same calculations were also conducted using cut points of 0.15, 0.30 and 0.40 x 10^9/l. However, there were no significant differences in any parameters between the groups using these cut points (data not shown).

Table 1. Subject characteristics of the patients with COPD.

	All subjects
N	64
post b.d. FEV1/FVC < 0.7	64 (100 %)
Smoking history ≥ 15 pack-years	64 (100 %)
Emphysema visible on HRCT	64 (100 %)
Age, years	58.3 (8.0)
Males/Females	47 (73.4 %) / 17 (26.6 %)
Regular ICS treatment before enrollment	7 (11 %)
Current/Ex-smokers	49 (76.6%) / 15 (23.4%)
Pack-years	42.3 (16.1)
Post b.d. FEV_1, L	2.1 (0.6)
Post b.d. FEV_1 ,% pred	60.8 % (15.3 %)
Percentage reversibility in FEV_1, %	14.8% (14.3)
GOLD-classes 1/2/3/4, n	5 / 46 / 12 / 1
St George Respiratory Questionnaire total score	33.5 (15.7)
Blood eosinophil count, $x10^9$/L	0.19 [0.11 – 0.28]
Serum total IgE, IU/L	95 [31 – 228]
$FENO_{0.05}$, ppb	9.9 [5.7 – 15.7]

Table 2. Proportions of subjects with COPD fulfilling different proposed criteria for ACO or asthma (n=64).

GINA / GOLD lung function criteria for ACO	post b.d. $FEV_1/FVC < 0.7$	64 (100 %)
	post b.d. FEV1 < 80 % predicted	59 (92 %)
	FEV_1 reversibility ≥ 12 % and 200 ml (n)	28 (43.8%)
	FEV_1 reversibility ≥ 12 % and 400 ml (n)	11 (17.2%)
GINA lung function criteria for asthma (if not presented already above)	FEV_1 reversibility ≥ 15 % and 400 ml (n)	10 (15.6 %)
	Average daily PEF-variability* > 10 % over 2 weeks	15 out of 61 (24.6%)
	Increase in pre b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	8 out of 44 (18.2 %)
	Increase in post b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	11 out of 41 (26.8 %)
Other criteria for ACO (if not presented already above)	Significant β_2-agonist induced reversibility in 2 weeks PEF-monitoring** (n)	28 (43.8%)
	Significant diurnal variation in 2 weeks PEF-monitoring*** (n)	3 (4.7%)
	Blood eosinophil count > 0.45 x·10^9/l	6 out of 56 (10.7 %)
	Serum total IgE level > 100 IU	27 out of 57 (47.4 %)
	$FENO_{0.05}$ > 50 ppb	3 (4.7%)

*calculated as (day's highest PEF – day's lowest PEF)/(mean of day's highest and lowest PEF) averaged over two weeks

**β_2-agonist induced improvement in PEF at least 60 l/min and 15 % on at least 3 occasions during the 2 weeks calculated as (post β_2-agonist PEF – pre β_2-agonist PEF)/(pre β_2-agonist PEF)

***diurnal variation in PEF at least 60 l/min and 20 % on at least 3 occasions during the 2 weeks calculated as (day's highest PEF – day's lowest PEF)/(mean of day's highest and lowest PEF)

Table 3. Differences in clinical features between subjects with and without significant β_2-agonist induced change in spirometry.

	β_2-agonist induced change in FEV_1 < 12 % and 200 ml	β_2-agonist induced change in FEV_1 ≥ 12 % and 200 ml	p-value
n (%)	36 (56.3 %)	28 (43.7 %)	n.a.
Males, n (%)	26 (72.2 %)	21 (75.0 %)	0.803
Regular ICS treatment before enrollment, n (%)	4 (11.1 %)	3 (10.7 %)	0.960
Age, years	57.6 (7.7)	59.3 (8.4)	0.385
BMI, kg/m^2	24.6 (4.4)	26.3 (4.5)	0.137
St George Respiratory Questionnaire total score	34.9 (16.7)	31.9 (14.5)	0.457
Pack-years	42.3 (20.1)	42.2 (9.1)	0.981
Current smokers / ex-smokers, n (%)	32 (88.9 %) / 4 (11.1 %)	17 (60.7 %) / 11 (39.3 %)	0.008
FEV_1 pre b.d., l	2.0 (0.6)	1.7 (0.6)	0.084
FEV_1 pre b.d., % predicted	57.4 (15.7)	48.9 (12.9)	0.023
FEV_1 post b.d., l	2.1 (0.7)	2.1 (0.6)	0.928
FEV_1 post b.d., % predicted	60.9 (16.5)	60.8 (13.7)	0.985
Mean β_2-agonist induced change in PEF during two weeks follow-up, %	9.5 (6.4)	13.6 (5.6)	0.009
Mean diurnal PEF-variation, %	7.7 (4.6)	8.4 (4.1)	0.504
Mean diurnal PEF-variation > 10 %	8 (24.2 %)	7 (25.0 %)	0.945
Increase in pre b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	2 (6.3 %)	10 (37.0 %)	0.003
Increase in post b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	6 (24.0 %)	6 (33.3 %)	0.501
Blood eosinophil count, $10^9/l$	0.21 [0.08 – 0.28]	0.17 [0.13 – 0.30]	0.789
Blood eosinophil count > 0.45 $x \cdot 10^9/l$	3 (10.0 %)	3 (11.5 %)	0.853
Serum total IgE level, IU/l	106 [30 – 264]	80 [29 – 174]	0.885
Serum total IgE level > 100 IU/l	16 (51.6 %)	11 (42.3 %)	0.483
$FENO_{0.05}$, ppb	9.7 [5.5 – 12.9]	11.6 [6.4 – 23.6]	0.801
$FENO_{0.05}$ > 50 ppb	0 (0 %)	3 (10.7 %)	0.079

Table 4. Clinical features in subjects divided into two groups based on blood eosinophil counts using a cut point of 0.20 x 10^9/l

	Blood eosinophils < 0.20 x 10^9/l	Blood eosinophils ≥ 0.20 x 10^9/l	p-value
N	30	26	n.a.
Females / males, n (%)	10 (33.3 %) / 20 (66.7 %)	5 (19.2 %) / 21 (80.8 %)	0.235
Regular ICS treatment before enrollment, n (%)	4 (13.3 %)	3 (11.5 %)	1.000
Age, years	60.0 (8.4)	58.0 (7.0)	0.334
BMI, kg/m^2	24.4 (4.0)	26.4 (4.9)	0.110
St George Respiratory Questionnaire total score	34.1 (13.6)	34.4 (17.2)	0.942
Pack-years	42.3 (15.4)	44.2 (17.9)	0.673
Current smokers / ex-smokers, n (%)	21 (70.0 %) / 9 (30.0 %)	22 (84.6 %) / 4 (15.4 %)	0.196
FEV_1 pre b.d., l	1.8 (0.6)	1.9 (0.6)	0.475
FEV_1 pre b.d., % predicted	54.3 (16.2)	52.0 (14.7)	0.589
FEV_1 post b.d., l	2.0 (0.7)	2.2 (0.7)	0.389
FEV_1 post b.d., % predicted	61.8 (15.9)	59.3 (15.6)	0.669
Mean β_2-agonist induced change in PEF during two weeks follow-up, %	12.7 (6.8)	10.6 (5.8)	0.226
Mean diurnal PEF-variation, %	8.1 (4.2)	8.0 (4.6)	0.946
Mean diurnal PEF-variation > 10%	6 (20.0%)	6 (23.1%)	0.709
Percentage reversibility in FEV_1, %	16.0 (15.9)	15.1 (12.8)	0.807
Increase in pre b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	5 (16.7 %)	6 (23.1 %)	0.582
Increase in post b.d. FEV_1 ≥ 12 % and 200 ml after 4 weeks of inhaled fluticasone	7 (23.3 %)	4 (15.4 %)	1.000
β_2-agonist induced change in FEV_1 ≥ 12 % and 200 ml	15 (50.0 %)	11 (42.3 %)	0.565
β_2-agonist induced change in FEV_1 ≥ 12 % and 400 ml	5 (16.7 %)	5 (19.2 %)	1.000
β_2-agonist induced change in FEV_1 ≥ 15 % and 400 ml	4 (13.3 %)	5 (19.2 %)	0.719
Serum total IgE level, IU/l	62 [15 – 123]	135 [53 – 266]	0.027
Serum total IgE level > 100 IU/l	9 (30 %)	16 (61.5 %)	0.023
$FENO_{0.05}$, ppb	9.8 [5.3 – 14.6]	10.9 [7.4 – 24.3]	0.243
$FENO_{0.05}$ > 50 ppb	0 (0 %)	3 (11.5 %)	0.094

Discussion

We found in subjects with well characterized COPD a great variation in how many subjects fulfill different criteria for ACO or asthma. Subjects with significant β_2-agonist induced reversibility in spirometry tend to have poorer pre-bronchodilator lung function and better response to inhaled corticosteroids but there were no differences between the groups in other parameters usually associated with asthma, such as blood eosinophil count, serum total IgE level, FeNO or diurnal variation of PEF. Higher blood eosinophil count was associated with higher serum total IgE level but not to other criteria of ACO.

We found that the prevalence of asthma-like features varied between 4.7 % (FeNO > 50 ppb and significant diurnal variation in 2 weeks PEF-monitoring) and 47.4 % (serum IgE > 100 IU/l) among subjects with definite COPD. Other studies have reported that depending on the criteria used as many as 6 – 27 % of subjects with COPD fulfill also criteria for ACO (20, 21). On the other hand, about 20 % of subjects with adult-onset asthma have been shown to have a significant smoking history and fixed airway obstruction compatible with ACO (22). These findings highlight similarities between subjects labeled as having asthma or COPD. Due to vague nature of these diagnostic labels and presence of many underlying endotypes, it may be that finding treatable traits and diagnosing patients accordingly would lead to better clinical outcomes and characterization than using labels like asthma, COPD and ACO (23).

Significant reversibility in FEV_1 in response to β_2-agonist is a feature commonly associated with asthma (10). However, a considerable proportion of subjects with COPD have been reported to have significant acute response to bronchodilators (24). Interestingly subjects with significant β_2-agonist induced reversibility in FEV_1 in our study had more often a positive response to ICS in pre-bronchodilator lung function. An obvious explanation would be that responsiveness to β_2-agonists would be a marker of eosinophilic steroid-sensitive inflammation and thus ICS responsiveness. However, there was no difference in blood eosinophil count between subjects with or without responsiveness to β_2-agonist. Further, change in post-bronchodilator FEV_1 after ICS treatment was not different according to responsiveness to β_2-agonists. In baseline, pre-bronchodilator lung function was lower but post-bronchodilator lung function was similar in subjects with responsiveness to β_2-agonists as compared to those without. It seems thus that responsiveness to β_2-agonists is not a reliable marker of eosinophilic inflammation or response to ICS, but merely reflects random variation in smooth muscle constriction in subjects with COPD. Those subjects who happen to have smooth muscle constriction at the time of spirometry have lower pre-bronchodilator lung function, significant response to β_2-agonist but similar post-bronchodilator lung function as compared to those subjects who happened to have less smooth muscle constriction at the moment of spirometry. This is supported by previous findings in large follow-up studies showing that at each visit roughly 25 % of subjects with COPD show significant

responsiveness to β_2-agonists but this is not a fixed characteristic but varies between individuals at each visit (25).

In some set of criteria for ACO also markers of type 2 inflammation have been included (12). In the current study, almost half of the patients fulfilled the criterion of having serum total IgE level at least 100 IU/l. However, only about 11 % of the subjects had blood eosinophil count at least 0.45 x 10^9/l and only about 5 % had FeNO at least 50 ppb. Since majority of the subjects were still active smokers and smoking is known to decrease FeNO (26, 27), it may be that FeNO is not a suitable tool to detect T2-high inflammation in these subjects. Blood eosinophil count has recently shown promise as a possible marker of responsiveness to ICS in subjects with COPD, but usually the best cut-point has been in the range of 0.15 – 0.3 x 10^9/l (28), being considerably less than the proposed criterion for ACO. This may be one of the reasons for a low proportion of subjects fulfilling the criterion of eosinophil count at least 0.45 x 10^9/l in the present study.

It is established in many studies that COPD patients with high eosinophil count or "atopic phenotype" respond better to ICS treatment than their peers with a lower eosinophil count (29-31). In our study higher blood eosinophil count correlated with higher IgE level in the blood which is logical as they are both associated with type 2 inflammation. However, in the current study there was no difference in response to ICS treatment in regards of improvement in FEV_1 between groups of high or low blood eosinophil count. This is in line with previous studies suggesting that high blood eosinophil count would best predict the ability of ICS to reduce the number of exacerbations in COPD rather than the ability of ICS to improve lung function (28). However, the small number of subjects in the present study of course diminishes statistical power to detect differences in treatment responses between the groups.

A strength of our study is the group of well characterized subjects. All the subjects had a reliable diagnosis of COPD according to a well-defined smoking history, permanent obstruction (post-bronchodilator FEV_1/FVC <0.70), radiologically evaluated emphysema and the series of lung function tests. Also, none of the patients had a previous diagnosis of asthma. An obvious weakness of the study is the relatively small number of subjects limiting statistical power.

In conclusion, some of the features associated to asthma or ACO are quite prevalent in subjects with COPD. Especially different criteria of responsiveness to β_2-agonists are frequently fulfilled and it is therefore important for clinicians to bear in mind that diagnosis of ACO or asthma in subjects with smoking history and typical findings of COPD should not be based on a single diagnostic criterium but on a more holistic view.

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