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Spirometric indices after bronchodilator tests in patients with various spirometric patterns

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Abstract : ***Background:*** *Spirometry tests after bronchodilator administration are used to evaluate the reversibility of airway obstructions and to determine degree of the response to the bronchodilator. However, the frequencies of bronchodilator responses in non-obstructive spirometry patterns have been assessed in few studies.* ***Patients and Methods:*** *one hundred thirty three subjects with respiratory symptoms who underwent reversibility spirometry were enrolled in this study. The data were analyzed retrospectively. The subjects were grouped into two categories of obstructive and non-obstructive (the non-obstructive group was further classified into normal, restrictive, and mixed subgroups) patterns based on the baseline ratio of forced expiratory volume in the first second to the vital capacity (FEV1/VC ratio) and the vital capacity (VC). The responder and non-responder subjects were stratified according to the FEV_1 response to bronchodilator* ***Results:*** *Of the 133 patients, the numbers of subjects with normal, obstructive, restrictive, and mixed patterns were 61, 51, 16, and 5, respectively. The frequency of positive response was highest among the obstructive cases (49%) followed by the mixed (40%) and restrictive (25%) patterns. The patients with normal spirometry patterns exhibited the lowest frequency (14.8%). All of the parameters increased following bronchodilator administration.* ***Conclusions****: Restrictive and mixed spirometry pattern also exhibit positive bronchodilator responses in some patients with respiratory symptoms. The bronchodilator reversibility test should not be ignored for patients exhibiting these patterns.*

Keywords: *bronchodilator, non-obstructive, respiratory symptom, spirometry*

I. Introduction

Spirometry is used to measure forced expiratory flow rates and volumes. It is the most commonly used pulmonary function test and is useful in the evaluation of patients with respiratory symptoms (e.g., dyspnea, coughing, and wheezing) or risk factors for respiratory disease. [1] Spirometry is typically used to detect, confirm, and monitor obstructive airway diseases. [2-5] An obstructive pattern is defined by a forced expiratory volume in the 1st second divided by the forced vital capacity - FEV1/FVC- below the lower limit of normal (LLN). A restrictive pattern is defined by a FVC < LLN and a FEV1/FVC > LLN, and a mixed pattern is defined as a FVC < LLN and a FEV1/FVC < LLN. [6]

Commonly, an inhaled bronchodilator (BD) is used by pulmonary function laboratories to determine whether a reversible airflow limitation is present. Spirometry measurements before (Pre-BD) and after (Post-BD) short-acting bronchodilator administration are recommended for the diagnosis of asthma and chronic obstructive pulmonary disease (COPD). [7]

Among the various spirometric parameters that are used to identify the bronchodilator response, FEV_1, FVC, forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$) and forced expiratory flow at 50% ($FEF_{50\%}$) are the most widely used. [8] FEV1 has been shown to be the best spirometric variable in terms of statistical power and reproducibility. [9, 10] A positive bronchodilator response is established based on an increase of $\geq$ 12% and 200 mL in FVC and/or FEV_1 compared with the baseline values following the administration of a bronchodilator. [11] Some studies have proposed at least a 30% increase in $FEF_{50\%}$ or $FEF_{25-75\%}$ as the criterion for responsiveness to a bronchodilator. [8, 12]

Patients may exhibit normal spirometry results between attacks. In some patients, the FVC may be reduced due to air trapping, which results in pseudo-restriction upon spirometry in the presence of increased or normal total lung capacity (TLC), increased functional residual capacity (FRC) and increased residual volume (RV). [13] Therefore, many clinicians routinely order pre- and post-bronchodilator testing, regardless of the pre-bronchodilator results, although the addition of a bronchodilator substantially increases time and expense. [14]

There are no available data concerning the evaluation of the bronchodilator responses of patients with non-obstructive (including normal, restrictive and mixed) spirometry patterns in Sulaymaniyah city.

The aims of this study were to assess the increases in spirometric parameters after bronchodilator administration in patients with respiratory symptoms regardless of their spirometric patterns and to elucidate the frequencies of responses of patients with non-obstructive patterns (i.e., patients in the normal, restrictive and

mixed groups) and comparing the mean changes in the parameters between the cases that were and were not responsive to the administration of a bronchodilator.

II. Methods

2.1 Test performance

This study was conducted at the pulmonary function laboratory of the Sulaymaniyah General Teaching Hospital using an Erich JAEGER GmbH, Wuerzburg, Germany MasterScreen™ PFT System device. The instruments were maintained according to the manufacturer's recommendations which included daily calibration with a 3-L syringe.

The patients were tested in standard conditions (i.e., in a sitting position, in the morning, at body temperature and pressure saturated; BTPS) using nose clips. Informed consent was obtained from each of the patients. Histories of respiratory symptoms and anthropometric parameters (i.e., gender, age, and body mass index (BMI, kg/m^2)) were recorded.

Post-bronchodilator spirometry was performed when requested by the ordering physician. For the testing of the bronchodilator responses, 5 mg of nebulized salbutamol (after dilution in distilled water at 1:3) was inhaled through a nebulizer device (PulmoStar DEVILBISS), and the patient breathed through a facial mask for 10 minutes. Post-bronchodilator spirometry was performed 15 min after salbutamol administration. All tests were examined in terms of the ATS/ERS acceptability and repeatability criteria. [15] Specifically, the test criteria included a satisfactory start of the test criteria (a back extrapolated volume < 0.150 L or 5% of the FVC), a satisfactory end of the test criteria (forced exhalation time ≥ 6 seconds or a plateau in the volume-time curve without early termination of expiration and without glottis closure) and adequate repeatability as defined by the highest and next highest FVC and FEV1 measures being within 150 mL of each other. Test that did not meet the acceptability and repeatability criteria were excluded.

2.2 Test subjects

All of the data (i.e., pre- and post-BD spirometry results and patient histories) from the subjects who were referred to the Pulmonary Function Laboratory of the Sulaymaniyah General Teaching Hospital from May 2013 to January 2015 were collected and retrospectively analyzed. The subjects with respiratory symptoms (i.e., shortness of breath, coughing, or wheezing) who were subjected to reversibility tests that were performed by the referring physician's orders were included regardless of the spirometry pattern. Subjects with tests that did not meet the ATS/ERS criteria and subjects below the age of 18 years were excluded from the study. Ultimately, 133 patients were enrolled in the study. The study was been approved by local research ethics committee of the Medical Faculty of Sulaimani University.

2.3 Bronchodilator reversibility

A FEV_1/FVC ratio below the 5th percentile of the predicted value was regarded as an obstructive spirometry pattern. The ERG/ERS reference equation was used to calculate the predicted value. [16]

In addition to FEV_1 as an index of bronchodilator responsiveness (absolute change from the pre-bronchodilator value in mL and the percentage change relative to pre-bronchodilator value), other spirometric indices (i.e., PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$ and VC) were computed and compared.

According to the response to the bronchodilator (response was defined by a ≥ 200 mL and 12% increase in FEV1), the selected subjects were divided into the following spirometry pattern groups: obstructive, normal, restrictive, and mixed. Furthermore, the subjects were divided into responders and non-responders. Body plethysmography was not performed to confirm the restrictive respiratory patterns due to limitations. We were only able to use spirometric indices (FVC, VC and FEV_1/ VC or FVC; whichever was greater) to identify the subjects with probable restrictive or mixed patterns, which do not necessarily indicate a restrictive respiratory disease.

The average increases in most of the spirometry indices (FEV_1, PEF, $FEF_{50\%}$, $FEF_{75\%}$, and VC) were measured and compared between these groups. The baseline spirometry parameters were compared between the responders and non-responders regardless of their spirometry patterns as were the mean changes in each of the parameters.

2.4 Statistical Analysis

The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17 computer software. Descriptive statistics are presented as the mean ± the standard deviations, frequencies, and percentages. The chi-square test was used for categorical variables, and independent t-tests and ANOVAs were used to compare means. Fisher's exact test was used to determine whether the numbers of patients who responded to the bronchodilator were significantly different between the groups. In all of the statistical analyses, the level of significance (P value) was set at ≤ 0.05. Linear logistic regression analyses were

used for the prediction of group membership and to provide knowledge about the strengths of the relationships between the variables.

III. Results

Of the 910 subjects evaluated in this study, 610 retained after the exclusion of those aged less than 18 years and those who did not meet the ATS/ERS acceptability and repeatability criteria. 15 These 603 subjects underwent spirometry, and 133 subjects received a bronchodilator. According to their baseline spirometry data, they were divided in to obstructive, normal, restrictive, and mixed pattern groups (51, 61, 16, and 5 subjects, respectively).

The demographic and general characteristics of the studied subjects are detailed in Table 1. The mean age was 49 (±14) years, and the subjects who exhibited a positive response to the BD (responders) were significantly younger (mean age ± SD: 44.3±14.1 years) than the non-responders (mean age ± SD: 50.9±13.9; p value = 0.01). The mean BMI was 29.2 (±6.6 Kg/m^2). The mean BMI was higher among the responders (29.4±6.7) than the non-responders (20±6.5), but this difference did not reach significance (p value = 0.7).

Table 1: Demographic and general characteristics of the studied subjects.

Variable	No.	%
Age mean ± SD* (49 ±14 years)		
18-29 years	13	9.8
30-39 years	18	13.5
40-49 years	44	33.1
50-59 years	27	20.3
≥ 60 years	31	23.3
Gender		
Male	53	39.8
Female	80	60.2
BMI mean ± SD (29.2 ± 6.6 Kg/m^2)		
Normal	34	25.6
Overweight	46	34.6
Obese	53	39.8
Smoking		
Non-smoker	72	54.1
Current smoker	23	17.3
Former smoker	23	17.3
Passive smoker	15	11.3
Response to bronchodilator		
Non-responder	93	69.9
Responder	40	30.1
Spirometry pattern		
Normal	61	45.9
Obstructive	51	38.3
Restrictive	16	12.0
Mixed	5	3.8
Total	133	100.0

*SD: standard deviation

Fig. 1 shows the frequencies of responsiveness of the different spirometry pattern groups. The percentage of responders was higher in the obstructive pattern group compared with the other groups.

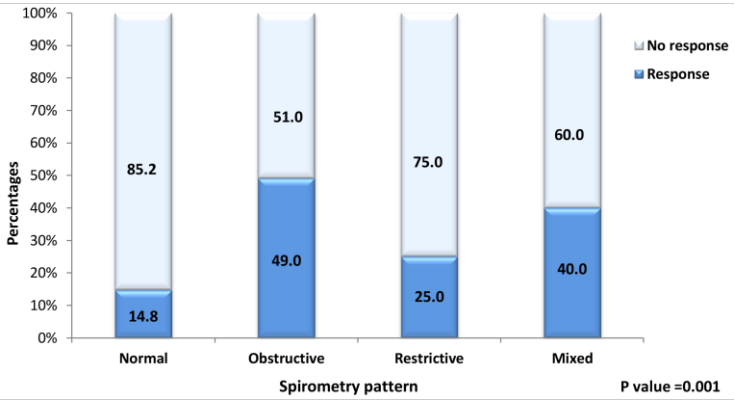

Figure 1: Percentages of subjects in each spirometric pattern group that responded to the bronchodilator.

The comparisons of the baseline spirometric parameters of the responders and non-responders are shown in Table 2. The mean baseline spirometric indices were significantly lower in the responders with the exception of VC (we observed slightly higher baseline VCs in the responders with a p value 0.5).

Table 2: Distribution of the baseline spirometric parameters (percent predicted) According to the response to the bronchodilator.

Parameters %P*	Non-responder		Responder		P
	Mean	SD †	Mean	SD	
FEV_1	74.5	20.4	67.4	17.2	**0.05**
PEF	66.8	23.8	55.9	17.2	**0.01**
$FEF_{25\%}$	64.1	29.7	60.1	88.5	0.6
$FEF_{50\%}$	51	33.4	32.9	21.4	**0.002**
$FEF_{75\%}$	42.1	33	27	25.9	**0.04**
VC	86.1	17.2	88.2	14.9	0.5

*%P: percent predicted
†SD: standard deviation

Table 3 shows the mean changes (mL) in the responders compared with those in the non-responders. The mean changes in all of the parameters were greater among the responders.

Table 3: Mean changes in the spirometric parameters according to the bronchodilator response.

Parameters	Total		R*		N-R†		P
	Mean	SD‡	Mean	SD	Mean	SD	
FEV1 (mL)	179	230	70	130	410	200	**<0.001**
PEF (mL)	398	1036	110	900	1100	900	**<0.001**
$FEF_{25\%}$ (mL/s)	460	900	150	700	1100	700	**<0.001**
$FEF_{50\%}$ (mL/s)	331	703	301	707	400	697	0.4
$FEF_{75\%}$ (mL/s)	109	464	105	539	118	274	0.8
VC (mL)	148	296	100	200	200	400	**0.03**

*R: responder
†N-R: non-responder
‡SD: standard deviation

The mean changes in all of the parameters for the different spirometry pattern groups are presented in Table 4. The greatest increases in all of the parameters were observed in the mixed pattern group.

Table 4: Mean changes in the spirometric parameters (mL) of the different spirometry pattern groups.

Parameter	Pattern	Mean	SD	P
FEV1 (mL)	Obstructive	250	200	**0.001**
	Normal	116	200	
	Restrictive	230	100	
	Mixed	414	50	
PEF (mL)	Obstructive	632	800	**0.02**
	Normal	188	110	
	Restrictive	183	700	
	Mixed	1228	1200	
$FEF_{25\%}$ (mL/s)	Obstructive	740	600	**0.02**
	Normal	239	900	
	Restrictive	321	120	
	Mixed	748	300	
$FEF_{50\%}$ (mL/s)	Obstructive	329	870	0.09
	Normal	398	507	
	Restrictive	26	779	
	Mixed	476	485	
$FEF_{75\%}$ (mL/s)	Obstructive	152	980	0.1
	Normal	130	378	
	Restrictive	-185	859	
	Mixed	260	339	
VC (mL)	Obstructive	144	300	0.07
	Normal	106	200	
	Restrictive	238	200	
	Mixed	418	200	

In Fig. 2, the percent changes in all of the parameters are compared between the obstructive and non-obstructive spirometry pattern groups. The percent changes were greater in the obstructive than the non-obstructive pattern group with the exception of VC; the percent change in VC was slightly higher in the non-obstructive subjects.

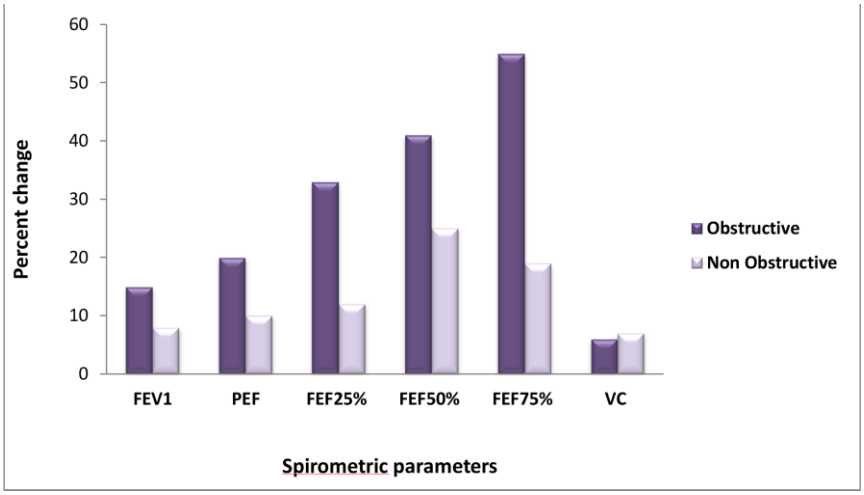

Figure 2: Percent changes in the spirometric parameters according to the obstructive And non-obstructive patterns.

A linear logistic regression analysis of all of the studied patients revealed that the baseline FEV_1 (% predicted) was a significant negative predictor of the FEV_1% change (p=0.02), In contrast, the BMI of the patients was a significant positive predictor of the VC% change (p=0.03; Table 5).

Table 5: Linear logistic regression analyses of FEV1% changes and VC% changes.

Variable	B*	S.E	P
FEV1% difference			
Constant	0.15	0.07	**0.04**
Age	0.01	0.7	0.8
BMI	-0.9	1.7	0.5
Baseline FEV1 (%P)	-0.9	1.8	**0.02**
VC% difference			
Constant	0.6	2.1	**0.01**
Age	-0.009	0.06	0.8
BMI	0.3	0.1	**0.03**
Baseline VC (%P)	0.05	0.06	0.3

*B: beta coefficient
†S.E: standard error

IV. Discussion

An obstructive spirometry pattern is indicated by a reduction of the FEV_1/FVC ratio to below the 5th percentile of the predicted values. In pulmonary function laboratories, BD is commonly administered to determine the reversibility of airflow obstruction. Some clinicians routinely order pre- and post- BD spirometry for cases in which airflow obstruction is suspected based on the symptoms and clinical findings regardless of the baseline spirometry results.

In this study and in agreement with the study of Hegewald MJ, [17] none of the demographic factors other than age were associated with the response to the bronchodilator. In our study, older subjects were less likely to respond to the bronchodilator. In previous studies age has been found to either be negatively correlated [9] (as in our study), positively correlated, [17, 18] or unrelated [19] to bronchodilator response. We found that the baseline FEV_1 s of the studied subjects significantly predicted the FEV_1% changes.

Several studies have examined the bronchodilator responses of obstructive cases, [2, 10], [20, 21] but only a few studies have determined the frequencies of responders among patients with non-obstructive patterns based on baseline spirometry. [9, 17, 22] In the present study, 14.8 % of the subjects with normal baseline test results responded to the bronchodilator; this finding agrees with the result of Mehrparvar AH et al, [22] who found that the frequency of responsiveness among normal subject was 12.7%, whereas a much smaller percentage (3.1%) of responders was found among normal subjects in the study of Hegewald MJ, et al. [17] In the later study, large number (1,394) of normal subjects who had undergone a bronchodilator test were evaluated. In our study,

the percentages of responders in the obstructive, restrictive, and mixed pattern groups were 49%, 25%, and 40%, respectively. Mehrparvar AH, et al [22] reported a higher frequency (60%) of responders among those who displayed the mixed pattern, but the percentage of responders in the restrictive group was 21%, which is similar to the result from our study. In both of these studies, the number of studied subjects with the mixed pattern was small compared with the numbers of subjects with the other spirometry patterns.

In this study, the mean increases in all of the parameters were higher among the responsive subjects. Mehrparvar AH et al, [22] assessed the spirometric parameters of an identically defined responder study group and found results similar to ours in terms of the mean FEV_1 increase (200 mL and 179 mL in their study and our study, respectively) and the mean increase in FEV_1 (450 mL and 410 mL, respectively). The mean increases in FEV_1 that have been reported in previous studies are 117 mL, 82 mL, and 77.2 mL, but these studies evaluated different study groups that included COPD patients, [21] a normal baseline spirometry group, [17] and healthy non-smoker subjects, [9] respectively.

The parameters with the greatest increases were $FEF_{25\%}$ and PEF followed by FEV_1 in the normal and obstructive pattern groups, while $FEF_{25\%}$ followed by VC exhibited the greatest increases in the restrictive and mixed pattern groups in the present study. The parameter with the smallest increase was VC. In a previous study from a neighboring country (Iran), the largest increase was observed in $FEF_{75\%}$. [22] We observed a 15% increases in FEV_1 in the obstructive cases, compared with the 10.7% increase reported in the study of Azevedo et al, [23] these authors examined subjects with asthma.

We observed statistically significant increases in most of the parameters (i.e., FEV_1, PEF, and VC) in all four of the spirometric pattern groups. The largest increases in the main spirometric parameters were observed in the individuals who exhibited the mixed pattern, and the smallest increases were observed in the normal pattern groups; these findings are analogous to those of the study of Mehrparvar AH et al. [22] The explanation for the observation of the largest increases in the mixed group is that these patients initially had obstructions that were mostly reversible with a bronchodilator, and some of the patients with severe respiratory symptoms exhibited pseudo-restriction (i.e., decreased VC due to entrapped air and increased RV that caused these patients to exhibit mixed obstructive and restrictive spirometry patterns), whereas the true abnormality is severe obstructive disease.

Few studies have evaluated the responses and changes in VC and IC after BD administration. [23, 24] Azevedo et al, [23] reported the VC increase that was greater than that observed in the present study (8.8 versus 6%, respectively), but our study sample was composed of subjects with respiratory symptoms regardless of diagnosis. In contrast, Azevedo et al, [23] included asthmatic patients with diagnoses of either moderate or severe asthma, which might explain the greater proportion of responsive subjects in this study group. Evaluations of the VC values of different spirometry pattern groups have not been reported in previous studies. In the present study, BMI was a significant predictor of changes in VC percent changes.

Study limitations: We did not classify the obstructive subjects according to the severity of obstruction, and there could be a strong association between severity and bronchodilator response. Moreover, the number of restrictive cases was very small. Furthermore, body plethysmography was not used to identify true restrictions; we relied only on spirometry results.

Finally, the modes of administration and doses of bronchodilators vary across different pulmonary function laboratories and across studies; therefore, our results may not be applicable to other laboratories. We recommend the expansion of this study in the future by increasing the numbers of studied subjects and the using of other test methods, including static lung volume parameters (TLC, RV, and FRC).

V. Conclusion

With the exception of the obstructive pattern, the other patterns (i.e., restrictive and mixed) also exhibited significant responses to the bronchodilator in some patients with respiratory symptoms.

In conclusion, some patients with restrictive or mixed spirometry patterns might respond to the bronchodilator (with normal post bronchodilator VC) these may suggest pseudo-restriction on spirometry due to moderate to severe obstruction; therefore bronchodilator use is important for the exclusion of pseudo-restriction on spirometry and of false diagnoses, especially in laboratories that with limitations regarding the measurement of static lung volumes (TLC, FRC and RV).

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