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TANAFFOS

Bronchodilator Response of FEV6 and FEV3 as Surrogates of Forced Vital Capacity

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Background: Spirometry as a non-invasive and inexpensive test is widely used for occupational health evaluations. Bronchodilator test is used for the assessment of airflow limitation and increase in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) is considered as a positive response. This study was performed to assess the response of forced expiratory volume in 6 seconds (FEV_6), forced expiratory volume in 3 seconds (FEV_3), and forced expiratory time (FET) to bronchodilator administration.

Materials and Methods: In this cross-sectional study, the response of FEV_3, FEV_6, FEV_1/FEV_3, FEV_1/FEV_6 and FET to bronchodilator administration was assessed in subjects referred to Yazd occupational medicine clinic regardless of their diagnosis. The average increase in spirometric parameters (*i.e.* FVC, FEV_1, FEV_1/FVC, FEV_3, FEV_6, FEV_1/FEV_3, FEV_1/FEV_6 and FET) was measured. The difference between baseline and post-bronchodilator spirometries was assessed by calculating absolute change and change from baseline as well. Data analysis was done by Student's t test, chi square test and Pearson's correlation test.

Results: Totally 104 subjects were entered in the study. FEV_1 showed the highest response to bronchodilator. FVC response to bronchodilator was correlated with FET, but such correlation was not observed for FEV_6 and FEV_3. The mean increase in FEV_6, FEV_3, and FET after bronchodilator administration was 50.90 ml (2.23%), 110.51 ml (3.08%) and -1.85 s, respectively.

Conclusion: FVE_6 can be used as a substitute for FVC for the assessment of bronchodilator response without the need for FET adjustment.

Key words: Spirometry, Bronchodilator test, FVC, FEV_6, FEV_1, FET

INTRODUCTION

Spirometry as a non-invasive and inexpensive test is widely used in occupational health evaluations. The most frequent parameters used for interpretation of this test include FVC, FEV_1, and FEV_1/FVC (1). Spirometry is a demanding maneuver requiring a long exhalation time to achieve American Thoracic Society/European Respiratory Association (ATS/ERS) criteria (1).

Studies have shown a high sensitivity and specificity for FEV_1/FEV_6 compared to FEV_1/FVC for diagnosis of airway obstruction (2- 4). FEV_1/FEV_6 is also recommended for detection of COPD in the primary-care setting (5).

Some spirometric variables (such as FEV_6, FEV_3, FEV_1/FEV_6 and FEV_1/FEV_3) have been suggested as alternatives to FVC, and FEV_1/FVC to find abnormal

spirometric patterns (2-4, 6, 7). Measurement of parameters such as FEV_6 is easier because the patients are not required to perform maximal end-expiration. This is important especially in occupational health settings requiring a large number of workers performing spirometry in a short time.

Among the aforementioned parameters, FEV_6 is the most frequently assessed parameter. There are several studies on the reliability and utility of this parameter for diagnosing obstructive and restrictive lung diseases (5, 8, 9). This parameter is reported to be less variable than other FEV_X parameters (10).

Bronchodilator test is recommended to assess airway responsiveness. Bronchial responsiveness is assessed by changes in spirometric parameters after the administration of short-acting β_2-agonists, such as salbutamol, or anticholinergic drugs such as ipratropium bromide (11- 13, 14). Positive bronchodilator test is a useful means that helps with the diagnosis of respiratory diseases such as asthma (15, 16).

According to ATS/ERS task force, bronchodilator response is measured using the percent change from baseline and absolute changes in FEV_1 and/or FVC (12). Twelve percent and 200 mL increase in FEV_1 or FVC compared to baseline value are suggestive of a significant response to bronchodilator (12, 13).

Kainu et al. proposed that 9% increase in FEV_1 from baseline is a positive response (17). It is also recommended that if only FVC is increased in bronchodilator test, forced expiratory time (FET) be assessed as well (18).

Since FEV_6 and FEV_3 are considered as surrogates of FVC, their response to bronchodilator administration is important. Thus, this study was designed to assess the response of these spirometric parameters to bronchodilator administration.

MATERIALS AND METHODS

In a cross-sectional study from November 2011 to November 2012, we assessed the response of FEV_3, FEV_6, FEV_1/FEV_3, FEV_1/FEV_6 and FET to bronchodilator administration. FEV_6 is the most reliable surrogate for FVC followed by FEV_3 as the second reliable parameter most commonly studied as an alternative to FVC.

Our study population consisted of all subjects referred to Yazd occupational medicine clinic and bronchodilator test was indicated for them regardless of their diagnosis.

There were four smokers among subjects who were excluded from the study. Those taking medications (systemic or inhaled) for respiratory diseases were excluded from the study.

Spirometry was performed for all subjects by a flow-volume type spirometer (Spirolab III, MIR, Italy) in our respiratory lab in a standard position (seated, body temperature and pressure saturated, in the morning) by an occupational medicine resident. This device is auto-calibrated. After baseline testing, a bronchodilator (salbutamol, 400µg, inhaled using a spacer in 4 separate doses) was administered and the test was repeated after 15 minutes.

At least three acceptable maneuvers were performed for each subject according to ATS/ERS taskforce guidelines (back extrapolation volume < 5% of FVC or 150 mL, 1s plateau in the volume–time curve, without coughing during the first second of the manoeuver, without early termination of expiration, and without glottic closure) (1).

The test with the highest sum of FVC and FEV_1 from three technically acceptable recordings was selected. All factors intervening or contraindicating spirometry were evaluated before the test (1). We used our population reference equations according to Golshan et al. (19).

The average increase in spirometric parameters (*i.e.* FVC, FEV_1, FEV_1/FVC, FEV_3, FEV_6, FEV_1/FEV_3, FEV_1/FEV_6 and FET) was measured. The difference between baseline and post-bronchodilator spirometries was assessed by calculating absolute change and change from baseline as well.

We used SPSS (ver. 19) for data analysis using paired t test, chi square test and Pearson's correlation test. Level of significance was set at 0.05. An informed consent was obtained from all participants. The study was approved by the Ethics Committee and the Research Vice Chancellor of Shahid Sadoughi University of Medical Sciences.

RESULTS

One hundred and four subjects were entered in the study. Table 1 shows the demographic data of all subjects.

Table 1. Demographic data of subjects.

Variables	Min	Max	Mean	SD*
Age (year)	20.00	80.00	36.45	10.11
Weight (Kg)	43.00	116.00	78.30	14.46
Height (cm)	157.00	189.00	172.67	6.63
BMI** (Kg/m^2)	14.20	37.18	26.23	4.59

* SD: Standard deviation

** BMI: Body mass index

Table 2 shows the baseline and post-bronchodilator values of different spirometric parameters.

Table 2. Baseline and post-bronchodilator values of different spirometric parameters.

		Min.	Max.	Mean	SD*	P value
FEV_1 (ml)	Pre**	970.00	4690.00	2920.00	700.00	<0.001
	Post**	980.00	4970.00	3170.00	750.00	
FEV_1% predicted	Pre	29.00	125.00	75.40	15.59	<0.001
	Post	33.00	113.00	81.57	15.27	
FVC (ml)	Pre	2000.00	7140.00	4100.00	1090.00	0.092
	Post	1680.00	6620.00	4170.00	1030.00	
FVC% predicted	Pre	45.00	136.00	87.90	19.02	0.194
	Post	45.00	123.00	88.98	16.93	
FEV_1/FVC	Pre	43.70	97.20	72.26	11.42	<0.001
	Post	48.90	96.30	76.87	10.16	
FEV_3 (ml)	Pre	1570.00	6310.00	3860.00	420.00	0.006
	Post	1620.00	5840.00	3970.00	930.00	
FEV_3% predicted	Pre	45.00	124.00	87.51	16.65	0.006
	Post	46.00	121.00	89.76	16.55	
FEV_1/FEV_3	Pre	55.00	97.00	77.33	8.95	<0.001
	Post	60.00	96.00	80.23	8.27	
FEV_6 (ml)	Pre	1980.00	6990.00	4110.00	1110.00	0.20
	Post	1680.00	6500.00	4170.00	1030.00	
FEV_6% predicted	Pre	50.00	185	88.35	20.62	0.53
	Post	45.00	122	89.02	17.18	
FEV_1/FEV_6	Pre	45.30	97.20	72.43	11.10	<0.001
	Post	50.00	96.00	76.79	10.14	
FET (s)	Pre	1.70	11.74	7.23	1.94	0.068
	Post	1.32	10.88	6.12	1.72	

* SD: Standard deviation

** Pre: Before bronchodilation, Post: After bronchodilation

The change in spirometric parameters was measured and is shown in Table 3.

Table 3. The mean change in spirometric parameters after bronchodilator administration.

	Min.	Max.	Mean	SD*
FEV_1 (ml)	-720.00	1510.00	243.36	323.00
FEV_1% predicted	-19.51	61.13	9.18	13.04
FVC (ml)	-1470.00	1860.00	69.90	418.76
FVC % predicted	-30.60	54.87	2.69	11.29
FEV_1/FVC	-17.74	55.11	7.12	9.38
FEV_3 (ml)	-1410.00	1650.00	110.51	374.86
FEV_3% predicted	-30.45	72.37	3.68	11.82
FEV_1/FEV_3	-34.02	44.83	3.72	8.33
FEV_6 (ml)	-1760.00	1080.00	50.90	401.00
FEV_6 % predicted	-30.60	35.71	2.23	10.24
FEV_1/FEV_6	-9.91	57.14	7.52	9.30
FET (s)	-52.34	159.92	-1.85	32.56

* SD: Standard deviation

Among all participants, 34.6% (36 subjects) showed significant response to bronchodilator according to ATS/ERS guidelines. Table 4 compares other spirometric parameters between responsive and non-responsive subjects. Among responsive cases, FEV_1 and FVC significantly increased in 34 (32.6%) and 14 (13.4%) cases, respectively; only in 2 cases (1.9%) responsiveness was only due to increased FVC and 22 cases (21.1%) showed responsiveness only due to increased FEV_1.

Table 4. Comparison of spirometric parameters among responsive and non-responsive subjects.

	Responsiveness	Number	Mean	SD*	P-Value
FEV_6 (ml)	Non-Res**	68	-103.58	348.68	<0.001
	Res**	36	338.33	330.59	
FEV_6 % predicted	Non-Res	68	-2.12	6.91	<0.001
	Res	36	10.32	10.59	
FEV_3 (ml)	Non-Res	68	-35.16	262.88	<0.001
	Res	36	455.92	377.94	
FEV_3 % predicted	Non-Res	68	-0.76	6.21	<0.001
	Res	36	14.21	15.06	
FET (s)	Non-Res	68	-0.18	1.39	0.43
	Res	36	-0.43	1.54	

* SD: Standard deviation

** Non-res: Non responsive to bronchodilation, Res: Responsive to bronchodilation

FEV_6 and FEV_3 change was significantly correlated with FVC change (r = 0.95, and r = 0.84, respectively).

Among all subjects, 48.1% showed obstructive pattern in their pre-bronchodilator test, which was decreased to 23.1% after bronchodilator administration; and 32.7% showed restrictive pattern, which reduced to 27.9% after bronchodilator administration. The comparison of change in spirometric parameters after bronchodilator administration showed a significant difference in FEV_1 (P = 0.002) and FET (P = 0.004) between the two groups. Other spirometric parameters were not significantly different between the two groups. Effect of age and BMI on the changes of spirometric parameters was observed only in FEV_1 (P = 0.001 for age and P = 0.04 for BMI). In other words, those with younger age and lower BMI showed a higher response to bronchodilator, although this association was not observed in other spirometric parameters.

FET did not significantly change after bronchodilator administration. The change in FET was not significantly different between the responsive and non-responsive cases. FET increased in only about 37% of cases. FVC increase after bronchodilator administration was significantly correlated with FET but this association was not seen for FEV_6 and FEV_3. In about 39% of cases, FVC decreased after bronchodilator administration.

DISCUSSION

Spirometry is the most common test for screening of respiratory functions in occupational health evaluations. Bronchodilator response test is a helpful procedure for detection of the reversibility of airflow limitation. In this study, we assessed the response of different spirometric parameters to bronchodilator administration. Recently, some spirometric parameters (i.e. FEV_6, FEV_3, FEV_1/FEV_6, FEV_1/FEV_3) have been proposed as alternatives to conventional ones. In this study, we assessed the response of theses parameters to bronchodilator administration.

Many studies have reported FEV_6 and FEV_1/FEV_6 as appropriate surrogates for FVC and FEV_1/FVC (2, 20, 21); however, Hansen et al. found that FEV_6 and FEV_1/FEV_6 had a low sensitivity for diagnosis of restrictive and obstructive spirometric patterns (8).

In the current study, the parameter with the highest response to bronchodilator was FEV_1, which was in agreement with the previous study (11) and those of Kainu et al (15), and Lamprecht et al (22). Increased FVC was observed in a few subjects consistent with other studies (11, 15). In responsive cases, the mean FEV_6 increase was lower than 12%; Kainu et al. reported 6% increase in FEV_6 to be significant (15).

This study showed that FVC response to inhaled bronchodilator in our sample was infrequent consistent with the results of Mehrparvar et al. (11) and Kainu et al. (15), although some studies have reported higher response rates for FVC which may be due to different study populations (23-24). There was no difference in the frequency of FVC response between obstructive and non-obstructive cases, which was inconsistent with the results of Kainu et al. (15) who reported FVC increase mostly in obstructive cases. However, most studies on bronchodilator response have been done on subjects with obstructive spirometric pattern (12, 24).

In our study, FVC decreased in a significant number of cases after bronchodilator administration which was in agreement with the findings of Kainu et al (15).

In our study, FVC increase after bronchodilator administration was significantly correlated with FET but this association was not seen for FEV_6 and FEV_3 consistent with the results of Kainu et al. (15). It is assumed that increased FVC is indicative of true bronchodilation when FET is not increased simultaneously (25). Thus, according to the results of this study, using FEV_6 or FEV_3 as surrogates of FVC for bronchodilator test does not need FET adjustment.

This study had some limitations. The study was done in an occupational medicine clinic; therefore, most individuals referred to this center were males, and we could not assess the effect of sex. We had few positive FVC bronchodilation responses, which limited further analysis.

Our sample size was limited; thus, we could not assess the effect of severity of airflow limitation on bronchodilator response.

This study confirmed the results of previous studies about bronchodilator response in spirometry considering different spirometric parameters. We conclude that FEV_6 can be used as a surrogate for FVC for assessing bronchodilator response without the need for FET adjustment in cases for whom bronchodilation is considered positive only due to increased FVC. Future studies with larger sample size are required to confirm this finding.

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