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# Bronchodilator reversibility: What are the differences between asthma and chronic obstructive pulmonary disease?

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**Abstract:**

**INTRODUCTION:** Currently, the bronchodilator reversibility is not recommended to differentiate asthma from chronic obstructive pulmonary disease (COPD); however, physiopathological specificities of each disease contribute to the differences in response to the drug.

**OBJECTIVES:** The objective of this study is to evaluate the differences in bronchodilator response between asthmatic and COPD patients and to determine which of the bronchodilation criteria have the best ability to detect the positive response in these patients.

**MATERIALS AND METHODS:** This was a cross-sectional study. The sample included 104 patients with asthma or COPD who performed lung function tests between January and March 2018. The whole sample was analyzed according to postbronchodilator variation ( $\Delta$ ) of lung function parameters, and the postbronchodilator reversibility was characterized using a multiple bronchodilation criteria. The drug used in reversibility test was salbutamol.

**RESULTS:** In this study,  $\Delta$  forced-expiratory volume in the 1<sup>st</sup> s ( $\Delta$ FEV<sub>1</sub>) and a  $\Delta$  Raw was statistically higher in the group with asthma compared with the group with COPD. In the asthma group, the criteria  $\downarrow$  functional residual capacity (FRC)  $\geq 10\%$ ,  $\downarrow$ Raw  $\geq 35\%$ ,  $\uparrow$  forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25%-75%</sub>)  $\geq 20\%$  and  $\uparrow$  FEV<sub>1</sub> and/or  $\uparrow$  forced vital capacity  $\geq 12\%$  and 200 mL were those that presented a greater capacity of detecting a positive response to bronchodilator. The criteria  $\uparrow$  FEF<sub>25%-75%</sub>  $\geq 20\%$  and  $\downarrow$  FRC  $\geq 10\%$  were those that had the greater ability of detecting airway reversibility in COPD group.

**CONCLUSION:** The analysis of postbronchodilator FEV<sub>1</sub> and raw modifications as well as the using of a combination of multiple bronchodilation criteria contribute to a deeper characterization of bronchodilator reversibility in asthma and COPD.

**Keywords:**

Asthma, bronchodilation criteria, bronchodilator response, chronic obstructive pulmonary disease

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## Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory pulmonary diseases with a high prevalence in the general population and have a substantial impact on the quality of life of the patient and in the health-care system.<sup>[1]</sup>

There are both similarities and differences between asthma and COPD which difficult the differentiation between them, but this identification is fundamental because the wrong diagnosis and inappropriate treatment will result in patients not getting the appropriate care.<sup>[2]</sup>

Asthma and COPD are both characterized by airway obstruction.<sup>[3]</sup> In asthma, the inflammation promotes the narrowing of airways due to the contraction of the smooth muscle, and the release of bronchoconstrictor regulators produced by inflammatory cells. The presence of cellular debris, mucus, and edema of the mucosa leads to airway obstruction.<sup>[4]</sup> The limitation of the airflow in the COPD is due to the involvement of small airways and the destruction of the lung parenchyma, being that changes irreversible.<sup>[4,5]</sup>

The remodeling of the airways existing in long-term asthmatic patients and in subjects with poor asthma control is responsible for only partial bronchial reversibility after bronchodilator therapy, making it difficult to distinguish between asthma and COPD.<sup>[6]</sup>

Asthma and COPD have many similarities which can lead to misinterpretations in the diagnostics and management of these diseases,<sup>[7]</sup> that's why the identification of methods that can help to differentiate both pathologies is essential.

The lung function tests have a central role in the diagnosis and follow-up of asthma and COPD, allowing the assessment of airway obstruction presence/severity and bronchodilator response.<sup>[8,9]</sup> In asthma, the airway obstruction could be present, whereas in COPD patients, the obstruction must be present. In lung function laboratories, it is usually the administration of bronchodilator in the presence of airway obstruction to evaluate the reversibility.

The differential diagnosis between asthma and COPD through the bronchodilator response is still controversial.<sup>[8]</sup> In the GOLD guidelines 2020,<sup>[8]</sup> the use of airway response to bronchodilator is not recommended to make the distinction between both pathologies. Nevertheless, some authors<sup>[1,10,11]</sup> highlighted the existence of differences in bronchodilator reversibility between asthma and COPD patients. The evaluation of bronchodilator response and the degree of reversibility

are important to differential diagnosis and to make a full characterization of each of the diseases.

The objectives of this article are to evaluate the differences in bronchodilator response between asthmatic and COPD patients and to determine which of the bronchodilation criteria have the best ability to detect the positive response in asthmatic and COPD patients.

## Materials and Methods

We conducted a retrospective, quantitative, and cross-sectional study. The sample included asthma or COPD patients that performed lung function tests in the Physiopathological Respiratory Unit of Centro Hospitalar Universitário Lisboa Norte–Hospital Pulido Valente (Portugal), between January and March of 2018. The investigation was approved by the Ethics Commission of Centro Hospitalar Universitário Lisboa Norte and Centro Académico de Medicina de Lisboa.

The data were collected from a database belonging to the Institution/Unit and includes information about the diagnosis, demographic/anthropometric data, and lung function results of the patients. Concerning the range of time defined, the database enrolled a total of 457 patients. However, after applying the inclusion and exclusion criteria, the sample remained included 45 patients diagnosed with asthma and 59 patients with COPD.

In this study, patients with 18 years minimum in asthma group or older than 40 years in the COPD group, with clinical diagnosis of asthma or COPD and the presence of airway obstruction who performed lung function tests that include spirometry, whole-body plethysmography with bronchodilation test at the same appraisal were included. The exclusion criteria were the presence of asthma/COPD overlap or other respiratory comorbidities, have performed the inhaler treatment previous to the test, do not accomplish the quality criteria in the lung function tests according to the American Thoracic Society and European Respiratory Society [ATS/ERS],<sup>[12]</sup> and have a restrictive pattern in whole-body plethysmography.

The equipment used for this study was a Jaeger® Screen Body Plethysmograph (Hoechberg, Germany 2016) which was calibrated on a daily basis according to fabricant instructions. The reference equations considered for the lung function tests were established by the European Community for Coal and Steel.<sup>[13]</sup> The lung function tests were complying the proposed guidelines by ATS/ERS-Standardization of spirometry<sup>[14]</sup> and standardization of measurement of lung volumes.<sup>[15]</sup>

Regarding the clinical features of the patients, none of them had an exacerbation in a year before lung

function evaluation, all had been diagnosed with asthma and COPD more than 5 years ago, were medicated for their respiratory disease and having suspended the bronchodilator drugs (short-acting beta<sub>2</sub>-agonist, short-acting anticholinergics, long-acting beta<sub>2</sub>-agonist [LABA], ultra-LABA, and long-acting anticholinergics) according withholding times (data collected by cardiopulmonary technician through pre-exam questionnaire).

The whole sample presented airway obstruction (forced-expiratory volume in the 1<sup>st</sup> s [FEV<sub>1</sub>]/VC <5<sup>th</sup> percentile of the predicted value<sup>[12]</sup>) and were submitted to spirometry and whole-body plethysmography before and after the administration of bronchodilator. This was carried with salbutamol (400 µg) using a pressurized inhaler with a controlled dosage in which the technique performed was that established by the ATS/ERS.<sup>[14]</sup>

To characterize the bronchodilator response, multiple bronchodilation criteria that include parameters obtained by spirometry and whole-body plethysmography were considered: Increase (↑) of FEV<sub>1</sub> and/or forced vital capacity (FVC) ≥ 12% and 200 mL,<sup>[12]</sup> ↑ of forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25%-75%</sub>) ≥ 20%,<sup>[16]</sup> decrease (↓) of residual volume (RV) ≥ 20%,<sup>[17]</sup> ↓ of functional residual capacity (FRC) ≥ 10% and the ↓ of airway resistance (Raw) ≥ 35%.<sup>[18]</sup> The existence of pulmonary hyperinflation was determined by the criteria RV, total lung capacity (TLC), or the relation RV/TLC higher than 95<sup>th</sup> percentile of the predicted value.<sup>[12]</sup>

A statistical analysis was performed using IBM® SPSS® Statistics for Windows version 20.0 (IBM Corp (Armonk, New York). Descriptive statistics were used to characterize the sample according to demographic, anthropometric, lung function, and bronchodilator response data. Main tendency measure (mean sample) and dispersion measures (standard deviation) were calculated for quantitative variables and frequency distribution for qualitative variables. Regarding inferential statistics, the Kolmogorov–Smirnov test was carried out to verify if variables being studied had a normal distribution. The *t*-Student's test to independent samples was applied, with the purpose of verifying whether the post bronchodilator variations (Δ) of the lung function parameters are statistically distinct between the group with asthma and the group with COPD. The level of significance considered in all statistical analysis was 0.05.

## Results

We studied 104 patients, 45 with asthma (40.0% male) and 59 with COPD (78.0% male). In asthmatic group 6.7%

were smokers, whereas in COPD group, these percentage was 64.4%. Pulmonary hyperinflation was found in 40.0% of asthmatic patients and 35.6% of COPD patients [Table 1].

The analysis of the Δ lung function parameters postbronchodilator revealed a statistically significant differences in the FEV<sub>1</sub> (L) (*P* = 0.03) and raw (%) (*P* = 0.049) between asthmatic group and COPD group [Table 2].

According to the bronchodilator criteria, the ↑ of FEV<sub>1</sub> and/or FVC ≥ 12% and 200 mL was observed in 40.0% of the asthmatic group and in 13.6% of the COPD group, the ↑ of FEF<sub>25%-75%</sub> ≥ 20% was verified in 42.2% and in 42.4%, the criteria ↓ of RV ≥ 20% was reported in 17.8% and in 5.1%, the ↓ of FRC ≥ 10% was found in 53.3% and in 23.7% and the ↓ of Raw ≥ 35% was observed in 44.4% and in 13.6% respectively [Figure 1].

## Discussion

Currently, the reversibility of airflow limitation to bronchodilator in lung function tests is not recommended to inform therapeutic decision. However, there are relevant modifications in lung function parameters which could potentially be distinct between both diseases. This was verified in the present study, once there were statistically significant differences between asthmatics and COPD participants in respect to Δ of some lung function parameters.

A statistically higher Δ FEV<sub>1</sub> (L) was noticed in spirometry in the asthma group compared with the COPD group. In the whole-body plethysmography, this difference was observed relatively to Δ Raw (%). According to the results, these variables are the best to differentiate asthmatics from COPD patients in

**Table 1: Characterization of the sample**

	Asthma (n=45)	COPD (n=59)
Gender, n (%)		
Male	18 (40.0)	46 (78.0)
Female	27 (60.0)	13 (22.0)
Age (years)	60.3±15.3	65.7±10.8
Height (cm)	160.5±7.55	163.9±7.81
Weight (kg)	69.6±12.7	71.3±12.1
BMI (kg/m <sup>2</sup> )	27.1±5.33	26.5±3.98
Smoking status, n (%)		
Smoker	3 (6.7)	38 (64.4)
Former smoker	5 (11.1)	21 (35.6)
Never smoker	37 (82.2)	0 (0)
Pack years	5.8±2.1	69.7±20.2
Pulmonary hyperinflation, n (%)		
Present	18 (40.0)	21 (35.6)
Absent	27 (60.0)	38 (64.4)

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease

**Table 2: Lung function characterization of the sample before and after bronchodilation**

	Asthma (n=45)			COPD (n=59)			P
	Pre-BD	Post-BD	Δ Post-BD	Pre-BD	Post-BD	Δ Post-BD	
FVC (L)	2.95±1.01	3.10±0.98	0.157±0.21	3.06±0.93	3.20±1.01	0.07±0.18	0.058
FVC (%)	100.4±18.4	105.9±17.9	6.20±8.40	95.4±20.0	97.7±18.1	2.80±6.49	0.062
FEV <sub>1</sub> (L)	1.81±0.76	1.99±0.78	0.18±0.16	1.77±0.65	1.86±0.66	0.09±0.12	0.003*
FEV <sub>1</sub> (%)	76.1±21.0	83.6±21.6	11.0±10.1	68.3±19.1	72.3±18.9	6.64±10.6	0.332
FEF <sub>25%-75%</sub> (L)	0.96±0.65	1.14±0.76	0.19±0.27	0.75±0.43	0.87±0.55	0.12±0.20	0.135
FEF <sub>25%-75%</sub> (%)	31.6±16.1	38.2±20.7	19.0±28.1	24.6±12.0	28.2±14.8	16.1±21.3	0.153
Raw (kpa/L/s)	0.473±0.233	0.334±0.199	-0.140±0.121	0.407±0.247	0.343±0.195	-0.07±0.137	0.487
Raw (%)	187.6±33.1	120.1±18.3	-27.7±20.9	168.3±20.9	123.7±30.4	-13.9±17.0	0.049*

Comparison of mean pre-post BD differences between asthmatics and COPD: t-student test to independent samples. \*Statistically significant differences; significance level of 0.05. Δ: Postbronchodilation variation, BD: Bronchodilation, FEF<sub>25%-75%</sub>: Forced-expiratory flow between 25% and 75% of vital capacity, FEV<sub>1</sub>: Forced-expiratory volume in the 1 s, FVC: Forced vital capacity; Raw: Airway resistance, COPD: Chronic obstructive pulmonary disease

regard of bronchodilator response. The FEV<sub>1</sub> and the Raw reflect the bronchial caliber, and hence, the results obtained suggest that bronchodilator promotes a greater increase in airway permeability in asthmatic airways than that occurred in COPD airways. These differences are justified by the inherent physiopathological characteristics of each disease. In asthma, the allergen leads to an exaggerated response of the airways, which is more sensitive to bronchodilator action,<sup>[19,20]</sup> whereas in the COPD, the progressive fibrosis in the airways, the loss of elasticity, and mucociliary dysfunction caused by the contact of airways with noxious substances, result in a less expressive bronchodilator response.<sup>[7,19,20]</sup>

Dias *et al.*<sup>[10]</sup> investigation revealed the existence of Δ FEV<sub>1</sub> (L and %) and Δ FVC (L and %) higher in asthmatic participants compared to COPD participants. However, these differences just had statistical significance in Δ FEV<sub>1</sub> (L and %). Silvestri *et al.*<sup>[1]</sup> carried out a study with a similar methodology and obtained matching results in relation to Δ FEV<sub>1</sub> (L) and Δ FVC (L). However, the differences obtained were statistically significant in the both parameters. In the two studies mentioned and in the present investigation, it was found significant differences in relation to Δ FEV<sub>1</sub> (L). Our study presented additional results regarding to Δ Raw (%), this parameter was not considered by the other authors because they only analyzed the spirometry. The size of the samples could justify the differences between the studies. Our investigation and Dias *et al.*<sup>[10]</sup> study included small samples (104 patients and 50 patients, respectively), whereas Silvestri *et al.*<sup>[1]</sup> included 211 individuals, which may mean that in the presence of a larger sample, the Δ FVC could become more evident and acquire statistical value.

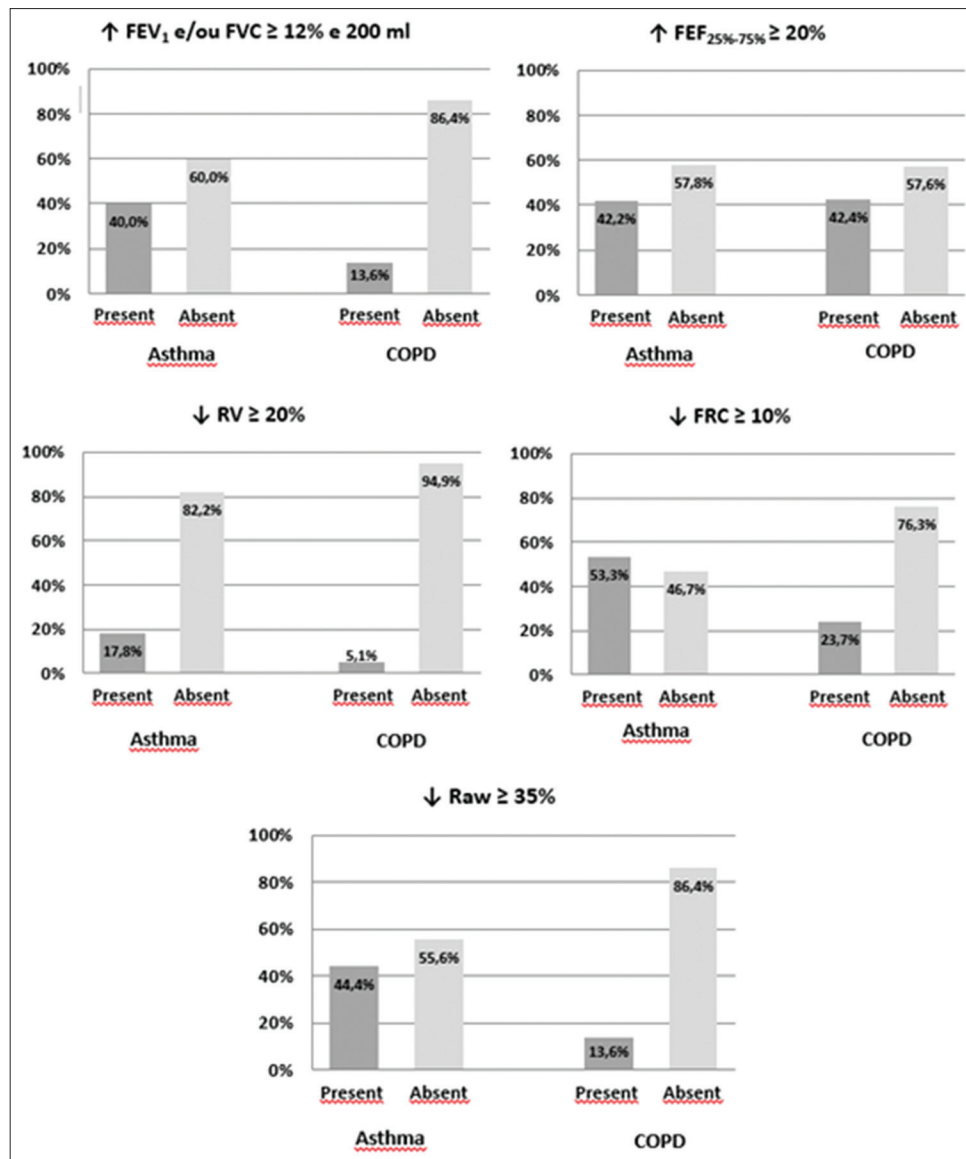
The evaluation of modifications promoted by the bronchodilator is not carried out by a simple observation of the Δ parameters. For the correct characterization of the airway response to bronchodilator-defined criteria are used. This investigation showed that in the asthmatic group,

the criteria which include parameters that reflect airway caliber (↑ of the FEV<sub>1</sub> and/or FVC ≥12% and 200 mL, ↑FEF<sub>25%-75%</sub> ≥20% and ↓ Raw ≥35%), revealed similar abilities in detection of positive bronchodilator response (40%, 42.2%, and 44.4%, respectively). The criteria with greater capacity of detecting airway reversibility in the COPD group were the ↑ FEF<sub>25%-75%</sub> ≥20% (42.4%). In both groups was observed the presence of pulmonary hyperinflation criteria, however, after the administration of the bronchodilator therapy, the pulmonary hyperinflation can potentially reduce; nevertheless, this phenomenon may not be perceived through the changes in FEV<sub>1</sub>, FVC, or FEF<sub>25%-75%</sub>. The criteria ↓ FRC ≥10% showed a better capacity in the detection of a positive bronchodilator response in asthmatics (53.3%) and COPD patients (23.7%) compared with the criteria ↓ RV ≥ 20% (17.8% vs. 5.1%). This could be due to the fact that the first criteria are less demanding relatively to percentage of reduction to classify the patients as responders.

Except the criterion ↑ FEF<sub>25%-75%</sub> ≥20%, all the other showed that asthmatic patients presented a much higher bronchodilator response comparatively to verified in COPD patients, which shows that the physiopathological differences of both pathologies could highlight an imbalance of lung function response to the administration of the bronchodilator therapy.

Despite the bronchodilator response is nowadays not valued for the differentiation between asthma and COPD, the results of this investigation showed that the airway response is crucial for a correct characterization of both diseases. Because both presents specific aspects in regard to how airways respond to the action of these drugs.

The lung function parameters where the differences in the response to the bronchodilator therapy were more evident were the FEV<sub>1</sub> and raw, the analysis of its change postbronchodilation is fundamental for helping



**Figure 1:** Characterization of bronchodilator response in asthmatics and chronic obstructive pulmonary disease patients according to several criteria. FEF<sub>25-75%</sub>: Forced expiratory flow between 25% and 75% of vital capacity, FEV<sub>1</sub>: Forced expiratory volume in the first second, FRC: Functional residual capacity, FVC: Forced vital capacity, Raw: Airways resistance, RV: Residual volume

in the differentiation between both the diseases. The bronchodilation criteria are also fundamental in this context, so the authors suggest the use of a combination of criteria with the intent to clarify the specificities of each one of these diseases relatively to the effects of this type of drug on the airways.

The present study presents as limitation the reduced number of members included in the sample, what may have conditioned the results, it would be important to develop further investigations with more patients to achieve more robust results.

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### Conflicts of interest

There are no conflicts of interest.

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