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ASSESSMENT OF BRONCHODILATOR RESPONSE THROUGH CHANGES IN LUNG VOLUMES IN CHRONIC AIRFLOW OBSTRUCTION

JUAN B. FIGUEROA-CASAS[1], ANA R. DIEZ[1, 2], MARIA P. RONDELLI[1, 2], MARCELO P. FIGUEROA-CASAS[2], JUAN C. FIGUEROA-CASAS[1, 2]

[1] *Departmento Medicina Respiratoria, Instituto Cardiovascular de Rosario;*
[2] *División Neumonología, Facultad de Ciencias Médicas, Universidad Nacional de Rosario*

Abstract Although FEV_1 improvement is routinely used to define bronchodilator (BD) response, it correlates poorly with clinical effects. Changes in lung volumes (LV) have shown better correlation with exercise tolerance and might be more sensitive to detect BD effects. We assessed the additional contribution of measuring LV before and after BD to detect acute improvement in lung function not demonstrated by FEV_1, and the influence of the response criteria selected on this contribution. We analyzed 98 spirometries and plethismographies performed pre and post BD in patients with airflow obstruction (FEV_1/FVC < 70%). BD response was defined for FEV_1 and FVC as per ATS guidelines and for other LV as $\Delta \geq 10\%$ of baseline ($\Delta \geq 5$ and $\geq 15\%$ were also analyzed). FEV_1 identified as responders 32% of patients. Greater proportions were uncovered by slow vital capacity (51%, $p<0.001$), inspiratory capacity (43%, $p<0.05$) and residual volume (54%, $p<0.001$). Slow spirometry identified 11% of responders additional to those detected by FEV_1 and FVC. Plethismography added 9% more. The magnitude of volume responses correlated with the degree of baseline hyperinflation. Percentages of responders varied greatly using different thresholds ($\Delta \geq 5$ and $\geq 15\%$). Mean change and proportions of responders for each LV varied significantly ($p<0.05$) whether change was expressed as percent of baseline or predicted values. A considerable proportion of patients with airflow obstruction shows acute response to bronchodilators identified by changes in lung volumes but not detected by an improvement in FEV_1. The selection of LV response criteria has important influence on the magnitude of this additional detection.

Key words: bronchodilator agents, lung volume measurements, COPD, pulmonary function tests

Resumen ***Evaluación de la respuesta a broncodilatadores a través de cambios en los volúmenes pulmonares en la obstrucción crónica al flujo aéreo.*** Si bien el aumento del VEF_1 es habitualmente utilizado para definir respuesta a broncodilatadores (BD), su correlación con efectos clínicos es pobre. Los cambios en volúmenes pulmonares (VP) han demostrado mejor correlación con tolerancia al ejercicio y podrían ser más sensibles para detectar efectos de los BD. Nosotros evaluamos la contribución adicional de medir VP antes y después de BD para detectar mejoría funcional aguda no demostrada por cambios del VEF_1 y la influencia del criterio de respuesta seleccionado en esta contribución. Se analizaron 98 espirometrías y pletismografías realizadas pre y post BD en pacientes con obstrucción al flujo aéreo (VEF_1/CVF < 70%). La respuesta a BD fue definida para VEF_1 y CVF según guías de la ATS, y para otros VP como $\Delta \geq 10\%$ del basal ($\Delta \geq 5$ y 15% fueron también analizados). El VEF_1 identificó como respondedores a 32% de los pacientes. Proporciones mayores fueron identificadas por capacidad vital lenta (51%, $p<0.001$), capacidad inspiratoria (43%, $p<0.05$) y volumen residual (54%, $p<0.001$). La espirometría lenta identificó 11% de respondedores adicionales a los detectados por VEF_1 y CVF. La pletismografía agregó 9% más. La magnitud de la respuesta de volumen se correlacionó con el grado de hiperinflación basal. El porcentaje de respondedores varió marcadamente usando diferentes criterios ($\Delta \geq 5$ y 15%). El cambio promedio y las proporciones de respondedores para cada VP variaron significativamente ($p<0.05$) según que el cambio fuese expresado como porcentaje del basal o del valor predicho. Una proporción considerable de pacientes con obstrucción al flujo aéreo presenta respuesta aguda a broncodilatadores identificada por cambios en volúmenes pulmonares pero no detectada por aumento del VEF_1. La selección de los criterios de respuesta tiene importante influencia en la magnitud de esta detección adicional.

Palabras clave: agentes broncodilatadores, medición de volúmenes pulmonares, EPOC, pruebas de función pulmonar

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Dirección postal: Dr. Juan C. Figueroa-Casas. Azcuénaga 8383, 2000 Rosario, Argentina
Fax: (54-341) 451-0708 e-mail: jcfigueroa@arnet.com.ar

The evaluation of patients with Chronic Obstructive Pulmonary Disease (COPD) includes pulmonary function tests before and after inhaling bronchodilators (BD). The usual criteria in daily practice to define acute functional response to BD is an increase in Forced Expiratory Volume in the first second (FEV_1) of 12 % of baseline and 200 ml.

However, FEV_1 measurement is affected by the influence of the preceding deep inspiration on airways caliber[1] and lung elastic recoil[2] (volume and time history). These factors may result in erroneous assessment of FEV_1 response induced by BD. It is also known that the change in FEV_1 post BD is a poor predictor of improvement in symptoms and exercise tolerance in patients with chronic airflow obstruction[3, 7]. For this reason, despite most COPD patients lack acute FEV_1 response to bronchodilators, these drugs are considered the mainstay of treatment for this disease[8].

As suggested by the initial work by Ramsdell[9], recent studies[10-12] have shown volume response to inhaled BD in COPD patients not responding by the customary FEV_1 measurement. However, criteria to define volume response have varied greatly among studies[9, 11-13]. In addition, several authors have demonstrated that indices of dyspnea and exercise tolerance correlate with changes in those lung volumes (LV) that reflect dynamic hyperinflation in COPD, better than they do with changes in FEV_1[14-17]. These findings have allowed to hypothesize that an improvement in LV after BD, even if not accompanied by an increment in FEV_1, might predict their clinical benefit[18, 19].

The aim of this study was to quantify the additional contribution of measuring different lung volumes before and after BD to detect acute improvement in lung function, by exposing changes not demonstrated by the traditional measurement of FEV_1. In addition, we studied the influence of using different criteria of volume response on the magnitude of that contribution.

Material and Methods

We undertook a retrospective analysis of all pulmonary function tests (PFT) performed at the Pulmonary Function Laboratory of our institution between 1996 and 2000. All those showing airflow obstruction during forced spirometry (FEV_1/ forced vital capacity < 70%) and also including plethismographic lung volumes measurements pre and post BD were selected.

All tests were performed in the sitting position, at baseline and 30 minutes after inhaling 200 mcg of salbutamol by metered dose inhaler. Spirometry was done with a Stead-Wells spirometer and static LV were measured with a body plethismograph, both from Collins Cybermedic (*Warren E. Collins, Inc., Braintree, USA*). The spirometric measurements were performed following American Thoracic Society (ATS) recommendations[20]. Lung volumes determinations were carried out with the technique described by Dubois[21]. The following parameters were recorded pre and post BD for analysis: FEV_1, forced vital capacity (FVC), slow vital capacity (SVC), inspiratory capacity (IC), total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV). Predicted normal values utilized were those from Morris et al[22] for FEV_1, FVC and SVC, Bates et al[23] for FRC and Goldman and Becklake[24] for RV. For TLC and IC derived predicted normals were used (SVC + RV and TLC - FRC respectively). The Carbon Monoxide Diffusing Capacity (DL_{CO}) was measu-red by the single breath method[25] applying predicted values published by Miller et al[26]. The diagnosis and clinical data provided by the referring physicians were recorded.

Bronchodilator response was defined, for FEV_1 and FVC, as an increase ≥ 12% of baseline value and 200 ml, according to ATS criteria[27]. For the remaining LV we defined a positive response as the presence of a change ≥10% (Δ≥10%) of the baseline value (increase for SVC and IC, decrease for FRC and RV). This threshold was selected as it is beyond the upper 95% confidence limit for the change in IC after inhaling placebo in COPD patients in a study by Pellegrino et al[28]. Nonetheless, due to the lack of widely accepted, standardized, criteria to define LV response to BD, we also analyzed two other possible response thresholds – Δ≥5% and Δ≥15% of baseline – which were assessed separately. Additionally, a response criteria of Δ≥10% of the predicted value was used in order to compare with the Δ≥10% of baseline value criteria.

Demographic data and functional parameters are expressed as mean and standard deviation. Differences between pre and post BD values were analyzed using paired Student's t test. This same test was applied to differences between the changes post BD expressed as % of baseline and those expressed as % of predicted values. Comparisons between the percentages of responders by each parameter and by different criteria for the same parameter were performed with the McNemar test. To assess possible correlation between functional parameters at baseline and their changes after BD the Pearson correlation coefficient was used. A p value < 0.05 was considered statistically significant.

Results

Ninety-eight PFT, all from different patients, were selected and analyzed. All patients were referred for evaluation of chronic airflow obstruction. Mean age was 61 ± 9.6 years. Seventy percent were male. Results of PFT before and after BD are shown in Table 1. All differences between pre and post values were significant ($p < 0.01$) except for FEV_1/FVC. Mean DL_{CO} was 65 (± 23.6)% of predicted.

Only 31 patients (32%) of the total met both criteria (increase in FEV_1 ≥ 12% of baseline and 200 ml) to be classified as responders by this sole measurement. FVC detected 43% as responders. Considering Δ≥10% of baseline as the response criteria, SVC identified 51% of patients as responders, IC 43%, FRC 32% and RV 54% (Figure 1). SVC, IC and RV detected a significantly higher number of responders than FEV_1 for the criteria of Δ≥5 and Δ≥10% (Figure 1).

Considering a Δ≥12% and 200 ml for FVC and Δ≥10% of baseline for static LV, 71 patients (72%) showed improvement in at least one LV. Grouping the measu-

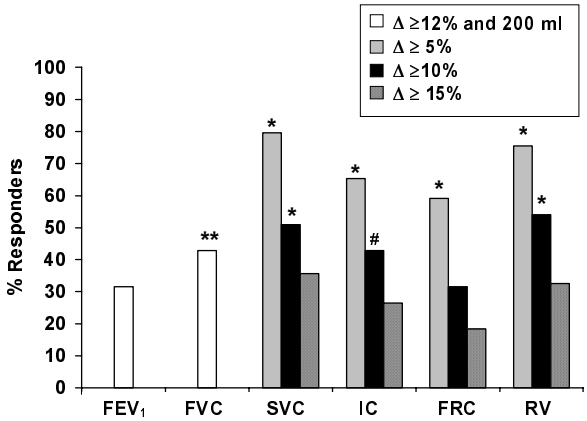

Fig. 1.– Proportion of responders in each parameter for the 3 possible volume response criteria (Δ≥5%, Δ≥10% and Δ≥15% of baseline). For FEV_1 and FVC the criteria is always increase ≥ 12% and 200 ml of baseline. Comparisons against FEV_1: *p≤0.001, # p<0.05, **p= 0.05.

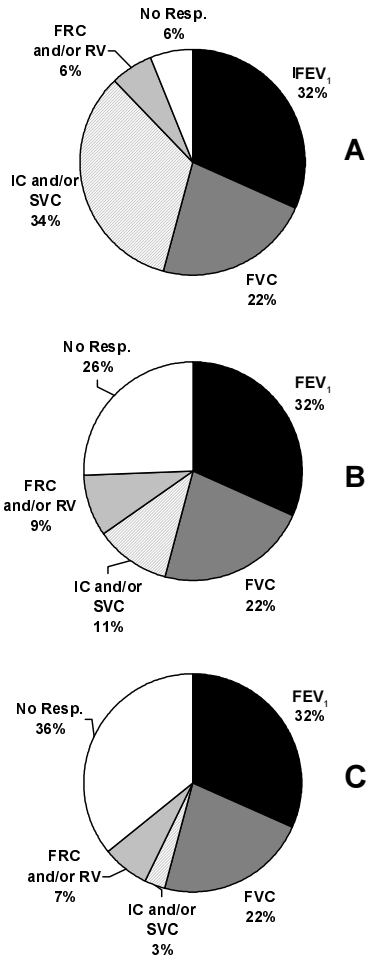

Fig. 2.– Percentages of additional responders detected by applying LV measurements in a stepwise manner for the 3 possible volume response criteria: A: Δ≥5%, B: Δ≥10% and C: Δ≥15%. For FEV_1 and FVC the criteria is always increase ≥ 12% and 200 ml of baseline. See text for details.

rements by maneuvers of different cost and complexity - as performed in clinical practice-forced spirometry (FEV_1+ FVC) revealed 54% of positive responses, slow spirometry (SVC + IC) 56% and plethismography (FRC + RV) 55%.

The percentages of responders that FVC, slow spirometry and plethismography added in a stepwise manner to that detected by FEV_1 are depicted in Figure 2. FVC added 22 % of responders to those identified by the FEV_1. For the criteria of Δ≥10% (Figure 2 B), LV measured by slow spirometry (SVC and/or IC) incorporated 11% of responders not identified by forced spirometry (FEV_1 and/or FVC). In turn, the plethismographic measurements (FRC and/or RV) detected an additional 9% not picked up by changes in either forced or slow spirometry.

The proportion of responders varied considerably according to the response criteria selected (Figures 1 and 2), obviously reaching the highest values with the lower threshold (Δ≥5%) and viceversa (Figure 2 A and 2 C). In addition, a significant difference was found when comparing the mean change obtained after BD for each parameter expressed as % of the baseline value versus the same change expressed as % of the predicted value. LV usually diminished in COPD (FVC, SVC, IC) showed a lower %Δ using as reference the predicted value. The opposite happened for LV usually increased in this disease (FRC, RV) (Table 1). The percentage of responders for each LV, except TLC, was significantly different applying the Δ≥10% of baseline criteria vs. the Δ≥10% of predicted one (Figure 3).

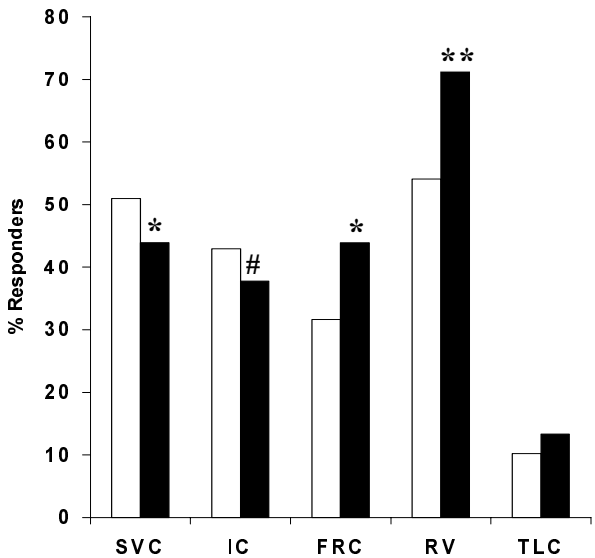

Fig. 3.– Comparisons of percentages of responders for each LV using criteria of Δ≥10% of baseline (□ white bars) vs Δ≥10% of predicted value (■ black bars). # p < 0.05, * p < 0.01, **p < 0.001.

TABLE 1.– *Functional parameters pre and post bronchodilators**

Parameter	Pre BD % predicted absolute value (L)	Post BD** % predicted absolute value (L)	Δ% of basal	Δ% of predIcted#	Δ absolute (L)
FEV_1	50 ± 24.6	55.3 ± 26.1	12.6 ± 14.7	5.3 ± 5.4	0.14 ± 0.14
	1.35 ± 0.70	1.49 ± 0.74			
FVC	77.3 ± 20.5	85.5 ± 19.5	12.5 ± 14.6	8.2 ± 8.4	0.31 ± 0.31
	2.94 ± 0.94	3.26 ± 0.92			
SVC	79.3 ± 21.1	89.3 ± 19.3	13.1 ± 13.2	9.3 ± 8.3	0.34 ± 0.30
	3.06 ± 0.94	3.40 ± 0.93			
IC	81.3 ± 22.8	87.8 ± 22.2	9.5 ± 13	6.5 ± 8.7	0.16 ± 0.22
	2.10 ± 0.67	2.26 ± 0.65			
TLC	120.9 ± 17.6	118.8 ± 16.8	– 1.6 ± 5.6	– 2.3 ± 7.3	– 0.13 ± 0.41
	7.12 ± 1.52	6.99 ± 1.46			
FRC	152.1 ± 36.5	142.1 ± 32.5	– 5.6 ± 8.7	– 9.4 ± 14.7	– 0.3 ± 0.45
	5.02 ± 1.45	4.72 ± 1.35			
RV	197.1 ± 57.7	173.5 ± 47.4	– 10.8 ± 11.8	– 23.6 ± 28.3	– 0.47 ± 0.54
	4.06 ± 1.31	3.59 ± 1.15			
FEV_1/FVC	44.5 ± 13.5	45 ± 14.8	0.7 ± 9.4		0.49 ± 4.1

** as mean ± SD*
*** p<0.01 for all comparisons vs pre BD, except for FEV_1–/FVC (p=0.24)*
 # p<0.0001 for all comparisons vs Δ% basal, except for TLC (p=0.004)

TABLE 2.– *Correlation coefficients between changes in LV post BD and baseline values of FEV_1, RV and FRC*

ΔLV**	FEV_1*		RV*		FRC*	
	r	p	r	p	r	p
ΔFVC	– 0.460	< 0.001	0.507	< 0.001	0.431	< 0.001
ΔSVC	– 0.415	< 0.001	0.565	< 0.001	0.471	< 0.001
ΔIC	– 0.377	< 0.001	0.442	< 0.001	0.404	< 0.001
ΔFRC	0.140	NS	– 0.343	< 0.001	– 0.293	< 0.005
ΔRV	– 0.085	NS	– 0.333	< 0.001	– 0.232	< 0.025

** baseline value as % predicted*
*** change post BD expressed as % of baseline*
NS: non significant

The degree of hyperinflation, assessed by baseline values of FRC and RV (% of predicted), correlated significantly with the Δ post BD (as % of baseline) in all LV. The severity of airflow obstruction, defined by baseline FEV_1 (% predicted), correlated with the change in FVC, SVC and IC (Table 2). A significant correlation was also found between ΔIC and ΔFRC (r=-0.47, p<0.001) as well as between ΔSVC and ΔRV (r = -0.52, p<0.001).

Discussion

This study confirms that the measurement of lung volumes before and after bronchodilators, in patients with airflow obstruction, identifies a considerable proportion with acute response to BD not detected by the traditional measu-rement of FEV_1. This volume response is greater as higher degrees of hyperinflation are present. As novel findings, this study quantifies the potential contribution of applying these tests in clinical practice. Secondly, it points out marked differences in the proportion of responders depending on the threshold selected to define a positive response as well as on the reference values chosen to calculate the percentage change. This supports the need for better defined criteria to standardize the test and compare results.

Our findings are in agreement with prior studies that showed significant changes in different LV after inhaling

BD without a similar change in FEV_1[9-12, 17, 18, 29, 30] stressing the importance of considering them as a positive response to BD. Several studies also found that, unlike FEV_1, the increase in IC post BD correlated with improvement in dyspnea and exercise tolerance[17-19, 30]. This suggests lesser dynamic hyperinflation on exertion and might give this parameter ability to predict a beneficial effect of long term BD treatment[18, 19]. A recent study by Corsico *et al.*[31], however, questions this concept by finding BD response on resting lung function not predictive of its benefits on exercise tolerance.

The response in FVC added a considerable amount of responders (22%) to the FEV_1 criteria, being evaluated in the same spirometric maneuver. Although ATS recommendations[27] include this measurement to define BD response, it is often not considered in daily PFT interpretation neither in clinical trials that define FEV_1 response to BD as the sole functional parameter of improvement or inclusion/exclusion criteria.

The change found after BD in SVC, IC, FRC and RV also added a considerable percentage of responders to those already identified by FEV_1 and/or FVC (Figure 2). SVC and IC summed up 11% of our patients as responders, while FRC and RV added 9% more not detected by both forced and slow spirometry (assuming as valid a $\Delta \geq 10\%$ of baseline criteria). The correlation found in our study between the magnitude of change in LV and the baseline values of FRC and RV (the greater the hyperinflation, the greater the change post BD) was also observed by O'Donnell *et al.*[11]. It also agrees with other reports showing an increase in IC post BD only in those patients exhibiting tidal expiratory flow limitation at rest, who tended to have more airflow obstruction ($<FEV_1$) and hyperinflation (> FRC)[10, 19, 32]. These findings indicate that measuring LV pre and post BD, at least those given by a simple slow spirometry, adds useful information for those patients with more severe airflow obstruction.

Our study stresses that the magnitude of the additional contribution provided by LV changes depends upon the threshold selected to define volume response. In our results, the percentage of responders –additional to the 32 % detected by FEV_1-ranged from 32 to 62% for the response criteria of $\Delta \geq 15\%$ and $\Delta \geq 5\%$ of baseline respectively (Figure 2). Any of these thresholds might be considered as arbitrary since there are no currently accepted ones to define volume response, except for FVC. The original measurements of FRC reported by Dubois et al.[21] had a variability (2 SD) of 3.7 to 5.6% of the mean. Holmes *et al.* found, administering BD to 5 normal subjects, a maximal change of –9.3% of baseline for RV and of lesser magnitude for FRC and TLC[33]. Other studies have used changes as distant as 4 and 15% of baseline to define volume response[28, 29]. For IC, a change of 10% of basal was considered significant analyzing its variability pre and post inhalation of placebo[28].

Furthermore, whether the change in LV is expressed as a percentage of the predicted or baseline value is most important to define LV response. As shown in our results, the mean change in LV as well as the proportion of responders for each LV were significantly different depending on the reference value used. A change ≥10 % of the predicted value has been considered a clinically meaningful variation[18]. In a recent study in COPD patients O´Donnell et al[11] found LV response in a higher percentage than we did, especially for RV and FRC. These differences might be due to the greater airflow obstruction (FEV_1 < 50%) of their group and, more importantly, to their use of a change ≥10% of the predicted value instead of the baseline value (in a more recent paper[12] the same author utilized a threshold of ≥ 20% of predicted to define response in some volumes). The use of the % of predicted is questionable as it may overestimate the number of responders for those volumes usually increased in COPD (RV, FRC) (it means a much lower threshold than the one resulting from the use of the % of baseline) and underestimate it for those volumes usually diminished (VC, IC). The opposite could happen using the % of baseline value. As illustration, for a patient with a basal RV of 200% of predicted (close to the mean basal RV of our sample) a reduction of 10% of predicted would mean a change of only 5% of the baseline measurement. In addition, it may be debatable whether using the same % of change for every volume is the most appropriate. These uncertainties, along with the significant differences we found in the proportion of responders depending on the various thresholds applied, emphasize the need for further studies designed to establish well defined response criteria for each volume.

Like Newton[12] and O'Donnell[11], we noticed a small but statistically significant mean decrease in TLC post BD. Earlier studies found similar results in few asthmatics[33], but not in COPD patients[10, 14]. A physiological explanation for a change like this remains unclear. The correlations found between ΔIC and ΔFRC as well as between ΔSVC and ΔFRC are consistent with the complementary changes in volumes expected to occur with decrease in air trapping following inhalation of BD.

Limitations of our study include its retrospective nature. Since our laboratory routinely performs PFT following the same protocol, we doubt that a prospective design would have substantially modified the results. The lack of symptom assessment after BD does not allow to correlate clinical improvement and LV changes. Additionally, although our group may have included some patients with asthma, the conclusions regarding the effects of BD on LV are equally valid for this condition.

In summary, this study indicates that a considerable proportion of patients with airflow obstruction shows acute response to bronchodilators identified by changes in lung volumes not detected by the traditional change in FEV_1.

More research is needed to define widely accepted criteria of volume response to BD. It will also be of interest to confirm in prospective studies whether the acute response in LV can predict clinical improvement, essentially dyspnea and exercise tolerance, with regular long-term administration of bronchodilators.

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