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RESEARCH ARTICLE

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Assessment of bronchodilator responsiveness to salbutamol or ipratropium using different criteria in treatment-naïve patients with asthma and COPD

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ABSTRACT

Background: The criteria for significant bronchodilator responsiveness (BDR) were published in 2005 by the European Respiratory Society/American Thoracic Society, which were revised in 2021, however, data on the agreement between these two recommendations in untreated patients with airflow limitation are missing.

Aims: We aimed to study BDR to salbutamol (SABA) or ipratropium bromide (SAMA) in patients with suspected bronchial asthma or COPD at initial clinical presentation using the 2005 and 2021 criteria and explore clinical factors associated with BDR+.

Methods: Symptomatic, treatment-naïve patients with expiratory airflow limitation ($n = 105$, 57 men, age (mean ± standard deviation): 65 ± 10 years) underwent BDR testing with 400 mcg salbutamol (day 1) or 80 mcg ipratropium bromide (day 2) and BDR was measured after 15 and 30 minutes. Clinical factors with risk for BDR+ were assessed with binomial logistic regression analysis.

Results: We found a good agreement between the number of 2005-BDR+ and 2021-BDR+ patients at 15 and 30 minutes post-salbutamol and post-ipratropium (88.6–94.8%). More patients showed BDR+ after 30 minutes than following 15 minutes using either criterion. When results at 30 minutes are considered, the number of patients with 2005-BDR+ (82%) was higher than that of 2021-BDR+ (75%), with the proportion of SAMA+ patients being higher than that of SABA+ (2005: 70% vs. 49%, Fisher exact $p < 0.01$; 2021: 64% vs. 41%, $p = 0.001$). 2005-BDR+ and 2021-BDR+ to SABA were associated with decreasing pre-BD FEV_1% predicted and the presence of cough. More patients with asthma were in the SABA+ group compared to the SAMA+ group (2005: 71% vs. 53%, Fischer exact $p = 0.04$; 2021: 77% vs. 52%, $p = 0.02$).

Conclusions: Fewer patients show BDR+ according to the 2021 criteria in comparison with the 2005 recommendations, and protocols for BDR testing may consider the assessment of response to both SABA and SAMA after 30 minutes.

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Bronchial asthma; chronic obstructive airway disease; bronchodilator; reversibility; responsiveness; cough

Introduction

Bronchodilator responsiveness (BDR) to inhaled short-acting bronchodilators is tested during the diagnostic workup and sometimes also during the follow-up of patients with obstructive airway diseases. In bronchial asthma, BDR testing is used to confirm excessive variability in lung function, and a high bronchodilator response is also a known risk factor for exacerbations [1]. In chronic obstructive pulmonary disease (COPD), the diagnosis is based on post-bronchodilator airflow limitation (i.e. $FEV_1/FVC < 0.70$), and the severity of airflow limitation should be assessed after the administration of at least one short-acting bronchodilator [2]. Patients with positive BDR can represent specific phenotypes [3,4]; however, the clinical relevance of the presence of a positive bronchodilator response in COPD is unclear [2].

Short-acting β_2-agonists (SABA) and muscarinic antagonists (SAMA) induce rapid bronchodilation and relief of airway obstruction-related symptoms (coughing, wheezing, dyspnea) by relaxing airway smooth muscle cells (ASMCs). SABAs work by stimulating ß$_2$-adrenoreceptors of the ASMCs to induce relaxation and widen the airways. The most generally used SABA is salbutamol (onset of action: within 3 min; peak activity: after 2.5 h) [5,6]. SAMAs bind to

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muscarinic receptors (M_1-M_3) on ASMCs, pre-synaptic nerve endings and parasympatic ganglia [7]. The bronchodilator effects of SAMAs are mainly mediated via the inhibition of acetylcholine effects via the ganglionic M_1 receptors and M_3 receptors on ASMCs [8]. The onset of action of ipratropium, the most widely used SAMA, is within minutes, with peak activity occurring between 1 and 2 hours [5,9]. In asthma and COPD, both SABA and SAMA are used in clinical practice during BDR testing [1,10,11] In COPD patients, a better BD response was observed when using SABA-SAMA combinations [11].

In 2005 the European Respiratory Society (ERS) and the American Thoracic Society (ATS) formulated recommendations and interpretive strategies to assess BDR [12], which were revised in 2021 [13]. The definition of a positive or significant BDR differs between the two documents i.e. the former recommendation is based on an absolute and a percentage change in FEV_1 or FVC following bronchodilation, while the post-bronchodilator percentage changes in comparison with the predicted values of FEV_1 and FVC are included in the latter version. Importantly, concerning the bronchodilator agent, the earlier document recommends the administration of SABA such as salbutamol in four separate doses of 100 mcg through a spacer, while the recent recommendations do not specify it. There are only few studies comparing the outcomes of BDR testing using the 2005 and 2021 ERS/ATS recommendations in patients with asthma and COPD, and it is not known if the results are influenced by the drug used for bronchodilation.

Thus, we aimed to study the concordance of the results of BDR testing to a SABA and a SAMA following the 2005 and 2021 definitions in a cross-over design in patients with respiratory symptoms and expiratory airflow limitation at initial evaluation by a respiratory specialist. We also explored the clinical factors which are linked with a significant BDR to either drug.

Materials and methods

Patients

Patients were recruited from Dunakeszi Pulmonology Outpatient Care Centre, Hungary, by a respiratory specialist between the 12th of November 2018 and the 4th of December 2019. The study included all patients above the age of 18 who were newly diagnosed with bronchial asthma or COPD according to guidelines [1,2]. Patients had been referred to the respiratory specialist by their general practitioners due to symptoms including dyspnea, chest tightness, cough, sputum production. Baseline spirometry confirmed expiratory airflow limitation (FEV_1/FVC <0.70), therefore variability of lung function was aimed to be confirmed by a positive bronchodilator responsiveness test [1]. Patients with an earlier diagnosis of asthma or COPD were excluded from the study. Patients did not use long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA), inhaled corticosteroid (ICS) medications, theophylline derivatives, oral corticosteroids, or any combination of these within one month prior to inclusion. Patients suffering from allergic respiratory diseases had to stop taking intranasal steroids and medications containing antihistamine drugs at least 48 hours before the examination. Other therapies could be continued. Patients were made familiar with the structure of the study and voluntarily agreed to participate, all patients signed a written informed consent. The study was approved by the ethics committee of the Health and Social Public Benefit Nonprofit Ltd. (Number: PEK 2018/PULM/01–1801).

Study design

This was a single-center, non-interventional pilot study. The study consisted of three examinations. On the first day of the study (day 1), clinical data were collected, baseline spirometry was recorded and bronchodilation reversibility testing with salbutamol was performed. One day later during the second examination (day 2), baseline spirometry and BDR testing with ipratropium bromide were carried out. The third examination took place after a 3–6-month follow-up period. After the first two examinations, the respiratory specialist made a primary diagnosis, and maintenance and reliever therapies were initiated following guidelines [1,2] LABA: $N = 4$, LAMA: $N = 21$, LABA+LAMA: $N = 4$, ICS: $N = 1$, LABA-ICS: $N = 40$, LABA-LAMA-ICS: $N = 12$. However, this therapy did not influence the outcomes of our study, as BDR testing preceded the initiation of inhaled therapy. The final diagnosis was established during the third examination [1,2], and the grouping of patients into the categories of asthma or COPD was done accordingly. The clinical diagnosis was re-assessed by a second respiratory specialist. Other clinical outcomes measured at this follow-up visit were not included in the current analysis. The study was performed in accordance with the 1964 Helsinki declaration and its later amendments. A flowchart of the study design is shown in Figure 1.

Collection of clinical data

On day 1, data on previous medical history were collected in detail alongside demographic data, body weight, height, number of exacerbations in the past year, smoking habits, and eosinophil cell count

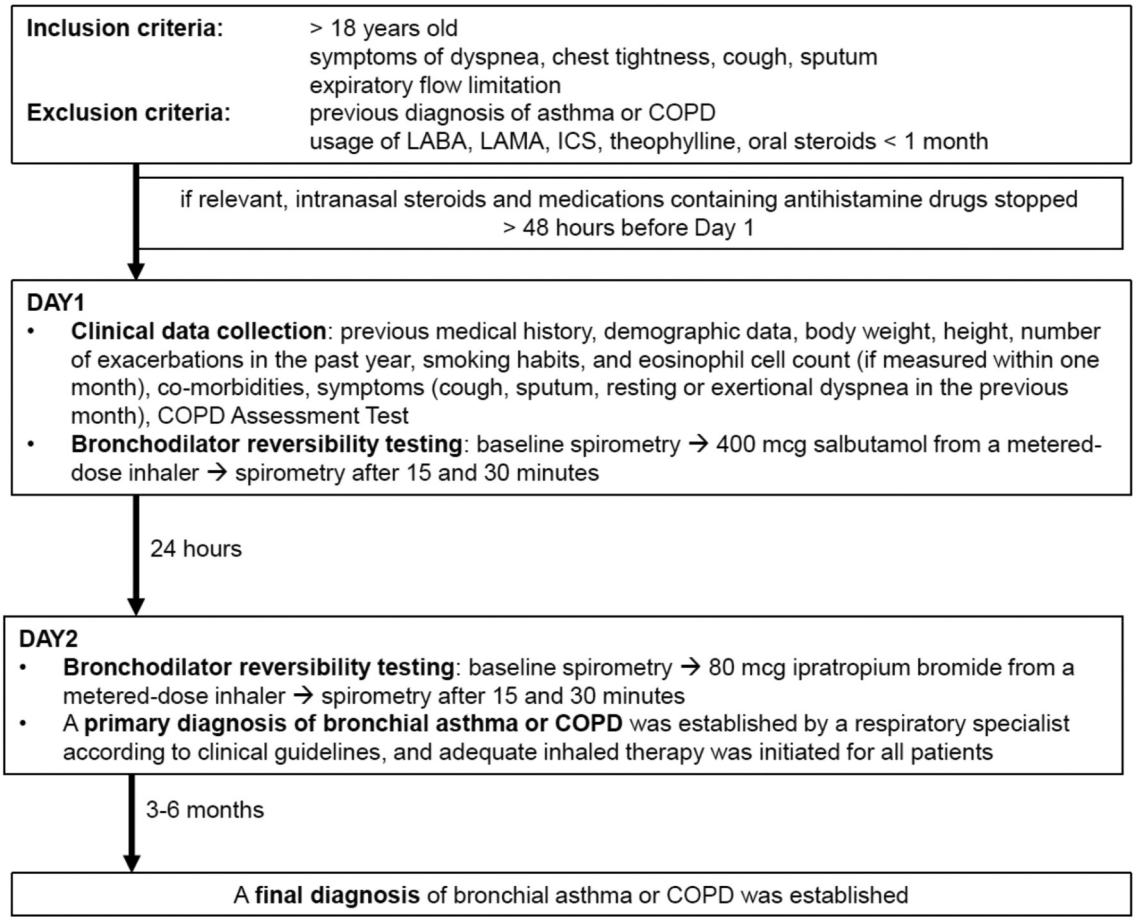

Figure 1. A flowchart of the study design.

measured on the day of the examination or within one month. Co-morbidities including nasal rhinitis, other allergic disease, ischemic heart disease, gastro-esophageal reflux disease, cardiac decompensation, acute myocardial infarction in the past, hypertension, atrial fibrillation, other arrhythmias, cerebrovascular events in the past, diabetes, benign prostate hyperplasia, glaucoma were reported by patients. Participants were asked if they experienced cough, sputum, resting or exertional dyspnea in the previous month, and subjects filled in the COPD Assessment Test (CAT) [14].

Spirometry and bronchodilator responsiveness testing

The spirometer was calibrated daily with a 3-L calibration syringe (PDD-301/sh, Piston Ltd, Budapest, Hungary). Each subject had three acceptable spirograms of FEV_1, FVC and PEF recorded before and also after BDR testing according to the ERS/ATS 2005 guideline [15], and the best result was recorded. Among the three acceptable maneuvers, the two highest FEV_1 and FVC could not differ more than 150 mL, otherwise more maneuvers were performed. BDR testing was done after administering a SABA from a metered-dose inhaler (four separate doses of 100 mcg, total dose: 400 mcg, day 1). Twenty-four hours after the examination (day 2), spirometry and BDR tests were performed with a SAMA from a metered-dose inhaler (four separate doses of 20 micrograms of ipratropium bromide, total dose: 80 mcg). Separate doses of the drugs were delivered at approximately 0.5–1.0 seconds apart. For each inhalation a spacer designed for the spirometer was used. The effects of the short-acting bronchodilators were assessed after 15 and 30 minutes on both days. The following criteria were used for a significant BDR: (1) following the 2005 ERS/ATS statement [12] an increase in FEV_1 and/or FVC ≥ 12% of control and ≥200 mL; (2) based on the 2021 ERS/ATS technical standard document [13] >10% increase in FEV_1 and/or FVC relative to the predicted value. Predicted values were determined using the appropriate Global Lung Function Initiative spirometry equation.

Thus, based on the results of BDR testing, patients were divided into four groups: (1) SABA+, (2) SAMA+, (3) SABA+SAMA+ and (4) non-responsive: SABA-SAMA-

Statistical analysis

Continuous data are shown as mean ± standard deviation (SD) and were analyzed using paired or unpaired t-test, ANOVA with Tukey post-hoc test. Categorical data were assessed with Fisher exact or chi-square tests. Results were considered statistically significant if p-values were less than 0.05. To assess clinical factors associated with BD response, binominal logistic regression was used. All analyses were performed with the R 4.0.2 statistical program [16].

Results

Bronchodilator response to SABA and SAMA

A total of 105 patients were included in the study (Table 1). The absolute increase in FEV_1 and FVC was greater after the administration of ipratropium than after salbutamol both at 15 and 30 minutes. The relative change (either to pre-BD or predicted values) in FVC was higher at 15 and 30 minutes after the administration of ipratropium than following salbutamol inhalation, while post-SAMA FEV_1 changes were higher than the corresponding post-SABA values only after 30 minutes. Both absolute and relative changes in FEV_1 and FVC were higher after 30 minutes of SABA or SAMA administration than the values measured after 15 minutes.

Using the 2005 ERS/ATS criteria, the proportion of patients with a significant BDR to ipratropium (either in FEV_1 or FVC or both) was higher at 15 and 30 minutes after drug inhalation than the number of patients with a positive BDR to salbutamol (SAMA+ vs. SABA+: $N = 51$ vs. $N = 36$, Fisher exact $p = 0.04$; $N = 73$ vs. $N = 52$, $p < 0.01$). When the 2021 recommendations were applied, a higher rate of significant BDR to SAMA was found at 30 minutes, but not at 15 minutes post-inhalation (at 15 minutes: $N = 43$ vs. $N = 32$, $p = 0.15$; at 30 minutes: $N = 67$ vs. $N = 47$, $p < 0.01$).

Importantly, the number of SABA+ or SAMA+ patients was higher after 30 minutes than after 15 minutes of drug inhalation both using the 2005 criteria ($N = 52$ vs. $N = 35$, $p = 0.02$; $N = 73$ vs. $N = 51$, $p < 0.01$) and the 2021 recommendations ($N = 47$ vs. $N = 32$, $p = 0.02$; $N = 67$ vs. $N = 43$, $p = 0.001$). At 30 minutes post-BD, 86 (82%) and 79 (75%) patients showed a significant BDR to either salbutamol or ipratropium evaluated according to the 2005 or 2021 criteria, respectively ($p = 0.31$).

Agreement between bronchodilator responsiveness according to the 2005 and 2021 ERS/ATS criteria

15 and 30 minutes after the inhalation of salbutamol, the identification of BDR+ patients showed a good agreement between the two criteria (Table 2). The number of patients with a significant response in FEV_1, FVC and both was not different using the 2005 and 2021 recommendations (at 15 minutes: $N = 22/6/8$ vs. $N = 18/7/7$, chi square $p = 0.86$; at 30 minutes: $N = 21/9/22$ vs. $N = 17/15/15$, $p = 0.22$).

The agreement in the outcomes between the 2005 and 2021 recommendation was better at 30 minutes after ipratropium inhalation than after 15 minutes (Table 3). We found no difference in the number of patients with a significant BDR in FEV_1, FVC or both between the 2005 and 2021 criteria either at 15 minutes ($N = 11/13/27$ vs. $N = 9/14/20$, $p = 0.74$) or at 30 minutes after drug administration ($N = 16/12/45$ vs. $N = 11/16/40$, $p = 0.46$).

Table 1. Results of bronchodilation reversibility testing with SABA or SAMA ($N = 105$).

	SABA	SAMA	p-values*
pre-BD FEV_1, L	1.83 ± 0.63	1.81 ± 0.60	0.40
pre-BD FEV_1, %pred	65 ± 19	64 ± 14	0.38
pre-BD FVC, L	3.18 ± 0.94	3.14 ± 0.88	0.23
pre-BD FVC, %pred	87 ± 19	86 ± 17	0.21
pre-BD FEV_1/FVC	0.57 ± 0.09	0.58 ± 0.09	0.50
Change in FEV_1 after 15 minutes	160 ± 152 mL	204 ± 142 mL	0.02
	10.0 ± 9.6%pre-BD	11.7 ± 9.0%pre-BD	0.17
	5.6 ± 5.0%pred	7.1 ± 4.8%pred	0.04
Change in FEV_1 after 30 minutes	203 ± 214 mL$^{\#\#}$	286 ± 170 mL$^{\#\#}$	<0.001
	12.2 ± 12.6%$^{\#}$	16.4 ± 9.7%$^{\#\#}$	0.004
	7.0 ± 6.8%pred$^{\#\#}$	10.0 ± 5.4%pred$^{\#\#\#}$	<0.001
Change in FVC after 15 minutes	140 ± 278 mL	300 ± 305 mL	<0.0001
	4.9 ± 10.5%pre-BD	9.7 ± 10.3%pre-BD	<0.0001
	3.6 ± 7.1%pred	7.9 ± 7.9%pred	<0.0001
Change in FVC after 30 minutes	205 ± 309 mL$^{\#\#}$	439 ± 370 mL$^{\#\#\#}$	<0.0001
	6.9 ± 10.9%pre-BD$^{\#\#}$	14.2 ± 11.8%pre-BD$^{\#\#\#}$	<0.0001
	5.4 ± 8.0%pred$^{\#\#\#}$	11.7 ± 9.1%pred$^{\#\#\#}$	<0.0001

Data are shown as mean ± SD and were compared with paired t-tests. *SABA vs. SAMA. $^{\#}p < 0.01$, $^{\#\#}p < 0.001$, $^{\#\#\#}p < 0.0001$ vs. corresponding values at 15 minutes. Pred: predicted.

Table 2. Agreement of bronchodilator responsiveness (BDR) to salbutamol after 15 and 30 minutes according to the 2005 and 2021 ERS/ATS criteria.

		Number of patients with a significant BDR according to the 2021 criteria		
		BDR +	BDR -	Total
	BDR after 15 minutes			
Number of patients with a significant BDR according to the 2005 criteria	BDR +	30	6	36
	BDR -	2	67	69
	Total	32	73	
		Agreement: 92.4%		
	BDR after 30 minutes			
	BDR +	46	6	52
	BDR -	1	52	53
	Total	47	58	
		Agreement: 93.3%		

Table 3. Agreement of bronchodilator responsiveness to ipratropium after 15 and 30 minutes according to the 2005 and 2021 ERS/ATS criteria.

		Number of patients with a significant BDR according to the 2021 criteria		
		BDR +	BDR -	Total
	BDR after 15 minutes			
Number of patients with a significant BDR according to the 2005 criteria	BDR+	41	10	51
	BDR-	2	52	54
	Total	43	62	
		Agreement: 88.6%		
	BDR after 30 minutes			
	BDR+	67	6	73
	BDR-	0	32	32
	Total	67	38	
		Agreement: 94.8%		

Clinical factors associated with BD responsiveness after 30 minutes

Pre-bronchodilator FEV_1% predicted and the presence of cough were significant determinants of BD responsiveness to SABA according to both the 2005 and 2021 ERS/ATS criteria (Table 4). As expected, an increasing FEV_1% predicted was related to a decreased likelihood of a significant BDR, and cough conveyed a considerable risk of positive responsiveness to salbutamol. Interestingly, regarding the 2005 recommendations, we found a trend for an increased risk of significant BDR in males, and in relation to decreasing body mass index.

With regards to BDR in response to SAMA, an increased comorbidity burden was related to the decreased likelihood of a significant BDR as judged by the 2021 criteria (Table 5). No clinical factors were associated with BDR when the 2005 ERS/ATS criteria were applied.

Clinical characteristics of patients with and without significant BDR after 30 minutes

When comparing the groups formed using the 2005 and 2021 ERS/ATS criteria, the SABA+ subgroup was the smallest in both cases (Table 6). Although 7 patients were regrouped not to have significant BDR according to the 2021 recommendations, the proportions of patients in the groups were not different between the two definitions of BDR (chi square $p = 0.72$). Among the clinical factors, only baseline FEV_1/FVC showed a difference among the groups using either sets of criteria. Interestingly, the rate of multimorbidity demonstrated a trend for difference among the groups when the 2021 definitions were applied.

Clinical diagnosis in the BDR groups

Fifty-three patients were diagnosed with bronchial asthma, and COPD was established in 52 subjects (Table 6). Using either sets of criteria, among patients who showed a significant BDR, a higher proportion of patients with asthma was found in the SABA+ group compared to patients in the SAMA+ group (2005 criteria: 71% vs. 53%, Fischer exact $p = 0.04$; 2021 criteria: 77% vs. 52%, $p = 0.02$).

Discussion

Assessment of bronchodilator responsiveness and recording of post-bronchodilator spirometric values are essential during the diagnosis and follow-up of patients with asthma and COPD. Short-acting β_2-agonists and muscarinic antagonists alone or in combination can be used for this purpose. Although the 2005 ERS/ATS guideline recommends the use of salbutamol, the 2021 document does not set specific recommendations regarding the protocol for BDR testing. In our study, for the first time we showed in a cohort of patients with respiratory symptoms and expiratory airflow limitation, that testing with ipratropium and salbutamol identify different sets of patients with significant BDR using either criterion, with good agreement between the two recommendations. Cough is a main determinant of significant BDR to salbutamol, and the final clinical diagnosis is related to BDR to different drugs.

Our data confirm that most patients with symptoms related to obstructive airway diseases show responsiveness to a short-acting bronchodilator. Notably, the 2005 ERS/ATS protocol recommends the use of 400 mcg inhaled salbutamol and a post-bronchodilator

Table 4. Binominal logistic regression analysis of factors associated with a significant bronchodilator response to salbutamol after 30 minutes ($N = 105$).

	BDR according to the 2005 ERS/ATS criteria			BDR according to the 2021 ERS/ATS criteria		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.00	0.96–1.05	0.88	1.01	0.97–1.05	0.64
Sex Female	reference					
Male	2.10	0.97–4.64	0.06	1.73	0.79–3.81	0.17
Body mass index, kg/m [2]	0.93	0.85–1.01	0.08	0.95	0.87–1.04	0.27
Smoking status	reference					
Non-smoker	1.10	0.4–3.02	0.86	0.91	0.33–2.51	0.86
Current smoker	0.67	0.19–2.33	0.53	0.43	0.11–1.54	0.20
Former smoker						
Pack-years	1.00	0.99–1.02	0.88	1.00	0.98–1.02	0.93
Co-morbidities						
0–1 co-morbidity	reference					
≥ 2 co-morbidities	1.53	0.71–3.33	0.28	1.06	0.49–2.3	0.88
Pre-BD FEV_1, L	0.65	0.34–1.21	0.18	0.57	0.29–1.07	0.09
Pre-BD FEV_1, %pred	**0.97**	**0.95–0.99**	**0.01**	**0.97**	**0.95–0.99**	**0.01**
Pre-BD FVC, L	0.98	0.65–1.47	0.91	0.96	0.69–1.44	0.83
Pre-BD FVC, %pred	0.98	0.96–1	0.14	0.99	0.97–1.01	0.22
Total CAT score	1.02	0.97–1.08	0.48	1.03	0.97–1.09	0.34
Cough						
no	reference					
yes	**6.55**	**1.64–43.86**	**0.02**	**12.0**	**2.23–223.08**	**0.02**
Sputum production						
no	reference					
yes	0.97	0.43–2.18	0.94	1.44	0.64–3.32	0.38
Dyspnea on exertion						
no	reference					
yes	0.84	0.27–2.52	0.75	0.91	0.3–2.81	0.87
Dyspnea at rest						
no	reference					
yes	0.69	0.25–0.88	0.48	0.67	0.23–1.83	0.44

BDR: bronchodilator responsiveness, CAT: COPD Assessment Test, CI: confidence interval, OR: odds ratio, pre-BD: pre-bronchodilator, pred: predicted.

Table 5. Binominal logistic regression analysis of factors associated with a significant bronchodilator response to ipratropium after 30 minutes ($N = 105$).

	BDR according to the 2005 ERS/ATS criteria			BDR according to the 2021 ERS/ATS criteria		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.97	0.92–1.01	0.19	0.97	0.93–1.02	0.25
Sex Female	reference					
Male	1.54	0.67–3.57	0.31	1.31	0.59–2.93	0.51
Body mass index, kg/m [2]	1.01	0.93–1.11	0.77	0.98	0.90–1.07	0.63
Smoking status	reference					
Non-smoker	1.41	0.46–4.03	0.53	0.98	0.33–2.76	0.97
Current smoker	1.00	0.27–3.72	1.00	0.81	0.22–2.92	0.74
Former smoker						
Pack-years	1.00	0.98–1.02	0.99	1.00	0.98–1.02	0.89
Co-morbidities						
0–1 co-morbidity	reference					
≥ 2 co-morbidities	0.55	0.23–1.28	0.17	**0.42**	**0.18–0.95**	**0.04**
Pre-BD FEV_1, L	1.14	0.57–2.35	0.72	1.14	0.59–2.28	0.70
Pre-BD FEV_1, %pred	0.99	0.97–1.01	0.52	1.00	0.97–1.02	0.89
Pre-BD FVC, L	1.32	0.82–2.19	0.26	1.44	0.91–2.36	0.13
Pre-BD FVC, %pred	1.00	0.98–1.03	0.86	1.02	0.99–1.04	0.21
Total CAT score	1.02	0.96–1.08	0.62	1.01	0.95–1.07	0.86
Cough						
no	reference					
yes	2.18	0.65–7.16	0.12	1.61	0.48–5.24	0.43
Sputum production						
no	reference					
yes	1.23	0.51–2.9	0.65	1.43	0.62–3.28	0.40
Dyspnea on exertion						
no	reference					
yes	0.81	0.21–2.59	0.73	0.60	0.16–1.91	0.41
Dyspnea at rest						
no	reference					
yes	1.81	0.59–6.8	0.33	1.73	0.60–5.80	0.33

BDR: bronchodilator responsiveness, CAT: COPD Assessment Test, CI: confidence interval, OR: odds ratio, pre-BD: pre-bronchodilator, pred: predicted.

Table 6. Clinical characteristics of groups based on BDR after 30 minutes.

		BDR according to the 2005 ERS/ATS criteria					BDR according to the 2021 ERS/ATS criteria				
	Total	SABA+	SAMA+	SABA+ SAMA+	SABA-SAMA-	p-value*	SABA+	SAMA+	SABA+ SAMA+	SABA-SAMA-	p-value*
Number	105	13	34	39	19	NA	12	32	35	26	NA
Age	65 ± 10	65 ± 6	63 ± 10	65 ± 10	68 ± 10	0.38	66 ± 5	63 ± 9	65 ± 10	67 ± 11	0.44
Male/female	57/48	8/5	17/17	25/14	7/12	0.22	8/4	17/15	21/14	11/15	0.44
BMI, kg/m [2]	27.0 ± 4.7	25.2 ± 5.2	27.8 ± 5.3	26.4 ± 4.3	27.8 ± 4.2	0.29	26.6 ± 5.1	27.3 ± 5.1	26.3 ± 4.6	27.5 ± 4.4	0.73
Smoking habit, N	20	3	6	7	4	0.95	2	5	8	5	0.78
Never smoker	20	2	7	6	5		1	7	5	7	
Ex-smoker	65	8	21	26	10		9	20	22	14	
Current smoker											
Pack-years	31 ± 24	23 ± 26	31 ± 23	31 ± 23	31 ± 26	1.00	40 ± 28	34 ± 22	28 ± 23	28 ± 24	0.38
Number of co-morbidities, N	50	2	18	20	10	0.10	2	17	20	11	0.09
0–1	55	11	16	19	9		10	15	15	15	
≥2											
Total CAT score	15 ± 7	14 ± 7	14 ± 6	16 ± 7	15 ± 7	0.68	14 ± 7	14 ± 6	16 ± 7	15 ± 8	0.43
Pre-BD FEV_1, L	1.82 ± 0.60	1.77 ± 0.55	1.93 ± 0.68	1.76 ± 0.57	1.75 ± 0.57	0.64	1.73 ± 0.55	1.97 ± 0.64	1.74 ± 0.59	1.77 ± 0.60	0.39
Pre-BD FEV_1, %pred	64 ± 17	61 ± 14	68 ± 20	61 ± 17	68 ± 13	0.24	58 ± 14	69 ± 19	61 ± 18	67 ± 14	0.15
Pre-BD FVC, L	3.16 ± 0.89	3.22 ± 0.87	3.31 ± 0.89	3.19 ± 0.91	2.82 ± 0.88	0.28	3.24 ± 0.93	3.40 ± 0.83	3.18 ± 0.91	2.82 ± 0.87	0.09
Pre-BD FVC, %pred	87 ± 17	86 ± 18	90 ± 18	85 ± 18	85 ± 15	0.50	85 ± 19	92 ± 17	86 ± 17	82 ± 16	0.14
Pre-BD FEV_1/FVC	0.57 ± 0.09	0.55 ± 0.09#	0.58 ± 0.11	0.56 ± 0.08 #	0.62 ± 0.05	**0.03**	0.54 ± 0.07 ##	0.58 ± 0.10	0.55 ± 0.09 ##	0.62 ± 0.06	**0.004**
FEV_1 change after SABA, mL	204 ± 214	311 ± 126	74 ± 150	354 ± 205	54 ± 108	**<0.001**	340 ± 119	81 ± 163	362 ± 210	79 ± 109	**<0.001**
FEV_1 change after SABA, %	12.2 ± 12.6	19.1 ± 8.6	4.4 ± 9.2	21.0 ± 11.4	3.5 ± 6	**<0.001**	21.7 ± 8.8	4.2 ± 9.0	21.8 ± 11.4	4.8 ± 6.0	**<0.001**
FEV_1 change after SAMA, mL	286 ± 170	127 ± 55	354 ± 130	361 ± 162	122 ± 100	**<0.001**	131 ± 70	357 ± 133	381 ± 155	134 ± 105	**<0.001**
FEV_1 change after SAMA, %	16.4 ± 9.7	7.3 ± 4.0	20.2 ± 7.9	20.9 ± 8.7	6.5 ± 5.2	**<0.001**	7.5 ± 4.4	19.9 ± 8.1	22.6 ± 7.9	7.8 ± 5.8	**<0.001**
Clinical diagnosis, N	53	9	10	28	6	**<0.001**	9	9	27	8	**<0.001**
Bronchial asthma	52	4	24	11	13		3	23	8	18	
COPD											

Baseline spirometric data are calculated from the individual mean values of pre-SABA and pre-SAMA measurements. Data are shown as mean ± SD. Subgroups were compared with ANOVA and Tukey post-hoc tests or chi-square tests*. #p<0.05, ##p<0.01 vs. SABA-SAMA-. BD: bronchodilator, BMI: body mass index, CAT: COPD Assessment Test, NA: not applicable, pred: predicted. NA: not applicable.

measurement after 15 minutes [12], but the more recent guidelines do not provide recommendations in this regard [13]. We used high doses of bronchodilator drugs to maximize the response; however different drug dosages have been applied in large previous trials. A lower dose of SABA was used in the PLATINO study on healthy volunteers and patients with obstructive airway diseases [17] and in a cohort of adult-onset asthma [18], while the same dose of salbutamol was given to patients with COPD in the ECLIPSE study as in our investigation [19], and the same doses of salbutamol and ipratropium were given in combination to patients with COPD in the ISOLDE study [11]. Furthermore, we found that more patients show a significant BDR (either to salbutamol or ipratropium) after 30 minutes post-bronchodilation than following 15 minutes, which highlights the importance of detailed testing protocols to capture all patients with BDR and to be able to compare results of different studies.

We found that at 30 minutes post-BD less patients were classified to have a significant BDR (to either or both drugs) using the 2021 criteria than according to the 2005 guideline (82% vs. 75%, Table 6). This supports the findings of previous studies on larger patient populations [20,21] with similar degree of difference between the two sets of criteria.

This is the first study to compare the agreement between criteria of the 2005 and 2021 ERS/ATS guidelines along two post-BD timepoints and two bronchodilator drugs in untreated patients with suspected asthma or COPD. The agreement was >90% in BDR to salbutamol after 15 and 30 minutes, however in case of ipratropium a better agreement was found after 30 minutes. This is in line with the results of Chaiwong et al., who found >90% agreement between the outcomes using the two sets of criteria after 400 mcg inhalation of salbutamol and post-BD measurements after 15–30 minutes [20].

Interestingly, a higher number of patients presented a positive response to ipratropium than to salbutamol after 30 minutes. This could be explained by the increased parasympatic bronchomotor tone described in COPD [8], and the higher number of patients with COPD in the SAMA+ subgroup than among patients with SABA+. However, it can be speculated that this effect is reduced when adequate inhaled maintenance treatment with long-acting bronchodialtors is initiated as no difference in efficacy was described between the two drugs in patients treated with COPD [11].

Our findings on the association of certain clinical factors and BD responsiveness to SABA corroborate previous data. In the PLATINO study, acute BD responsiveness to inhaled SABA was related to lower pre-BD FEV_1 in subjects with reversible airway obstruction and in patients with COPD who were mainly not on inhaled medication [17]. Similar to our findings, there was no relationship between BD positivity to SABA and age in asthma patients at diagnosis [18], and age, sex and smoking history did not influence reversibility testing with SABA in COPD [22]. Cough in the past 4 weeks conveyed a high chance of BD responsiveness to salbutamol in our study. Likewise, morning cough was a significant predictor of BD positivity to SABA in a sample from the general population not using an inhaled medication [23]. This can be explained by the observation that salbutamol but not ipratropium reduces cough response under experimental settings [24]. On the contrary, significant BDR to ipratropium bromide using the 2021 criteria was related to the number of comorbidities, which is also reflected by a trend for less comorbidities in SAMA+ and SABA+SAMA+ groups than in the other groups. However, this should be further explored in larger scale studies.

Marked bronchodilator responsiveness can characterize clinically important subgroups of patients with asthma and COPD who are already on medication. In the ECLIPSE cohort, COPD patients with bronchodilator responsiveness to salbutamol at baseline had a higher rate of decline in FEV_1 in a 3-year period [3]. In contrast, positive BD testing to salbutamol was associated with decreased mortality and longer time to the first exacerbation in COPD patients during a mean observation time of 5 years [4]. The rate of BD responsiveness shows a direct dose-response relationship with long-term mortality in patients with asthma [25]. Moreover, bronchial responsiveness is a risk factor for exacerbation-prone asthma in a Chinese cohort [26]. In this regard, our findings show that administering only salbutamol does not identify all treatment-naïve patients with BDR, and patients showing reversibility to ipratropium could be undetected and misclassified as non-reversible.

Our study has limitations. We conducted a cross-sectional single-center study with a limited number of participants. The set ratio of FEV_1/FVC <0.70 was used to assess airflow limitation, however the use of the lower limit of normal could have given a more accurate assessment (four patients out of the hundred and five did not meet this criterion). We did not assess the intra-subject variability of BDR and did not measure the response in patients on inhaled therapy. Importantly, studies with larger sample sizes should confirm the clinical risk factors related to

significant BDR. Furthermore, the long-term clinical implications of the BDR groups described at diagnosis such as its value for predicting exacerbations or lung function decline should be addressed by future studies.

In conclusion, our data show a good agreement in the outcomes of the 2005 and 2021 ERS/ATS BDR criteria, however less patients with suspected asthma or COPD presented BDR+ according to the 2021 recommendations. We found a higher rate of BDR+ to ipratropium than to salbutamol, and higher rates of patients with BDR+ to both SABA and SAMA were noted after 30 minutes than following 15 minutes. Significant BDR to salbutamol is related to pre-BD FEV_1 values and the presence of cough. Our data suggest the combined use of SABA and SAMA and 30-minute post-BD time to more precisely identify patients with significant BDR.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [Z.L.], upon reasonable request.

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