Original Article

Comparison of spirometric changes in the response to bronchodilators of patients with asthma or chronic obstructive pulmonary disease*

Comparação da variação de resposta ao broncodilatador através da espirometria em portadores de asma ou doença pulmonar obstrutiva crônica

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Abstract

Objective: Making the differential diagnosis between asthma and chronic obstructive pulmonary disease (COPD) based on the response to inhaled bronchodilators by means of spirometry is controversial.The objective of this study was to identify the most useful spirometric variables in order to distinguish between asthma and COPD. **Methods:** Retrospective study conducted from April of 2004 to January of 2006, comparing the spirometric parameters of 103 nonsmoking patients with asthma to those of 108 patients with COPD who were smokers for more than 10 pack-years. All of the patients included in the study were older than 40 and presented stable disease at the time of the test. **Results:** Initial forced expiratory volume in one second (FEV_1) was the same in the two groups (pre-bronchodilator FEV_1 = 51%). However, patients with COPD were older (66 ± 9 years *vs.* 59 ± 11 years, p < 0.001) and more frequently male (73% *vs.* 27%, p < 0,001).After the use of the bronchodilator, the median absolute difference in FEV_1 was 0.25 L (range, –0.09 to 1.13 L) in patients with asthma and 0.09 L (range, –0.1 to 0.73 L) in those with COPD (p < 0.001).The highest sensitivity (55%), specificity (91%) and likelihood ratio (6.1) for asthma diagnosis was obtained when the percentage increase in postbronchodilator FEV_1 in relation to the predicted FEV_1 ($\Delta\%predFEV_1$) was equal to or greater than 10%.Isolated significant increases in forced vital capacity were more common in patients with COPD. **Conclusions:** In patients over the age of 40 and presenting obstructive lung disease, a $\Delta\%predFEV_1 \geq 10\%$ is the best spirometric parameter to distinguish asthma from COPD.

Keywords: Spirometry; Respiratory function tests; Lung diseases, obstructive.

Resumo

Objetivo: O diagnóstico diferencial entre asma e doença pulmonar obstrutiva crônica (DPOC) através da resposta aos broncodilatadores inalatórios na espirometria ainda é controverso. O objetivo deste estudo foi detectar quais variáveis espirométricas melhor diferenciam asma de DPOC. **Métodos:** Estudo retrospectivo realizado entre abril de 2004 e janeiro de 2006, comparando-se os parâmetros espirométricos de 103 pacientes asmáticos, não fumantes, com os de 108 pacientes portadores de DPOC, fumantes de mais de 10 anos-maço. Todos os pacientes tinham mais de 40 anos e apresentavam doença estável no momento do exame. **Resultados:** O volume expiratório forçado no primeiro segundo (VEF_1) pré-broncodilatador foi igual nos dois grupos (VEF_1 = 51%), mas os portadores de DPOC eram mais velhos (66 ± 9 anos *vs.* 59 ± 11 anos, p < 0,001) e, na sua maioria, do sexo masculino (73% *vs.* 27%, p < 0,001). A mediana da variação absoluta do VEF_1 pós-broncodilatador foi de 0,25 L (intervalo, –0,09 a 1,13 L) nos pacientes com asma e de 0,09 L (intervalo, –0,1 a 0,73 L) nos com DPOC (p < 0,001). A melhor combinação de sensibilidade (55%), especificidade (91%) e razão de verossimilhança (6,1) para o diagnóstico de asma foi obtida quando a percentagem de incremento do VEF_1 pós-broncodilatador em relação ao VEF_1 previsto foi igual ou maior que 10% (p < 0,001). Variações significativas isoladas da capacidade vital forçada foram mais comuns nos pacientes com DPOC. **Conclusões:** Em portadores de doenças pulmonares obstrutivas com mais de 40 anos, a $\Delta\%prevVEF_1 \geq 10\%$ constitui o melhor parâmetro espirométrico para diferenciar asma de DPOC.

Descritores: Espirometria; Testes de função respiratória; Pneumopatias obstrutivas.

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Introduction

It remains controversial whether the differential diagnosis between asthma and chronic obstructive pulmonary disease (COPD) can be made on the basis of the response to inhaled bronchodilators, as determined through spirometry. The COPD consensus established by the American Thoracic Society (ATS) and European Respiratory Society (ERS) states that, although some degree of bronchodilation can be seen in patients with COPD, a pronounced postbronchodilator increase in forced expiratory volume in one second (FEV_1) is indicative of a diagnosis of asthma.[1] The most recent version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that the degree to which airflow is reversible should not be used as a criterion in making the differential diagnosis between asthma and COPD.[2]

Bronchodilator response is typically determined based on differences between prebronchodilator and postbronchodilator FEV_1, as well as on prebronchodilator/postbronchodilator differences in forced vital capacity (FVC). Currently, FEV_1 is considered the functional parameter that best characterizes bronchodilator response. However, some patients, especially those with severe obstruction, can present isolated increases in FVC, which should be taken into consideration, since FVC correlates better with dyspnea and exercise performance.[3-5]

Bronchodilator response can be expressed in a number of ways.[6-8] Various cut-off points have been proposed in order to define what constitutes a significant bronchodilator response in individuals with obstructive disorders.[7,8] In addition, bronchodilator response can vary longitudinally.[9]

Divergences among the findings of previous studies in which attempts were made to differentiate between asthma and COPD based on bronchodilator response can be explained by a number of factors: small sample size; the inclusion of smokers among the asthma patients; use of low doses of inhaled albuterol; inclusion of younger patients with asthma; and greater degree of obstruction among the patients with COPD.[10-12]

The present study was designed to evaluate the various spirometric patterns that best represent bronchodilator response in the differentiation between asthma and COPD, while attempting to avoid the limitations of previous studies.

Methods

This was a retrospective analysis of spirometric patterns in patients with asthma or COPD under regular outpatient treatment at the Pulmonology Clinic of the São Paulo Hospital for State Civil Servants. The study design received the unconditional approval of the Ethics Committee of the Hospital.

The spirometric tests met all of the acceptability and reproducibility criteria established by the Brazilian Thoracic Association (BTA).[7] The tests were conducted using two different spirometers (SensorMedics, Yorba Linda, CA, USA; MultiSpiro Inc., Irvine, CA, USA) and in two phases: prebronchodilator; and postbronchodilator (15 min after the administration of 400 µg of albuterol via a metered-dose inhaler with a spacer. Reference ranges were calculated based on equations recently formulated for the Brazilian population.[13] Only the tests in which there was airway obstruction (with or without a reduction in FVC), defined as a FEV_1/FVC ratio below the lower limit of normality, were considered.

The diagnosis of asthma or COPD was made by attending pulmonologists, during routine treatment, based on the clinical criteria established by the BTA.[14,15] A total of 1,061 spirometric tests, all conducted between April of 2004 and January of 2006, were evaluated: 620 were indicative of a diagnosis of asthma, and 441 were indicative of a diagnosis of COPD. From among those indicative of asthma, 284 were selected based on the following criteria: patient over 40 years of age; stable disease at the time of the test; and no history of smoking. From among those indicative of COPD, 346 were selected based on the following criteria: patient over 40 years of age; stable disease at the time of the test; and current or former smoker with a smoking history of at least 10 pack-years. After this initial selection, the patient charts were reviewed in order to confirm the diagnoses, as well as to exclude patients with other, concomitant lung diseases or with pulmonary manifestations of systemic diseases. Cases in which the chart indicated a change in the diagnosis were also excluded. The final sample consisted of 211 spirometry tests: 103 from patients diagnosed with asthma; and 108 from patients diagnosed with COPD.

The bronchodilator response was evaluated in four different ways: 1) postbronchodilator percentage increase in FEV_1 over baseline (Δ%bslnFEV$_1$); 2) postbronchodilator percentage increase in FEV_1 in relation to the predicted value (Δ%predFEV$_1$); 3) absolute difference between baseline and postbronchodilator FEV_1 (ΔabsFEV$_1$); and 4) absolute difference between baseline and postbronchodilator FVC (ΔabsFVC).

Sensitivity, specificity, predictive values and likelihood ratios were calculated for the various response expressions.[6,7] In a recent spirometry study, FEV_1 and FVC were evaluated before and after bronchodilator use in individuals without lung disease.[16] The authors found that, in individuals over the age of 40, FEV_1 can increase after bronchodilator use by as much as 0.30 L in men and 0.20 L in women. This response expression was also evaluated in the present study.

Bronchodilator responses were classified as follows: 1) absent - no significant increase in FEV_1 or FVC; 2) FEV_1 response in isolation - isolated FEV_1 response $\geq$ 0.30 L in men or $\geq$ 0.20 L in women; 3) FVC response in isolation - isolated FVC response $\geq$ 0.35 L; and 4) FEV_1 and FVC response - significant increase in both parameters.

The statistical analysis was conducted using the Statistical Package for the Social Sciences, version 10 for Windows 95 (SPSS Inc., Chicago, IL, USA). Values are expressed as mean $\pm$ standard deviation or as median and range. Variations in bronchodilator responses within groups were compared using paired t-tests. Variations in bronchodilator responses between groups were compared using t-tests for independent samples, Mann-Whitney tests for independent samples or chi-square (χ^2) tests. Sensitivity, specificity, positive predictive value and negative predictive value for the various qualitative patterns of bronchodilator response were calculated using asthma as a reference. The various expressions of bronchodilator response were correlated with baseline FEV_1 and with age using Spearman's correlation coefficient (r_s). An analysis of covariance was performed in order to correlate bronchodilator response, expressed as ΔabsFEV$_1$, with clinical diagnosis and with gender. Values of $p \leq 0.05$ were considered statistically significant.

Results

Of the 211 patients evaluated in this study, 103 (49%) had received a diagnosis of asthma, and 108 had received a diagnosis of COPD. Despite the fact that patients below the age of 40 were excluded from the analysis, mean age was higher in the COPD group Among the patients with COPD, the median smoking history was 50 pack-years (range, 15-234 pack-years). The baseline percentage FEV_1 values were statistically similar in the two groups evaluated (Table 1).

Comparing prebronchodilator and postbronchodilator values, the mean increase in FVC was from 2.39 L to 2.68 L among the patients with asthma ($p < 0.001$) and from 2.91 L to 3.09 L among the patients with COPD ($p < 0.001$). The mean increase in FEV_1 was from 1.32 L to 1.59 L among the patients with asthma ($p < 0.001$) and from 1.49 L to 1.61 L among the patients with COPD ($p < 0.001$). The remaining parameters also presented statistically significant variations in the median values obtained for both groups (Table 2).

When the spirometric values were evaluated separately in accordance with the variations in FEV_1, FVC or both, we found that 86% of the isolated FEV_1 responses occurred in asthma patients, whereas 83% of the isolated FVC responses occurred in asthma

Table 1 - General characteristics of the patients.

Variable	Asthma (n = 103)	COPD (n = 108)	p
Gender (M/F)	28/75	83/25	< 0.001
Age (years), mean $\pm$ SD	58.97 $\pm$ 10.63	66.36 $\pm$ 8.95	< 0.001
Baseline FVC%, mean $\pm$ SD	74.54 $\pm$ 17.46	78.63 $\pm$ 17.04	0.087
Baseline FEV_1%, mean $\pm$ SD	51.28 $\pm$ 15.43	51.21 $\pm$ 18.29	0.885
Degree of obstruction			
Mild/moderate/accentuated	23/52/28	26/52/30	0.935

COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; and FEV_1: forced expiratory volume in one second.

Table 2 - Functional variations after bronchodilator use in individuals with asthma or chronic obstructive pulmonary disease.

Expression	Asthma median (range)	COPD median (range)	p
$\Delta absFEV_1$ (L)	0.25 (–0.9 a 1.13)	0.09 (–0.1 a 0.73)	<0.001
$\Delta\%bslnFEV_1$ (%)	20.95 (–6 a 73)	7.82 (–14 a 67)	<0.001
$\Delta\%predFEV_1$ (%)	10.20 (–4 a 33)	3.30 (–6 a 21)	<0.001
ΔabsFVC (L)	0.25 (–0.25 a 1.09)	0.17 (–0.5 a 0.84)	<0.01
Δ%bslnFVC (%)	13.70 (–10 a 61)	5.55 (–12 a 49)	<0.001
Δ%predFVC (%)	8.70 (–8 a 29)	4.40 (–11 a 19)	<0.001
$\Delta absFEV_1$/FVC (%)	3.42 (–6 a 14)	1.00 (–11 a 10)	<0.001

COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; Δabs: absolute difference between baseline and postbronchodilator FEV_1, FVC or FEV_1/FVC; Δ%bsln: postbronchodilator percentage increase in FEV_1 or FVC over baseline; and Δ%pred: postbronchodilator percentage increase in FEV_1 or FVC in relation to the predicted value.

patients (Table 3). When both responses were present, 84% of such responses occurred in asthma patients, and the difference was statistically significant ($\chi 2 = 52.41$, $p < 0.001$). Patients presenting isolated FVC responses had lower baseline percentage values of FEV_1 than did those presenting other types of responses (39% *vs.* mean values > 50% in the remaining patients, $F = 5.07$, $p = 0.002$). There was a weak, yet significant, inverse correlation between prebronchodilator FVC and ΔabsFVC ($r_s = -0.23$, $p = 0.001$). Among the patients with COPD, there were three cases in which the absolute variation in FEV_1 was greater than 400 mL (440, 640 and 730 mL). In those three cases, the patient charts revealed emphysema on a tomography scan of the chest and a lack of clinical-spirometric improvement after treatment with inhaled corticosteroids.

Table 3 - Responses of forced expiratory volume in one second and forced vital capacity in individuals with asthma or chronic obstructive pulmonary disease.

Type of response	Asthma	COPD	Total
None	43	79	122
Isolated FEV_1[a]	19	3	22
Isolated FVC[b]	4	19	23
FEV_1 and FVC	37	7	44
Total	103	108	211*

COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; and FEV_1: forced expiratory volume in one second. [a]Increase in $FEV_1 \geq 0.30$ L for men and ≥ 0,20 L for women. [b]Increase in FVC ≥ 0.35 L. *$\chi^2 = 52.41$, $p < 0.001$.

In Table 4, the sensitivity, specificity, predictive values and likelihood ratios are shown for the various expressions of bronchodilator response, using asthma as a reference.

The ideal expression of bronchodilator response should not vary more than the magnitude of the baseline FEV_1 value. In the sample as a whole, there was no dependence in relation to baseline FEV_1: $\Delta absFEV_1$ ($r_s = 0.096$; $p = 0.167$) and $\Delta\%predVEF_1$ ($r_s = 0.080$; $p = 0.246$). The $\Delta\%bslnFEV_1$ proved to be dependent on the baseline VEF_1 ($r_s = -0.200$; $p = 0.004$). In both groups, the absolute variation in postbronchodilator FEV_1 presented an inverse correlation with age: $r_s = -0.31$ ($p = 0.001$) for asthma; and $r_s = -0.296$ ($p = 0.002$) for COPD. In the analysis of covariance, clinical diagnosis and gender were found to influence bronchodilator response, as expressed by the absolute variation in FEV_1.

Discussion

Our findings show that it is possible to differentiate between asthma and COPD based on the spirometric response to the use of a bronchodilator. A greater than 10% increase in FEV_1 in relation to the predicted value presented the greatest discriminatory power in distinguishing asthma from COPD.

Asthma and COPD both result from the interaction of genetic and environmental factors. The Dutch hypothesis proposes that asthma, chronic bronchitis and emphysema should be considered different expressions of the same disease. Common risk factors for the development of asthma or

Table 4 - The different bronchodilator response expression/cut-off point combinations and their diagnostic capacity for asthma.

Expression	SE (%)	SP(%)	PPV(%)	NPV(%)	LR	p
$\Delta absFEV_1 \geq 0.20$ L	56	75	68	64	2.24	<0.001
$\Delta absFEV_1 \geq 0.30$ L	40	92	82	61	5.00	<0.001
$\Delta absFEV_1 \geq 0.30$ L for men and ≥ 0.20 L for women	54	91	85	68	5.85	<0.001
$\Delta\%bslnFEV_1 \geq 12\%$	71	70	69	72	2.36	<0.001
$\Delta\%predFEV_1 \geq 7\%$	63	69	66	66	2.03	<0.001
$\Delta\%predFEV_1 \geq 10\%$	55	91	85	68	6.11	<0.001
$\Delta absFEV_1 \geq 200$ mL + $\Delta\%bslnFEV_1 \geq 12\%$	56	82	75	66	3.11	<0.001
$\Delta absFVC \geq 200$ mL	59	57	57	60	1.37	0.016
$\Delta absFVC \geq 350$ mL	40	76	61	57	1.66	0.014

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; Δabs: absolute difference between baseline and postbronchodilator FEV_1 or FVC; Δ%bsln: postbronchodilator percentage increase in FEV_1 or FVC over baseline; Δ%pred: postbronchodilator percentage increase in FEV_1 or FVC in relation to the predicted value; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; and LR: likelihood ratio.

COPD include bronchial hyperresponsiveness and β_2-adrenergic receptor polymorphisms.[17,18] Variable airway obstruction has been proposed as an asthma-defining characteristic. However, that does not always differentiate between asthma and COPD, especially in older individuals with long-standing disease. There are critical differences between asthma and COPD that influence their management and prognosis.[19,20]

To distinguish between asthma and COPD, various resources are available. The most relevant lung function parameters are the diffusing capacity of the lung for carbon monoxide and the bronchodilator response.[21,22] However, there is as yet no consensus as to which index best expresses bronchodilator response, or even as to what cut-off value would indicate a positive bronchodilator response.

In the present study, the groups were similar in terms of the initial degree of obstruction but dissimilar in terms of age and gender, both of which influenced the bronchodilator response. Asthma with persistent airway obstruction is most common in older women, which increases the difficulty in making the differential diagnosis with COPD.[23] In our sample, the asthma group consisted of only nonsmokers, and the COPD consisted of only smokers, thereby reducing the chance of incorrect classification. However, these restrictions also reduced the external validity of the study.

Various expressions of bronchodilator response, with different cut-off points, have been described. Two types of studies have been used to derive cut-off points intended to characterize a significant bronchodilator response. Postbronchodilator variations can be considered significant if they exceed those observed in individuals without lung disease, or if they exceed the spontaneous variation/variation observed after the use of a placebo, in patients with airflow limitation. In three different studies involving individuals without lung disease, the upper limits of the postbronchodilator response were observed (8, 9 and 10%, respectively).[7] In a recent study, it was demonstrated that, in individuals without lung disease, the response is reduced with age, but that, in general, variations of > 0.20 L in men and > 0.30 L in women constitute the limits of the response in individuals over the age of 40.[16] In the present study, a 10% increase in FEV_1 over the predicted value presented the best discriminatory power for distinguishing between asthma and COPD, underscoring the fact that, in individuals with asthma, bronchial tone is truly elevated. Responses > 0.20 L in women and > 0.30 L in men were slightly less definitive. In two other studies,[8,24] the best differentiation between asthma and COPD was also obtained through the use of a ≥ 10% postbronchodilator increase in FEV_1 over the predicted value. In a study involving 660 patients with COPD, a postbronchodilator increase in FEV_1 of 9% over predicted was observed in 23%, although this value varied in subsequent tests.[25]

Certain functional variables, whose values exceed those observed after the use of a placebo, present variations greater than those occurring spontaneously. Such variables include FEV_1 above 0.20 L, FEV_1 above baseline and the combination of the two, as well as FEV_1 > 7% above the predicted value.[7] Although such responses are more often observed in individuals with asthma, they are also common in individuals with COPD. Therefore, it is not surprising that these expressions of postbronchodilator response present greater sensitivity and lower specificity for the diagnosis of asthma.[9-12] The author of one study suggested that a $\Delta absFEV_1 \geq 200$ mL is the expression that is most efficient in differentiating between asthma and COPD but found that the likelihood ratio was greater for variations in FEV_1 > 9% of the predicted value.[12]

Among the forms used in order to express bronchodilator response, the $\Delta\%bslnFEV_1$ presents greater apparent responses when FEV_1 is lower, thereby overestimating the response.[25] In the present study, we were concerned with matching the severity of airway obstruction in the two groups, in order to minimize the influence that baseline FEV_1 had on the rate of bronchodilator response. We found that neither $\Delta\%predFEV_1$ nor $\Delta absFEV_1$ correlated with baseline FEV_1. The combined use of absolute and percentage variations, expressed as a simultaneous increases in FEV_1 of > 12% of the baseline value and 0.20 L, partially negates the influence that the baseline value has on the response. In the present study, this response expression presented sensitivity similar to that of a > 10% increase in FEV_1 over predicted, albeit with less sensitivity and a lower likelihood ratio. Variations greater than 0.20 L in women are indicative of abnormal bronchial tone.[16]

In the present study, three COPD patients presented absolute postbronchodilator variations in FEV_1 of more than 400 mL. In those three cases, tomography scans of the chest revealed extensive emphysema, and no improvement was seen after treatment with inhaled corticosteroids. In one study, bronchial hyperresponsiveness was found to correlate with structural changes in patients diagnosed with COPD who were referred for resection of pulmonary nodules.[26] The provocative concentration causing a 20% fall in FEV_1, after correction for the baseline value of FEV_1, was found to correlate with lung elastic recoil and with airway thickness, including that of the smooth muscle mass. The most responsive patients also presented low numbers of alveolar attachments in the external walls of the airways. Patients with emphysema could have pronounced bronchodilator responses, due to the potential amplification of these mechanisms. In another study, we evaluated a patient with extensive emphysema who presented sharp variations in postbronchodilator FEV_1.[27] That patient was submitted to lung volume reduction surgery, after which the bronchodilator response disappeared, which might be explained by the increase in the radial traction of the airways after the procedure.

Patients with COPD, especially those with pronounced obstruction, can, after the use of a bronchodilator, present an isolated increase in FVC, which has been correlated with a reduction in dyspnea and with an increase in exercise capacity.[3,4]Variations in FVC ≥ 0.35 L are above the 95th percentile of random variation.[7] Variations in FVC of 12% and 0.20 L, similar to the values proposed for FEV_1, continue to be erroneously considered significant.[28] It is therefore understandable that this cut-off point has little discriminatory power for differentiating between asthma and COPD.[12]

In the present study, significant, isolated variations in FVC were more common in patients with COPD, and such variations were associated with a greater degree of obstruction. Isolated volume responses to bronchodilator use in patients with COPD are known to be associated with accentuated emphysema and probably result from an alteration in the effect that lung inflation has on airway diameter.[29] Patients with asthma can also present isolated postbronchodilator FVC responses. In those patients, there is probably an increase in the residual volume caused by the closing down of the small airways, which reopen after bronchodilator use.

Bronchodilator responses can be categorized as flow responses or volume responses.[30] When postbronchodilator variations in FEV_1 are proportional to the postbronchodilator variations in FVC and are accompanied by a normal or reduced postbronchodilator FEV_1/FVC ratio, they can simply reflect lung volume recruitment and should be considered volume responses.[3] Although FEV_1 and FVC are both volume measures, postbronchodilator variations in these measures can reflect increased expiratory flows. When there is an isolated postbronchodilator variation in FEV_1, it is likely that there is bronchial dilation primarily of the central airways,

whereas an isolated postbronchodilator variation in FVC is indicative of bronchial dilation primarily of the peripheral airways. Therefore, both also reflect increased flow, albeit in different segments of the tracheobronchial tree. Therefore, it seems more appropriate to designate these responses simply FEV_1 responses, FVC responses or FEV_1-FVC combination responses, rather than refer to them as flow responses or volume responses.

We can conclude that, in individuals over the age of 40 with obstructive lung disease, it is possible to differentiate between asthma and COPD based on the spirometric response to bronchodilator use. A ≥ 10% increase in FEV_1 over the predicted value proved to have the greatest discriminatory power in discriminating between asthma and COPD. Alternatively, the expression $\Delta absFEV_1$ (≥ 0.30 L for men and ≥ 0.20 L for women) can be employed. Further studies involving age- and gender-matched samples of individuals with asthma and individuals with COPD are needed in order to obtain more specific results.

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