

# Original Article

## Measuring forced expiratory volume in one second alone is not an accurate method of assessing response to bronchodilators in chronic obstructive pulmonary disease\*

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### ABSTRACT

**Objective:** To assess the frequency of variation in forced expiratory volume in one second after bronchodilator use in a sample of patients with chronic obstructive pulmonary disease, correlating such variation with clinical and demographic variables and evaluating the frequency of response presented in forced vital capacity, slow vital capacity, inspiratory capacity, residual volume, airway resistance and specific airway conductance. **Methods:** A total of 64 patients with chronic obstructive pulmonary disease were submitted to whole body plethysmography, and reversibility of bronchoconstriction after the administration 400 µg of fenoterol was quantified. **Results:** A response in forced expiratory volume in one second was observed in 31% of the patients. Excluding patients presenting a response in forced expiratory volume in one second, 5% presented responses in 5 of the other 6 parameters, 10% presented responses in 4 parameters, 17.5% in 3 parameters, 27.5% in 2 parameters, and 25% in only 1 parameter. **Conclusion:** When included in the evaluation of bronchodilator response together with forced expiratory volume in one second, static lung volumes, airway resistance and airway conductance allowed a broader evaluation of those patients presenting a functional pharmacodynamic response. These results are in accordance with the observation that bronchodilator use provides clinical improvement and relief of dyspnea to many patients with chronic obstructive pulmonary disease, even to those in whom such treatment leads to no improvement in forced expiratory volume in one second.

**Keywords:** Pulmonary disease, chronic obstructive/drug therapy; Bronchodilator agents/therapeutic use; Airway resistance/drug effects; Respiratory function tests; Vital capacity; Forced expiratory volume

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## INTRODUCTION

Patients diagnosed with chronic obstructive pulmonary disease (COPD) present various functional alterations. The most typical finding in these patients is the persistent reduction in forced expiratory flow.

Clinical studies assessing the reversibility of obstructive ventilatory disorders in COPD are usually based on measurements of expiratory flow and their variation after the use of inhaled bronchodilators. Forced expiratory volume in one second (FEV<sub>1</sub>) is the most common parameter used.<sup>(1)</sup> Significant variations in FEV<sub>1</sub> after bronchodilator use have been observed in approximately 30% of patients with COPD.<sup>(2-3)</sup>

Although some studies showed poor response to bronchodilators in FEV<sub>1</sub> in patients with COPD, these drugs have always been the main therapeutic resource used to combat this illness and are widely prescribed.<sup>(2-5)</sup>

The functional limitation in patients with COPD, classically determined through the measurement of FEV<sub>1</sub>, correlates well with limited exercise tolerance, ability to perform day-to-day activities, severity of dyspnea and lower quality of life. Spirometry, and FEV<sub>1</sub> in particular, is a good marker for the staging of the disease.<sup>(3)</sup> Although it has not been well established in the literature, some studies have shown that bronchodilators may reduce dyspnea, independent of any improvement in spirometric values.<sup>(5-7)</sup> In addition, patients who respond to bronchodilators have been shown to also respond better to long-term treatment with corticosteroids and long-acting bronchodilators, thereby improving prognoses.<sup>(4,8)</sup>

The principal double-blind, randomized studies involving large samples of patients with COPD assessed FEV<sub>1</sub> as the main outcome measure. The need for other parameters to evaluate the bronchodilation response, such as exercise tolerance and other spirometric variables that could better predict the clinical response, came into question when the results of the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study were published.<sup>(9)</sup> Those results showed that, even with the lack of functional improvement, the frequency of symptoms and exacerbations decreased with the use of inhaled corticoids.

In order to find the answer to this question, some more recent studies were aimed at evaluating

the response to bronchodilators using other parameters, such as quality of life, severity of dyspnea, exercise tolerance and functional parameters that reflected the reduction in pulmonary hyperinflation.<sup>(5,10)</sup> In various studies involving patients with airway obstruction, there was response to bronchodilators using parameters other than FEV<sub>1</sub><sup>(5,11-17)</sup>.

Based on these assumptions, we proposed this study with the objective of assessing the frequency of an FEV<sub>1</sub> response to a bronchodilator in a group of patients with COPD, correlating this response to clinical data, comparing the groups with and without an FEV<sub>1</sub> response and assessing other functional parameters (forced vital capacity - FVC; slow vital capacity - SVC; inspiratory capacity - IC; residual volume - RV; airway resistance - AR; and specific airway conductance - sGaw).

## METHODS

A prospective study was conducted involving patients diagnosed with COPD, confirmed by clinical, radiological and functional criteria, who were referred to the Laboratório de Função Pulmonar (Pulmonary Function Laboratory) of the Pavilhão Pereira Filho (Pereira Filho Ward) of the Irmandade da Santa Casa de Misericórdia Hospital in the city of Porto Alegre, located in the state of Rio Grande do Sul, Brazil.

Based on a modified version of the Global Initiative for Chronic Obstructive Lung Disease,<sup>(4)</sup> we used the following inclusion criteria: being older than 40 years of age, smoking for over 20 years; presenting one or more COPD symptoms (dyspnea, cough, chronic expectoration, limited exercise tolerance); demonstrating an FEV<sub>1</sub> < 80% or an FEV<sub>1</sub>/FVC < 70 %; having a normal chest X-ray or a chest X-ray showing alterations consistent with COPD. Exclusion criteria were having a history of asthma, having been recently diagnosed with asthma, presenting any other significant pulmonary disease, being considered unfit to perform the test, and having -1 antitrypsin deficiency.

From January to December of 2002, 65 consecutive patients met the criteria and agreed to participate in the study. Subsequently, these patients were submitted to whole body plethysmography using a Vmax22 Autobox (Sensor Medics Corp., Yorba Linda, CA, USA).

The test consisted of simple spirometry with a flow-volume curve, measuring lung volumes and airway resistance through plethysmography, together with a test of the pulmonary diffusing capacity for carbon monoxide, all conducted in accordance with the guidelines established by the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Society of Pulmonology and Phthysiology).<sup>(18)</sup>

At the end of the first step, 400 µg of fenoterol were administered to all patients using a metered-dose inhaler with a spacer attached. Fifteen minutes after administration, all measurements were repeated. We used the tables of predicted values devised by Morris et al. (for spirometric tests),<sup>(19)</sup> Goldman and Becklake (for lung volumes),<sup>(20)</sup> and Burrows et al. (for diffusion)<sup>(21)</sup>

For assessing response to the bronchodilator, we used the following criteria: FEV<sub>1</sub> - an increase in volume of 200 mL and 7% above the predicted value; FVC - an increase in volume of 350 mL in absolute values; SVC - an increase of 15% over baseline; IC - an increase of 15% over baseline; AR - a reduction to 35% below baseline; sGaw - an increase of 50% over baseline. These criteria are in accordance with the guidelines for pulmonary function tests established by the SBPT.<sup>(18)</sup> An additional criterion was RV reduced to 20% of the predicted value, in accordance with Newton et al.<sup>(22)</sup>

As criteria for reproducibility and acceptance of the maneuvers, we used those recommended by the SBPT<sup>(18)</sup> for the FVC maneuver, and those recommended by Ruppel for the other maneuvers.<sup>(23)</sup>

Statistical analysis was carried out using the Statistic Package for Social Science program, version 11.0. Pearson's chi-square test and Student's t-test were used for independent samples, and Student's t-test alone was used for equality of the means, analysis of variance was used to compare values obtained in the present study with those obtained in other studies. Values of  $p < 0.05$  were considered statistically significant.

The Ethics in Research Committee of the Santa Casa de Porto Alegre Hospital approved the present study.

## RESULTS

The initial sample comprised 65 patients, who were submitted to plethysmography. However, one patient was excluded from the study after presenting normal results in the plethysmographic testing.

TABLE 1

Demographic and clinical aspects of 64 patients with chronic obstructive pulmonary disease

Variável	Média
Age*	60,5±11,6
Females	55,0%
Caucasians	96,9%
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Current smoking**	40,6%
Age at initiation of smoking*	15,6±4,5
Pack-years*	56,6±36,8
Dyspnea**	95,3%,
Wheezing**	76,6%
Chronic cough and expectoration**	20,3%

\* Values expressed as mean ± standard deviation

\*\* Values expressed as percentage of patients

Therefore, the study sample comprised 64 patients. Of those 64, 5 did not complete all of the measurements proposed due to difficulties in performing the plethysmographic technique properly.

In the study sample, 35 (55%) were female and the mean age was 60.5 ± 11.6 years. Table 1 shows the clinical characteristics of the patients.

Prior to administration of the bronchodilator, FEV<sub>1</sub> ranged from 0.52 to 2.74 liters, with a mean of 1.22 ± 0.51 L, the FEV<sub>1</sub> percentage ranged from 17% to 87%, with a mean value of 50.3% ± 16.5%, the mean

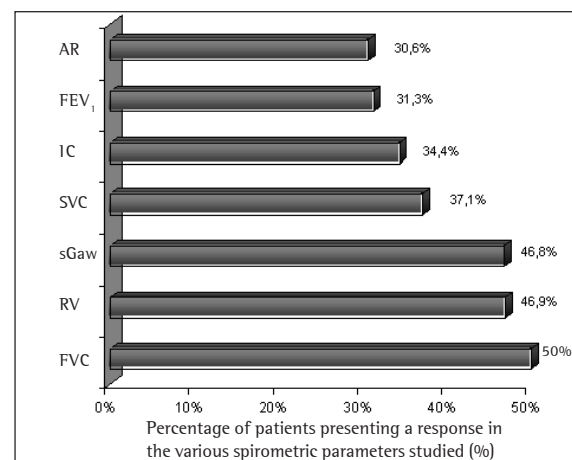


Figure 1 - Percentage of patients presenting a response in the various spirometric parameters studied in a sample of 64 patients with chronic obstructive pulmonary disease. AR: airway resistance; FEV1: forced expiratory volume in one second; IC: inspiratory capacity; SVC: slow vital capacity; sGaw: specific airway conductance; RV: residual volume; FVC: forced vital capacity

diffusing capacity for carbon monoxide was 74.2%  $\pm$  28.9%, and mean RV was 196.5%  $\pm$  73.5%.

After the administration of the bronchodilator, there were average increases of 6.3% in FEV<sub>1</sub>, 11.7% in FVC, 7.5% in SVC, 7.4% in IC and 10.4% in sGaw. There were mean decreases of 26.7% in RV and 85.2% in AR. For all parameters, the baseline means were significantly different from those obtained after the use of the bronchodilator.

There was significant FEV<sub>1</sub> response in 31.3% of the patients. Figure 1 shows the frequencies of response to the bronchodilator in each of the functional parameters studied.

Table 2 shows a comparison between the two groups. The percentage of response was significantly different between the groups for FVC ( $p < 0.001$ ), SVC ( $p = 0.002$ ) and AR ( $p = 0.023$ ).

There was no significant difference in FEV<sub>1</sub> between the groups regarding age ( $p = 0.103$ ) or smoking (mean pack-years;  $p = 0.969$ ). The frequency of symptoms (dyspnea, wheezing and chronic expectoration) was also similar in both groups.

In the group of patients presenting an FEV<sub>1</sub> response, the proportion of males was significantly higher (75% versus 14% in the group of patients presenting no FEV<sub>1</sub> response).

The patients were stratified into three groups according to the percentage of predicted FEV<sub>1</sub> in the pre-bronchodilator step: 19 patients (29.7%) presented an FEV<sub>1</sub> = 60% of predicted; 27 patients (42.2%) presented an FEV<sub>1</sub> between 40% and 59%

TABLE 2

Percentage of response in the various spirometric parameters in 64 patients with chronic obstructive pulmonary disease by FEV<sub>1</sub> response

Parameter	FEV <sub>1</sub> response (n = 20)	No FEV <sub>1</sub> response (n = 44)	P
FVC	90%	31,8%	< 0,001*
SVC	65%	23,8%	0,002*
IC	45%	35%	0,453
RV	55%	47,5%	0,584
AR	50%	21,4%	0,023*
sGaw	63,2%	38,1%	0,069

\*Statistically significant

FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; RV: residual volume; AR: airway resistance; sGaw: specific airway conductance

TABLE 3

Percentage of response in the various spirometric parameters studied in 64 patients with chronic obstructive pulmonary disease, separated by prebronchodilator FEV<sub>1</sub> percentage of predicted

	FEV <sub>1</sub> $\geq$ 60% (n = 18)	FEV <sub>1</sub> 40%-59% (n = 27)	FEV <sub>1</sub> < 40% (n = 19)	p
FEV <sub>1</sub>	16,7	37,0	36,8	0,289
FVC	22,2	59,3	63,2	0,020*
SVC	11,1	34,6	66,7	0,002*
IC	44,4	38,5	31,3	0,732
RV	38,9	50	62,5	0,389
AR	16,7	42,3	27,8	0,184
sGaw	38,9	57,7	35,3	0,275

\*Statistically significant

FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; RV: residual volume; AR: airway resistance; sGaw: specific airway conductance

of predicted; and 18 patients (28.1%) presented an FEV<sub>1</sub> < 40% of predicted.

We evaluated the percentage of FEV<sub>1</sub> response and response in the other parameters by group (Table 3). The percentages of FVC and SVC response differed among the groups. The patients with the most severe obstruction presented greater variations with the use of the bronchodilator.

Of the 59 patients studied, 53 (89.8%) presented a response in at least one of the parameters under study (Table 4). In the group of patients presenting

TABLE 4

Number of parameters in which a bronchodilator response was observed in the chronic obstructive pulmonary disease patients studied

Nº Parameters	Nº of Patients	% of Patientes
0	6	10,2
1	10	15,6
2	12	18,8
3	10	15,6
4	9	14,1
5	5	7,8
6	6	9,4
7	1	1,6
Total	59	100

Five patients were excluded from the study because they were unable to complete the maneuvers for all parameters

an FEV<sub>1</sub> response, 26% presented responses in 5 of the other parameters, 21% presented responses in 4 parameters, 26% in 3 parameters, 16% in 2 parameters, and 5% in only 1 parameter. In the group of patients presenting no FEV<sub>1</sub> response, 5% presented responses in 5 of the other parameters, 10% in 4 parameters, 17.5% in 3 parameters, 27.5% in 2 parameters, and 25% in only 1 parameter.

## DISCUSSION

There are few studies in the literature evaluating parameters other than FEV<sub>1</sub> in assessing COPD patient response to bronchodilators. In addition, there have been few prospective studies including only patients with COPD. Some authors have included asthmatic patients or performed retrospective studies in which the clinical diagnosis was uncertain. Furthermore, the criteria for defining response to bronchodilators have varied widely among studies, making it difficult to draw comparisons. In the present study, we opted to use the response criteria recommended by the SBPT.<sup>(18)</sup>

In our study sample, males presented significant greater FEV<sub>1</sub> responses. A possible explanation for this result is the fact that, prior to the use of the bronchodilator, mean FEV<sub>1</sub> percentage of predicted was lower among the males than among the females. Similar to other comparisons, and as reported in the literature, patients who presented lower spirometric values generally responded better to the bronchodilator in terms of static volumes,<sup>(6,15)</sup> as well as in FEV<sub>1</sub>, which is in accordance with the findings of another study.<sup>(24)</sup>

The other clinical aspects studied in the sample (smoking and patient-reported symptoms) were not found to correlate with the initial FEV<sub>1</sub>. Nor were there any differences regarding either of those aspects between the group of patients presenting an FEV<sub>1</sub> response and that of those presenting no such response. This is in contrast to the findings of some other authors concerning smoking and the FEV<sub>1</sub> response correlation with chronic expectoration and wheezing, which would reflect a more significant bronchial, nonparenchymal component in this group of patients.<sup>(25)</sup>

In our study sample, an FEV<sub>1</sub> response was seen in 31.3% of the patients, which is in accordance with the approximately 30% found in the literature.<sup>(2,22,26)</sup>

In the present study, more patients presented

an FVC response than any other type of response. An FVC response was observed in 90% of the patients presenting an FEV<sub>1</sub> response, whereas the FVC response was seen in only 31.8% of the patients presenting no FEV<sub>1</sub> response ( $p < 0.001$ ).

Similar to what occurred with FVC, there was statistically significant difference between the percentage of SVC response in the group of patients presenting an FEV<sub>1</sub> response (65%) and that seen in the group of patients presenting no FEV<sub>1</sub> response, with a variation of only 23.8% ( $p = 0.002$ ).

Both SVC and IC have been studied as the parameters that best correlate with response to a bronchodilator and improvement in exercise tolerance.<sup>(5,15,27)</sup>

Some authors have reported that patients with COPD develop progressive air trapping upon exertion without altering total lung capacity, presenting increased functional residual capacity and decreased IC.<sup>(28-29)</sup> By reducing this dynamic hyperinflation, bronchodilator use can increase IC and decrease the functional residual capacity. Recently, IC has been studied in the assessment of the performance of new medications in patients with COPD since IC better reflects reductions in hyperinflation than do other parameters.<sup>(30)</sup>

Some authors studied individuals with asthma and COPD in order to determine whether IC and parameters derived from the partial expiratory flow-volume curve detects response to a bronchodilator in patients who present no FEV<sub>1</sub> response.<sup>(16)</sup> Those same authors observed CI responses in 42% of the patients presenting FEV<sub>1</sub> responses and in 26% of the patients presenting no FEV<sub>1</sub> responses. In the present study, these values were 40% and 35%, respectively.

Ramsdell and Tisi studied 241 patients with obstructive disease in order to determine whether, even in the absence of a forced expiratory flow response, there could be changes in SVC and in static volumes.<sup>(11)</sup> The authors reported isolated volumetric response in 19% of the patients, isolated flow response in 20%, a combined response in 7% and no response to in 54%.

Another study involving 84 smokers with emphysema and presenting no FEV<sub>1</sub> response to bronchodilators was conducted. The best responses were, in descending order, in RV (in 61%), IC (in 44%), FVC (in 40%) and SVC (in 30%).<sup>(15)</sup> Although these values were different than those obtained in



the present study, the authors also found RV to be the best parameter in the group presenting no FEV<sub>1</sub> response (48% responding), followed by IC (35%), FVC (32%) and SVC (24%).

Another study investigated the lung volume response to a bronchodilator in 957 patients with pulmonary hyperinflation.<sup>(22)</sup> An FEV<sub>1</sub> response was seen in 33% of the patients with severe hyperinflation and in 26% of those with moderate hyperinflation. When response in any of the parameters was taken into consideration, 76% of the patients with moderate hyperinflation and 62% of those with severe hyperinflation presented responses. The findings in the present study were similar, with the exception of total lung capacity, which was excluded from our analysis because it was extremely inconsistent in a great number of patients and reduced in many others.

When we separated the patients into three groups by baseline FEV<sub>1</sub>, we found a higher response in vital capacity (both SVC and FVC) in the groups with lower baseline FEV<sub>1</sub> values (i.e. greater disease severity). It has been reported in other studies a higher response that patients with a higher degree of obstruction present greater responses, both in vital capacity and in static volumes.<sup>(14,22)</sup>

In the 1970s, the few available studies evaluating AR and sGaw reversibility habitually considered the assumed that, since these parameters presented higher sensitivity, they were indispensable for the assessment of reversibility.<sup>(1)</sup> Some authors concluded that was not true, and that expiratory flows would still be used as the main criteria for defining response to bronchodilators.<sup>(1,10)</sup>

According to some authors, determining AR through plethysmography is a better method of assessing response to a bronchodilator in patients with COPD than is oscillometry.<sup>(12)</sup> This finding is in contrast with that of a prior study, in which the superiority of the plethysmographic technique in assessing response to a bronchodilator in patients with COPD was not confirmed.<sup>(10)</sup> In another study involving patients with COPD, a good AR response was also reported, although it was suggested that AR should be used in conjunction with the determination of forced expiratory flow.<sup>(17)</sup>

In the present study, the percentage of patients presenting an AR response was lower than that seen for any other type of response. When all patients were assessed, the percentage of patients presenting

an AR response, although small, was almost equal to that of those presenting an FEV<sub>1</sub> response (30.6% versus 31.3%). In addition, when we compared the group of patients presenting an FEV<sub>1</sub> response with that of those presenting no FEV<sub>1</sub> response, AR was significantly higher in those presenting an FEV<sub>1</sub> response. However, the percentage of patients presenting a response in sGaw, which is the inverse parameter of resistance, was high (46.8%) in the present study, making it the parameter with the third highest percentage of response. When only the patients presenting no FEV<sub>1</sub> response were assessed, sGaw was the parameter with the second highest percentage of response: 38.1% of the patients. Some authors concluded that FEV<sub>1</sub> was superior to sGaw as an indicator of bronchodilator response.<sup>(1)</sup> However, in the present study, although the response in FEV<sub>1</sub> better correlated with the dose of the medication used (various doses of isoproterenol and fenoterol were tested), sGaw was the parameter with the best response in absolute numbers. These data partially correlated with the findings of the present study, in which sGaw was also found to vary widely in the group of patients presenting no FEV<sub>1</sub> response. This finding was confirmed in another study carried out in 1994, in which sGaw was the parameter with the least percentage variation in relation to the baseline value.<sup>(12)</sup>

When we analyzed the parameters in conjunction, we obtained a percentage of 89.9% of response in at least one parameter. However, for this analysis, 5 of the 64 patients were excluded, which caused a result bias, with an increase in the percentage of positive responses. Nevertheless, if we suppose that these 5 excluded patients would not respond to the bronchodilator, we would still obtain a percentage of response higher than 80%. It is important to highlight, however, that the use of multiple tests for the interpretation of abnormalities or functional variations increases the rate of false-positive results, which might have influenced the results in the present study.

In summation, analyzing our results and comparing them with results in the literature has led us to conclude that the 31.3% FEV<sub>1</sub> response seen in the present study was similar to that reported in the literature. In addition, a greater number of males presented an FEV<sub>1</sub> response. The parameter that more frequently presented variation after bronchodilator use was FVC, followed by RV, sGaw

and SVC. Among the patients presenting no FEV<sub>1</sub> response, more presented a response in RV, followed by sGaw, IC and SVC. The majority of the patients (89.8%) presented a response in at least one of the parameters tested, (89.8%) although only 31% presented an FEV<sub>1</sub> response. The study of IC, SVC, static volumes and AR/sGaw can improve the assessment of bronchodilator response considerably when these parameters are compared to the isolated analysis of expiratory flow.

In the present study, we demonstrated that there were responses to the bronchodilator in various functional parameters of patients with COPD. The clinical impression that, even without an FEV<sub>1</sub> response, patients may experience relief of dyspnea and present clinical improvement was corroborated by the results we obtained. Functional outcomes other than FEV<sub>1</sub> are useful in determining reversibility in COPD and must be used in order to more accurately assess the real extent of bronchodilator response in this patient population. This might have been a limitation of this study since clinical parameters were not included. We also consider the use of international prediction tables, as opposed to those that use equations based on the population in Brazil, a limitation of the study that might have influenced some results.

Another aspect that, to a certain extent, limited our ability to draw conclusions was that cutoff values used to identify significant variations in the bronchodilator response were based on those used in previous studies. These cutoff values are often arbitrary or extrapolated from values used for other parameters. Studies including normal individuals receiving placebos are necessary so that confidence intervals, and therefore cutoff values, can be defined. Such cutoff values would allow the accurate identification of significant responses to bronchodilators.

Although plethysmography is a more costly test and is inaccessible to many pulmonologists, its use may reveal bronchodilator response variations that are not found through simple spirometry. However, the results obtained herein suggest that, even when the plethysmographic technique is not feasible, special attention should be given to postbronchodilator variations in FVC, SVC and IC. Other alternatives that deserve further study are the use of the oscillometric technique for measuring AR and the helium dilution method for the determination of static lung volumes.

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