The Effect of Inhaled Salbutamol on Residual Capacity in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: It is now hypothesized that anti-asthmatic agents such as bronchodilators can reduce residual capacity and Residual Volume (RV) along with inducing no change in Total Lung Capacity (TLC). In the present study, an attempt was made to assess RV following administration of salbutamol inhaled in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods: This prospective interventional case series was conducted on 119 patients with COPD who referred to Rasoul-e-Akram Hospital in Tehran, Iran in 2015. At the beginning of the study, the patients were assessed using spirometer and plethysmograph (BodyBox) and RV was measured. Then, inhaled 400 μg salbutamol (Four puffs) was administered and the RV, TLC and the ratio of RV to TLC (RV/TLC) was measured again 15 min later.

Results: Regarding the change in parameters of lung volumes after salbutamol administration, although Forced Expiratory Volume in one second (FEV_1) and FEV_1/FVC (Forced Vital Capacity-FVC) ratio is significantly increased, the deduction of RV and TLC would be much more. RV decreased from 217.02±123.72% before intervention to 167.50±30.91% after that (p<0.001). There was also no difference between men and women in the change of RV (142.99±52.30% *vs.* 37.78±36.99%, p=0.37). Compared to smokers, nonsmokers had experienced more reduction in RV (142.50±60.06% *vs.* 57.79±11.20% p=0.01). The change in RV was adversely associated with age. There was no relation between COPD severity and the change in RV and also RV to TLC.

Conclusion: The use of salbutamol inhaled in COPD patients even 15 min after administration leads to significant decrease in RV and RV to TLC ratio even more than increment in FEV_1 and FEV_1/FVC ratio.

Keywords: Bronchodilator agents, Chronic obstructive pulmonary disease, Pulmonary disease, Residual volume, Salbutamol, Total lung capacity

Introduction

The presence of persistent and progressive airflow obstruction is the main characteristic of Chronic Obstructive Pulmonary Disease (COPD). In development of expiratory airflow limitation in COPD condition, the end expiratory lung volume should be raised to permit a higher expiratory flow rate (Dynamic hyperinflation) as well as stop exercising quickly that are manifested as dynamic hyperinflation and euvolumic responses (1,2). The potential consequences of these responses include limitation of exercise tolerance as well as breathlessness. In previous studies, it has been revealed that short-acting bronchodilators may relieve breathlessness and reduce exercise intolerance (3,4). However, the beneficial change in spirometric parameters following bronchodilator therapy is remained uncertain (5). In this regard, it seems that the reduction in end expiratory lung volume in both rest and exercise can be done after prescribing short acting inhaled drugs leading to reduction of dyspnea (6). In other word, treatment with bronchodilators can reduce chest wall volumes, improve lung function, as well as improve exercise capacity in COPD patients (7). Investigators in their study sought to better characterize the response of Residual Volume (RV) and Total Lung Capacity (TLC) to bronchodilators. They retrospectively assessed pulmonary function tests of 965 subjects with obstructive lung disease. They reported that reduced RV weakly correlated with response to ForcedExpiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC). TLC had no significant association with either FEV1 or FVC. They concluded finding patients whose RVs improve in response to bronchodilators represents an important subgroup of those with obstructive lung disease. The identification of this subgroup better characterizes the heterogeneity of obstructive lung disease (8).

It was believed that response to bronchodilator more than 12% and 200 *ml* is in favor of asthma diagnosis but nowadays we know that about 15 to 20% of COPD patients have significant response to bronchodilator in spirometry and it is a well-known fact that a percentage of patients with chronic severe asthma have persistent airflow obstruction and they do not respond to bronchodilator. Therefore, using only post bronchodilator response could lead to misdiagnosis of asthma and COPD patients (9).

To date, the response of lung volumes including inspiratory capacity to inhaled bronchodilators remains unclear. It has been now hypothesized that anti-asthmatic agents such as both short and long-acting-agonist drugs can also reduce Residual Capacity (RC) and RV along with inducing no change in TLC (8,10,11). In the present study, an attempt was made to measure RV following administration of salbutamol inhaled in patients with COPD.

Material and Methods

A prospective study was performed for assessment of pulmonary function test among 119 COPD patients between July 2015 and January 2016 at respiratory clinic of Rasoul-e-Akram Hospital, Tehran, Iran. Patients with 18–79 years of age with an FEV1/FVC less than the lower limit of normal (FEV1<70%) based on the National Health and Nutrition Education Survey (NHANES) III were included in the study (12). According to convenience sampling method, all patients who met study criteria during study period were considered for investigation. Study participants had no history of using bronchodilators within the previous 12 hrs and those with history of simultaneous pulmonary disorders were excluded from the study population. Smokers were defined as patients who had smoked at least 100 cigarettes in their life time without paying attention to their smoking status. It means that at the time of interview, they could be current smoker or former smoker. Next, patients were classified as those who had never smoked or smoked lower than 100 cigarettes in their life labelled as non-smoker patients. COPD in non-smoker patients usually occurred by some factors:

- occupational exposures such as farming, carpet weaving, bread baking, indoor air pollution (Specially in female COPD patients)
- passive exposure to smokers
- air pollution
- low socioeconomic status
- Alpha-1 antitrypsin deficiency

In passive smokers, infections of respiratory ducts, increased susceptibility of airway cells and occupational factors were reported as COPD causes.

The baseline characteristics of study participants including age, sex, past medical history and physical examination data were collected by interview and recorded into the study checklist.

At the beginning of the study, researchers described the study purpose and procedures for the participants and then according to the 2005 American Thoracic Society and European Respiratory Society (ATS/ERS) recommendations, spirometer (JAEGER, Germany) and plethysmograph were used. As the study intervention, 400 μg (Four puffs) inhaled salbutamol was administered for participants and RV was reassessed 15 min later with previous devices. FEV1 was used for determination of COPD severity among participants and patients who had FEV1 higher than 80% of the predicted value were categorized as mild (Stage I), those between 50 and 80% as moderate (Stage II) and those between 30 and 50% as severe (Stage III) and finally, patients who had FEV1 less than 30% of predicted value were categorized as very severe type (Stage IV) group.

Statistical analysis

Study data were entered into the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for analysis. For descriptive analysis, mean and standard deviation for quantitative and frequency and percentages for qualitative variables were used. Students t-test for comparing continuous variables between study groups and the chi-square test (or Fisher's exact test if required) for the categorical variables were applied as well. Changes in RV after using salbutamol compared to before using it were assessed using the paired t test. All statistical analysis results with the $p<0.05$ were assumed as significant.

Results

Finally, 119 (95 men) COPD patients were assessed. Mean of age were 66.35±10.01 years. Mean of height and weight among study participants were 164.70±8.76 cm and 68.88±15.52 *kg* respectively. Mean of Body Mass Index (BMI) was 25.32±5.09 kg/m^2. Mean Body Surface Area (BSA) of study participants was 1.75 ± 0.21 *m2* (Table 1). In total, 76.5% were smoker (82.1% in men and 54.2% in women, ($p=0.004$). After inhalation of salbutamol spray as study intervention, FEV_1 and FEV_1/FVC ratio significantly increased in comparison with the study's beginning stages before the intervention. Contrary to that, mean of RV (217.02±123.72% *vs.* 167.50 ± 30.91%; $p<0.001$) and TLC significantly decreased after study intervention. More details about these comparisons are presented in table 2.

The difference between FEV_1 level before and after study intervention was similar among men and women (8.18±5.80% *vs.* 6.92±5.29%; $p=0.33$). Mean of increase in FEV1/FVC ratio was significantly higher among men in comparison with women (5.37±2.14% *vs.* 5.34±0.86%; $p=0.02$). RV difference between men and women was not significant (142.99%±2.30% *vs.* 37.78±36.99%; $p=0.37$). The same non-significant difference was seen in RV to TLC ratio between men and women (25.62±18.55% *vs.* 17.04±12.83%; $p=0.70$). Although the changes in FEV_1 was not related to smoking, the increase of FEV_1/FVC ratio among

Table 1. The anthropometric data

	Sex	N	Mean	Std. deviation	Std. error mean
Age (year)	M	95	66.36	10.411	1.068
	F	24	66.33	8.453	1.725
Weight (*kg*)	M	95	68.41	19.017	1.951
	F	24	67.92	19.724	4.026
Height (*cm*)	M	95	167.58	6.131	0.629
	F	24	157.21	5.397	1.102
BSA	M	95	1.77	0.205	0.021
	F	24	1.67	0.227	0.046

Table 2. The change in lung capacities after administration of salbutamol

Parameter	Before intervention	After intervention	p-value
FEV_1 (%)	47.24 ± 16.13	55.17 ± 18.95	< 0.001
FEV_1/FVC (%)	57.79 ± 10.05	59.33 ± 11.73	0.002
RV (%)	217.02 ± 123.72	167.50 ± 61.06	< 0.001
RV/TLC (%)	170.52 ± 27.62	152.24 ± 30.91	< 0.001

smoker participants was significantly lower than nonsmokers (5.34±0.92% *vs.* 5.32±3.56%; p=0.03).

Non-smokers in comparison with smokers had significantly higher decline in RV (142.50±60.6% *vs.* 57.79±11.20%; p=0.01). The same significant difference was seen in RV to TLC ratio between non-smoker and smoker participants (25.35±20.18% *vs.* 15.36±11.36%; p=0.03).

Regarding association between lung parameters and baseline characteristics, the change in FEV_1/FVC after using salbutamol was positively associated with patients' age and height. The change in RV was adversely associated with age (r=-0.192, p=0.04). Among all of COPD patients, 1.7% had mild COPD, 36.1% had moderate COPD, 45.4% had severe COPD, and 16.8% had very severe COPD. Those patients with more severe COPD experienced lower change in FEV_1 and FEV1/FVC ratio, but there was no relation between COPD severity and the change in RV and also RV to TLC. Considering at least 15% changes in RV as the significant difference, the change in RV was considered significant in 51.3% of cases (Table 3).

Discussion

Almost all previous studies on effects of bronchodilators such as salbutamol on lung volumes have emphasized these effects on RV and TLC; however, these changes have been examined in long-term administration of these drugs. This study shows that salbutamol administration even after 15 min, causes much more significant reduction of RV and RV/TLC ratio, in comparison to the significant increase in FEV_1 and FEV_1/FVC. In fact, short time after using bronchodilator, the significant change in all lung volume and thus lung capacities were shown indicating effectiveness of bronchodilators on improving lung capacity, even after a 15 *min* of using inhaled bronchodilator. These changes can be due to decrease in bronchial muscle contraction, reduction in inflammation process in airways, and also reduction in pulmonary vascular resistance.

Some similar findings have been reported in previous observations. Tantucci et al., after bronchodilator administration, reported that the patients exhibited a significant decrease in RC associated with an increase in inspiratory capacity (13). In another study by Newton et al., salbutamol significantly reduced the mean TLC, FRC and RV and increased both the IC and FVC, but FEV_1 improved in a minority of patients (14). Alvirety et al. indicated that salbutamol increased FEV_1, FVC and inspiratory capacity and reduced Functional Residual Capacity (FRC) and RV significantly (15). Balestra et al. also indicated that except for TLC, all parameters including RV, vital capacity, forced inspiratory vital capacity, FVC, Forced Expiratory Volume in one second FEV_1 and the FEV_1/VC ratio showed statistically significant changes after bronchodilation (16). In total, acute change following administration of lung capacities especially reduction of RC is expected that help to improve vascular and bronchial lung beds in COPD patients.

O'Donnell *et al* reported that in hyperinflated chronic obstructive pulmonary disease patients, small bronchodilator-induced increases in resting and inspiratory capacity during exercise allow greater tidal volume expansion and ventilation with less respiratory discomfort while operating within the fixed mechanical constraints of a markedly diminished inspiratory reserve volume. They concluded that small changes in resting inspiratory capacity after bronchodilator can predict

Table 3. The correlation between baseline characteristics and change in lung volumes

		DIFF. FEV_1	DIFF. FEV_1.FVC	DIFF. RV	DIFF. RV.TLC
Age (year)	r	0.167	0.196*	-0.192*	0.154
	p-value	0.072	0.032	0.039	0.099
Weight (*kg*)	r	0.022	-0.008	-0.026	-0.139
	p-value	0.818	0.933	0.784	0.138
Height (*cm*)	r	-0.122	0.266**	0.005	-0.081
	p-value	0.190	0.003	0.957	0.389
BSA	r	0.029	0.068	-0.031	-0.182
	p-value	0.755	0.463	0.740	0.051

important clinical outcomes (6). Dellaca et al. in their study reported that bronchodilators have complex effects on lung mechanics in COPD, and expiratory flow limitation affects both this and the response of some respiratory variables to treatment (17). McCartney et al. reported that generally RV was nonresponsive to bronchodilators based on spirometry. Improvement in RV in their study was shown only among subgroup of patients with obstructive lung disease (18).

There are some COPD patients who have considerable improvement in their symptoms and signs and exercise tolerance after optimal treatment, but their spirometry is not improved as well, because spirometry is not sensitive enough to determine air trapping. The treatment response can be evaluated in these patients by plethysmography and significant decline in RV and RV/TLC indicates good response to treatment and decrease in air trapping. On the other hand, there are some symptomatic patients with acceptable spirometry, while their RV and RV/TLC are increased. In these patients, Body Box can be used for early diagnosis of COPD.

Conclusion

Our study findings showed that after bronchodilator administration, the decline in RV and RV/TLC ratio in COPD patients were higher than the increase in FEV1 and FEV1/FVC. This finding might be helpful in early diagnosis of COPD in patients who have risk factors for obstructive lung disease and assessment of therapeutic response in COPD patients.

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