Forced vital capacity as a primary clinical outcome measure of bronchodilator reversibility in chronic obstructive pulmonary disease

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Background Spirometry is the most reproducible and objective measurement of airflow limitation. The effectiveness of inhaled bronchodilator in individual patients with chronic obstructive pulmonary disease (COPD) is assessed by comparing measurements from pulmonary function tests made before and after administration. Generally forced expiratory volume in one second (FEV1) is the marker used with the global initiative for COPD (Global Initiative for Chronic Obstructive Lung Disease) guidelines. An increase in FEV1 that is both greater than 0.2 l and 12% above the prebronchodilator FEV1 value is considered significant.
The aim of this study is to assess forced vital capacity (FVC) as a clinical outcome measure of bronchodilator reversibility in patients with COPD.

Patients and methods This was a prospective study conducted on 163 patients with COPD at Suez Chest Hospital during the period from first of October 2016 till the end of March 2017. Patients were diagnosed based on clinical and spirometric criteria, and then reversibility test was done using inhaled short-acting B2-agonist. All patients were subjected to COPD Assessment Test questionnaire.

Results Overall, 14.11% of patients had significant increase in FEV1, whereas 54.6% of patients had significant increase in FVC after bronchodilator inhalation. There was a highly significant positive correlation in FEV1 and FVC value before and after bronchodilator inhalation, and there was a highly significant direct correlation between ΔFEV1 and ΔFVC. There was a statistically significant relation between age and COPD Assessment Test score and ΔFVC.

Conclusion ΔFEV1 underestimates the true effect of bronchodilator as airway obstruction increases. The addition of ΔFVC to the evaluation will help physicians to better interpret airways reversibility tests, particularly in more severe patients, without adding spirometric maneuvers or measurements. Patients with COPD, even if nonresponders in terms of FEV1, may benefit from bronchodilators because they can breathe at a lower lung volume owing to reduced air-trapping, notwithstanding the fact that they are still flow limited. ΔFVC correlates better than ΔFEV1with the degree of airway obstruction and the clinical status of the patients.
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Introduction

Spirometry is the most widely used and objective tool of measuring the airflow limitation. The value of inhaled bronchodilator in patients with chronic obstructive pulmonary disease (COPD) is measured by comparing the spirometric parameters taken before and after inhalation. Forced expiratory volume in one second (FEV1) is the marker used with the global initiative for chronic obstructive pulmonary disease [Global Initiative for Chronic Obstructive Lung Disease (GOLD)] guidelines. An improvement in FEV1 that is both greater than 0.2 l and 12% above the prebronchodilator (pre-BD) FEV1 value is considered a positive response [1].

The COPD Assessment Test (CAT) is a well-established, short and simple patient-administered questionnaire, with good discriminative characteristics, used in routine clinical practice to evaluate the clinical status of patients with COPD. The CAT provides indicators of the symptomatic effect of COPD, but it does not classify patients into symptom severity groups regarding treatment. The equivalent cutoff point of the CAT is 10, below is considered as low-symptom patients, whereas equal or above 10 is considered as high-symptom patients [2].

Aim

The aim is to assess forced vital capacity (FVC) as a primary clinical outcome measure of bronchodilator reversibility (BDR) in patients with COPD.

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Patients and methods

This study was conducted at Suez Chest Hospital during the period from first of October 2016 till the end of March 2017. It included 163 patients with COPD who were admitted at an outpatient clinic. Informed consent was taken from all patients who were invited to participate in the research as regards confidentiality, right to refuse or withdraw, and in case of refusing to participate in the research, the patient will be followed up and will receive his treatment as planned. The consent was revised and approved by the ethical committee of scientific research.

The diagnosis of COPD was established by clinical assessment and spirometric tests according to the GOLD guidelines [3].

All patients with COPD older than 30 years, both males and females, were enrolled in the study. Patients were first assessed clinically and diagnosed as COPD and then were referred for spirometric and reversibility test to assess and classify disease severity.

All patients were subjected to the following:

(1) Full history taking and clinical examination, with special emphasis on risk factors for COPD and contraindications of spirometry; to support the diagnosis and rule out other medical conditions that may interfere with the spirometry.
(2) Face-to-face CAT questionnaire. It comprises eight easy and straightforward questions most patients should be able to understand and answer easily [2]. The CAT is available in more than 90 different languages; we used the Arabic version in the current study [4].
(3) Spirometry as a baseline test using SP-1 Spirometer (Med-Electronics Co Ltd., Virginia Manor Road Beltsville, USA), with Disposable Flow Sensor, model 2008.
(4) Reversibility test using inhaled short-acting B2-agonist (400 μg Salbutamol). Spirometry was done again 15 min after the bronchodilator was given. The presence of a post-BD FEV1/FVC ratio less than 0.7 proves the presence of persistent airflow obstruction [3].

Exclusion criteria

The following were the exclusion criteria:

(1) Current respiratory tract infection or exacerbation of COPD.
(2) Administration of systemic corticosteroid within a month before spirometry.
(3) Contraindication of spirometry procedure, for example, recent myocardial infarction (MI) (1 month), eye surgery, recent stroke, hemoptysis, thoracic/abdominal surgery, known thoracic, aortic or cerebral aneurysm, uncontrolled hypertension, recent pneumothorax, or pulmonary embolism [5].

Statistical analysis

IBM computer was used for data analysis using statistical package for the social science, version 12 as follows:

(1) Quantitative variables were described as mean, SD, and range.
(2) Qualitative variables were described as number and percentage.
(3) To compare qualitative variables between groups, we used χ^2 test.
(4) To compare two independent quantitative variables in parametric data, unpaired t test was used.
(5) In nonparametric data, Mann–Whitney test was used instead of unpaired t test.
(6) Analysis of variance test is used to test any significance difference between means of two or more quantitative variables in parametric tests.
(7) Spearman's correlation test was used to rank variables versus each other positively or inversely.
    (a) P value more than 0.05 was considered insignificant.
    (b) P value less than 0.05 was considered significant.
    (c) P value less than 0.01 was considered highly significant.

Results

The current study included 163 patients with COPD. The mean±SD age was 58.748±10.727 years. Overall, 94.48% of patients were males and 5.52% were females. Mean±SD baseline spirometric parameters were as follows: pre-BD FVC=2.17±0.734 l, post-BD FVC=2.35±0.784 l, pre-BD FEV1=1.24±0.444 l, and post-BD FEV1=1.33±0.474 l.

Patients were classified according to CAT questionnaire as follows: 68 (41.72%) low-symptom patients and 95 (58.28%) high-symptom patients. Patients were categorized regarding disease severity based on GOLD classification as follows: mild (two patients, 1.23%), moderate (46 patients, 28.22%), severe (85 patients, 52.15%), and very severe (30 patients, 18.40%).

Table 1 shows the range and mean of the differences between FEV1 and FVC before and after

bronchodilator inhalation in both liters and percentage. Overall, 60.73% of the patients were between 50 and 69 years of age, as shown in Table 2.

Spirometric results show that only 14.11% of patients had significant increase in FEV1 (12% increase calculated from the pre-BD value and a 0.2 l increase), 81.6% had nonsignificant increase, whereas 4.29% had no change at all after inhalation of bronchodilator. Regarding FVC, 54.6% of patients had significant increase in FVC after bronchodilator inhalation, 42.94% had nonsignificant increase, whereas only 2.45% had no change as shown in Tables 3 and 4, correspondingly.

There was a highly significant positive correlation in both FEV1 and FVC values before and after bronchodilator inhalation as shown in Tables 5 and 6, respectively. Moreover, there was a highly statistical significant direct correlation between ΔFEV1 and ΔFVC (Table 7). It also shows that number of patients who showed significant reversibility response of FVC was much more prominent than those who showed the same response of FEV1 after bronchodilator (54.60 and 14.11%, respectively).

Table 1 Distribution of studied cases regarding Δforced expiratory volume in one second and Δforced vital capacity

	Range	Mean±SD
ΔFEV1 (l)	−0.08 to 0.32	0.093±0.060
ΔFEV1%	−4.26 to 13.75	7.582±4.060
ΔFVC (l)	−0.14 to 0.67	0.185±0.105
ΔFVC%	−4.24 to 13.99	8.604±3.756

FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 2 Distribution of patients regarding age groups

Age groups (years)	*N* (%)
30–39	9 (5.52)
40–49	19 (11.66)
50–59	50 (30.67)
60–69	49 (30.06)
70–79	34 (20.86)
80–89	2 (1.23)
Total	163 (100.00)

Table 3 Distribution of patients regarding Δ forced expiratory volume in one second after bronchodilator administration

Percentage ΔFEV1	*N* (%)
No change	7 (4.29)
Nonsignificant increase	133 (81.60)
Significant increase	23 (14.11)
Total	163 (100)

FEV1, forced expiratory volume in one second.

Table 4 Distribution of patients regarding Δforced vital capacity after bronchodilator administration

Percentage ΔFVC	*N* (%)
No change	4 (2.45)
Nonsignificant increase	70 (42.94)
Significant increase	89 (54.60)
Total	163 (100)

FVC, forced vital capacity.

Table 5 Correlation between forced expiratory volume in one second before and after bronchodilator inhalation

Time	FEV1 value		Paired differences	Paired samples test	
	Range	Mean±SD	Mean±SD	*t*	*P* value
Before	0.38–3.2	1.243±0.435	−0.093±0.060	−19.836	<0.001
After	0.4–3.32	1.336±0.465			

FEV1, forced expiratory volume in one second.

Table 6 Correlation between forced vital capacity before and after bronchodilator inhalation

Time	FVC value		Paired differences	Paired samples test	
	Range	Mean±SD	Mean±SD	*t*	*P* value
Before	0.72–5	2.174±0.721	−0.185±0.105	−22.536	<0.001
After	0.81–5.67	2.359±0.784			

FVC, forced vital capacity.

Table 7 Relation between Δforced expiratory volume in one second and Δforced vital capacity

	Percentage of change [*N* (%)]		χ^2	
	FEV1	FVC	χ^2	*P* value
No change	7 (4.29)	4 (2.45)	59.263	<0.001
Nonsignificant increase	133 (81.60)	70 (42.94		
Significant increase	23 (14.11)	89 (54.60)		
Total	163 (100)	163 (100)		

FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

There was no statistical significance between ΔFEV1 (response to bronchodilator) and either of age of patient, CAT score or GOLD staging. Although there was a significant statistical relation between ΔFVC (bronchodilator response) and both age of patient and CAT score, no correlation was found with GOLD staging.

Discussion

COPD is one of the most important leading causes of death around the world and is defined to have a progressive, partially irreversible airflow obstruction owing to a chronic inflammation in the air passages. Many studies have started to question if the reversibility of FEV1 is the perfect tool in COPD or there may be other relevant parameters when evaluating the response [6–9].

Falco *et al.* [7] conducted a retrospective study upon 594 patients with COPD between January 2013 and June 2014. They reviewed the pulmonary function of the patients to study the differences in bronchodilator response regarding parameters of the flow and the volume in patients diagnosed with COPD at different severity staging of GOLD. The age range in the sample was 40–93 years, with mean of age of 64.3 years. Overall, 66.5% were males, mean baseline FVC was 2.88 l, and mean FEV1 was 1.63 l. In the current study, the mean age was lower, as we included patients older than 30 years, unlike Falco and colleagues who included patients older than 40 years. Moreover, we had a lower percent of female (5.52%) patients, than Falco and colleagues (33.5%), which may be because of the more widespread smoking habits among females in the western society.

In 2008, Ben Saad *et al.* [8] enrolled 168 consecutive male patients with COPD [clinically diagnosed COPD as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS)], all exceeding 40 years of age, between March 2006 and June 2007 for spirometry and reversibility testing to monitor and classify disease severity. Spirometric functions were performed using a body plethysmograph. The mean age was 63 years, as they included patients more than or equal to 40 years old. The baseline values of the patients were as follows: FEV1=1.46 l and FVC=2.62 l. The post-BD values of the patients were as follows: FEV1=1.59 l and FVC=2.89 l. These values were higher than our study, as we recorded baseline values of FEV1=1.24 l and FVC=2.17 l and the post-BD values of FEV1=1.33 l and FVC=2.35 l. This difference may be attributed to different disease severity in the studied population.

The study of Ben Saad *et al.* [8] calculated the change of FEV1 and FVC after the BD and they were as follows: ΔFEV1=0.14 l and the Δ% is 11%, whereas ΔFVC=0.27 l and Δ% is 12%. In the current study, ΔFEV1 was 0.09 l and the Δ% is 7.5%, whereas ΔFVC=0.18 l and Δ% is 8.6%. Again the lower values of our study may be explained by the difference in disease severity.

In the current study, we tried to relate the quantification of the effect of COPD on the patient's health using the CAT questionnaire to the functional assessment, so primarily, we classified patients according to symptomatic health effect using CAT questionnaire as follows: low-symptom category (<10) (68) patients and high-symptom category (≥10) (95) patients. Secondarily, we categorized the patients according to disease severity [3], and the results were as follows: 1.23% of patients were mild, 28.22% were moderate, 52.15% were severe, and 18.4% were very severe. These results were not in accordance with the results of Ben Saad *et al.* [8] who found that 10% of their patients were mild, 45% were moderate, 39% were severe, and 11% were very severe disease. Similarly, Falco *et al.* [7] found that 25.1% of their patients were mild, 51.2% were moderate, 20.2% were severe, and 3.5% were very severe disease, and the difference between the results of these two results and the results of the current study was because more than half of our patients (52.15%) belonged to the severe stage, which may explain the lower values we found as baseline FVC and FEV1.

Schermer *et al.* [10] assumed that the link between flow and volume responses would reverse along with the progression of COPD. They used the database of a primary care diagnostic center containing pre-BD and post-BD parameters of patients referred for spirometry by their general practitioners (n=2210). Patients more than or equal to 40 years with a smoking history were categorized into GOLD stages (20.0% were mild, 58.7% were moderate, 19.3 were severe, and 2.0% were very severe).

The comparison between the three previous studies [7,8,10] and the current study regarding the GOLD stage classification may obviously pronounce the awareness defect in our society, where patients sought medical advice at a late disease stage.

In the current study, 14.11% of patients had significant response of FEV1 (23 patients), whereas 54.6% of patients had significant response of FVC (89 patients) after bronchodilator inhalation. Thus, FVC

detected 40.49% more responders than FEV1. These results were similar to the results of Ben Saad *et al.* [8] who found that FVC detected 57% more patients than FEV1. These results were also in accordance with Falco *et al.* [7] who stated that there was a heterogeneous response in their population with 13.3% subjects showing isolated volume response, slightly more patients (19.9%) exhibiting changes in both volume and flow and only 5.1% improving FEV1 with a little change in FVC, whereas 61% were nonresponders.

Quanjer *et al.* [11] conducted a multicentric study to collect BDR test data from patients in the Netherlands, the United States, and New Zealand (n=15 278; female subjects, 51.7%) and from surveys in Canada, Norway, and five Latin-American countries (n=16 250; female subjects, 54.7%) with a total number of 31 528. They investigated the association of BDR criteria on age, sex, height, ethnicity, and respiratory impairment severity. They found that ΔFEV1 was 0.173 l and ΔFVC was 0.245 l. They concluded that the ΔFEV1 and ΔFEV1/FVC first increase, and then decline, as airway obstruction becomes more pronounced; the response declines with age, becoming slightly negative after the age of 50 years. In contrast, ΔFVC increases progressively from within the normal range of the FEV1/FVC ratio to severe airflow limitation, exceeding the relative change in FEV1 in severe and very severe obstruction. The current study also found that ΔFVC showed a significant relation with higher age group (50–59 years). ΔFVC increased with the level of airflow obstruction. This 'volume response,' that is increasing improvement in FVC with the level of airflow limitation, makes it a more sensitive parameter to measure the BDR than FEV1 that shows response decline as airways obstruction worsens.

In the current study, when comparing the Δ in both FEV1 and FVC with the age of the patient, CAT score, and GOLD classification, we found that ΔFEV1 had no relation with the three previous parameters. Regarding ΔFVC, it showed a significant statistical relation with the age group of the patient, being more prominent in the group of 50–59 years. It also showed significant relation with the low symptoms CAT score patients. Lastly, it was not related to the GOLD classification.

Being able to combine our functional assessment with a relevant clinical status is very crucial especially that it was more prominent with low-symptom score which makes it sensitive to early clinical variability, and this finding strongly supports the report of Quanjer *et al.* [11] that clinical judgment should prevail over statistical considerations. Although the emphasis is often still on evaluating the BD response in FEV1, the progressively larger FVC response as airflow limitation becomes more pronounced, which points to a clinically important reduction of hyperinflation with beneficial effects on dyspnea, exercise performance, and gas exchange. Including the FVC response increases the number of positive responses in those with airways obstruction by more than 50%, and is particularly relevant in elderly patients with severe airways obstruction.

Our results also were similar to Omata *et al.* [9], who conducted a study on 63 subjects with COPD. Reversibility was measured by the change in FEV1 and FVC after the inhalation of salbutamol (300 μg); they calculated the relation between BD reversibility and the respective items of health-related quality of life (HRQoL) and activities of daily living. The acute FVC response to BD was significantly correlated with numerous HRQoL items, unlike the FEV1 response. Thus, they questioned that the reversibility assessment using FVC measurement may become a more useful clinical marker regarding HRQoL and that this measurement may provide different clinical point of view than that provided by FEV1.

Although we could not demonstrate a significant statistical relation between both ΔFEV1 and ΔFVC and the GOLD stages, yet we found that 14 cases of FEV1 responders were in stages III and IV in comparison with 61 cases of FVC responders who were in stages III and IV. This came in accordance with Falco *et al.* [7] who stated that the magnitude of ΔFEV1 decreased as the GOLD stage became more severe and the ΔFVC increased in the more severe GOLD stages. Similarly, Schermer *et al.* [10] who found that ΔFEV1 decreased as the GOLD stage was more severe, whereas ΔFVC changed in the opposite direction.

In 2016, Jarenbäck *et al.* [12] studied 81 smokers/exsmokers (41 controls and 40 COPD) performed spirometry, impulse oscillometry, single-breath helium dilution carbon monoxide diffusion, and body plethysmography at baseline, after salbutamol inhalation and then after a further inhalation of ipratropium. They almost came to the same conclusion as the current study, that volume and resistance responses do not follow the flow response (expressed as FEV1); they found that resistance parameters were more significant in less advanced stage, whereas parameters reflecting volume response (e.g. FVC) were more prominent in patients with more severe stages of COPD.

Extending the same concept to include the severity grading is not unexpected. Hence, in 2015, Pisi *et al.* [13] conducted a study to challenge the use of FEV1 as the one and only lung function parameter for severity grading in COPD because of its dependence on dominant phenotype (i.e. either predominant emphysema or chronic bronchitis). The study included 98 subjects with a clinical and spirometric diagnosis of COPD, and then underwent full lung function examination. Spirometry and absolute lung volumes were obtained with the subjects sitting in a body plethysmograph. They came to a conclusion that the FEV1 is biased by intrathoracic gas compression more in subjects with dominant emphysema than in those with chronic bronchitis. This variably and significantly affects the severity grading systems recommended by the current guidelines.

In the current study, 37 patients previously diagnosed on clinical basis as having COPD were excluded; these patients were found to have full spirometric reversibility after short-acting bronchodilator inhalation and were diagnosed as patients with asthma.

Although the best parameter for the interpretation of BD tests is still debatable, yet we are convinced that adding FVC as a substantial parameter will add much accuracy to the judgment. This idea contradicts the conventional practice guidelines, but we now have convincing data that FVC correlates better with the degree of airway obstruction and the clinical data health status of the patients.

Conclusion

ΔFEV1 underestimates the true effect of bronchodilator as airway obstruction increases. The addition of ΔFVC to the evaluation will help physicians to better interpret airway reversibility tests, particularly in more severe patients, without adding spirometric maneuvers or measurements. Patients with COPD, even if nonresponders in terms of FEV1, may benefit from bronchodilators because they can breathe at a lower lung volume owing to reduced air-trapping, notwithstanding the fact that they are still flow limited. ΔFVC correlates better than ΔFEV1with the degree of airway obstruction and the clinical status of the patients.

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Conflicts of interest

There are no conflicts of interest.

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