Original Contributions

Change in Forced Expiratory Time and Spirometric Performance During a Single Pulmonary Function Testing Session

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BACKGROUND: Among patients with obstructive lung disease, the correlation between clinical improvement and bronchodilator response is poor. Forced expiratory time (FET) may explain some discrepancy, but FET has received little attention. METHODS: We analyzed change in FET during the 3 initial satisfactory flow-volume loops in 102 consecutive patients, 37 with normal spirometry and 65 with airflow obstruction referred to a Veterans Administration pulmonary function testing (PFT) laboratory over 5 months. Patients included both PFT-naïve and PFT-experienced individuals. We also evaluated the relationship between FET and spirometric performance (sum of forced expiratory volume in the first second and forced vital capacity) and the effect of inhaled bronchodilator on FET among patients with airflow obstruction. RESULTS: Normals and patients with airflow obstruction showed significant increments in FET and in spirometric performance during the 3 initial successive pre-bronchodilator attempts (p < 0.001 for both groups). This was true for PFT-naïve and PFT-experienced individuals. There were significant associations between increments in FET and improvements in spirometric performance in all subgroups. After inhaled bronchodilator there was a further FET increment among patients with airflow obstruction (p = 0.009), but there was no significant difference between bronchodilator responders and nonresponders. CONCLUSIONS: Patients with normal pulmonary function and those with obstruction develop longer FET during the initial phases of spirometric testing, regardless of previous PFT experience. Longer FET is associated with better spirometric performance. Bronchodilator administration is associated with modest prolongation of FET, but change in FET did not help identify bronchodilator responders. *Key words: pulmonary function test, forced expiratory time.* [Respir Care 2006;51(3):246–251. © 2006 Daedalus Enterprises]

Introduction

Simple spirometry remains the cornerstone of pulmonary function testing (PFT). The test is easily performed by most patients, and key spirometric indices such as forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) are often employed in clinical decision making.

A detailed standardized spirometry methodology has evolved and has been widely disseminated and accepted.[1,2] Furthermore, the reproducibility of FEV_1 and FVC has been well characterized for a single individual undergoing multiple spirometry tests over various time periods, including within-day and between-day intervals.[3,4]

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The spirometric response to inhaled bronchodilators has also been avidly studied and characterized, but controversy attends the clinical applicability of the test in many settings. Patients with asthma frequently demonstrate a "positive" test, most recently defined by the American Thoracic Society as a 12% and 200-mL increment in FEV_1 or FVC after bronchodilator administration.[2] However, many chronic asthmatics demonstrate "fixed" obstruction, perhaps related to airway remodeling[5,6] or because of tolerance (ie, resistance) to the effect of bronchodilators.[7] Conversely, patients with chronic obstructive pulmonary disease (COPD) classically do not show a positive response, but there are many exceptions. For example, the severity of the baseline airflow obstruction,[8] the number of bronchodilator tests attempted,[8] and use of body plethysmographic and/or inspiratory indices all can affect response.[9–14] Furthermore, there is a notoriously poor correlation between bronchodilator response, as defined above, and symptom improvement, as measured with the Borg dyspnea scale, walk distance, and other clinically relevant metrics.[15,16]

An additional variable that could mediate the association between bronchodilator response and clinical improvement is the forced expiratory time 100% (FET). Though FET has not received much attention, a few studies have identified "volume responders"; that is, patients who develop a substantial bronchodilator response in terms of FVC only, and appear to mediate this improvement via a prolongation of FET.[17] In some of these patients the forced expiratory volume in the first 3 seconds (FEV_3) and in the first 6 seconds (FEV_6) were unchanged after bronchodilator administration, suggesting that the improvement in FVC was effected via prolonged expiratory effort rather than true bronchodilation.

We have observed anecdotally that, while some substantial bronchodilator responses are accompanied by prolonged FET, in other cases the FET is shortened or virtually unchanged. To begin to ascertain the clinical importance of these patterns, it is first important to understand what happens to the FET during a standard spirometry session, both in normals and in the presence of disease. We had 3 specific goals. First, we sought to characterize the change in FET during successive maximal exhalations in patients with normal lung function and in those with airflow obstruction during routine spirometry. Second, we wished to assess whether change in FET was associated with change in spirometric performance. Third, we sought to characterize change in FET after bronchodilator administration among patients with airflow obstruction. We hypothesized that (1) FET might increase as patients became more familiar with the forced expiratory maneuver, particularly in those with no previous PFT experience, (2) FET increase might be associated with improvement in spirometric performance, and (3) FET might further lengthen in patients with substantial bronchodilator response.

Methods

Patients

We retrospectively analyzed the PFTs of 128 consecutive patients referred to the PFT laboratory of the Philadelphia Veterans Affairs Medical Center, between September 1998 and January 1999. There were 110 outpatients and 18 inpatients. The majority of patients were referred for suspected COPD or asthma. We required "normals" to demonstrate FEV_1 and FVC both $\geq$ 80% of predicted, absolute FEV_1/FVC $\geq$ 0.7, and forced expiratory flow in the middle half of the FVC (FEF_{25-75}) of $\geq$ 50% of predicted.[2] A restrictive impairment was defined as FEV_1 and FVC each < 80% of predicted, with FEV_1/FVC of at least 0.7. An obstructive impairment was defined as FEV_1/FVC < 70% of predicted.[18]

Definitions and Equipment

A single technician, who had more than 25 years of experience, performed all testing according to standard techniques. We excluded patients who were unable to perform at least 3 pre-bronchodilator loops, each with an FET of at least 6 seconds.[1] A flow spirometer (GS, Collins, Ferraris Respiratory, Braintree, Massachusetts) was used to determine the cutoff point for terminating a spirogram. Specifically, when flow diminishes to < 20 mL/0.5 s, an end-of-test marker (an asterisk) appears on the graphic display. The patient is then instructed to inspire maximally. We classified patients as PFT-naïve if there was no record of prior pulmonary function testing, or as PFT-experienced if they had undergone prior PFT studies at the Philadelphia Veterans Affairs Medical Center. We used standard American Thoracic Society criteria to classify patients as bronchodilator responders or nonresponders.[1] Spirometric performance was indexed by the sum of FEV_1 and FVC. We defined the best spirogram as the one with the largest sum of FEV_1 and FVC.[19,20]

Classification of the initial 128 patients according to the above criteria identified 65 with airflow obstruction and 37 normals (Fig. 1). We excluded 26 patients on the basis of spirometry values that suggested a restrictive or nonspecific impairment.

Statistical Analysis

All analyses were carried out with statistical software (Stata 8.2, Stata Corporation, College Station, Texas). To assess the effect of successive spirometry attempts on FET, we used a mixed linear model (the "xtreg" command in the
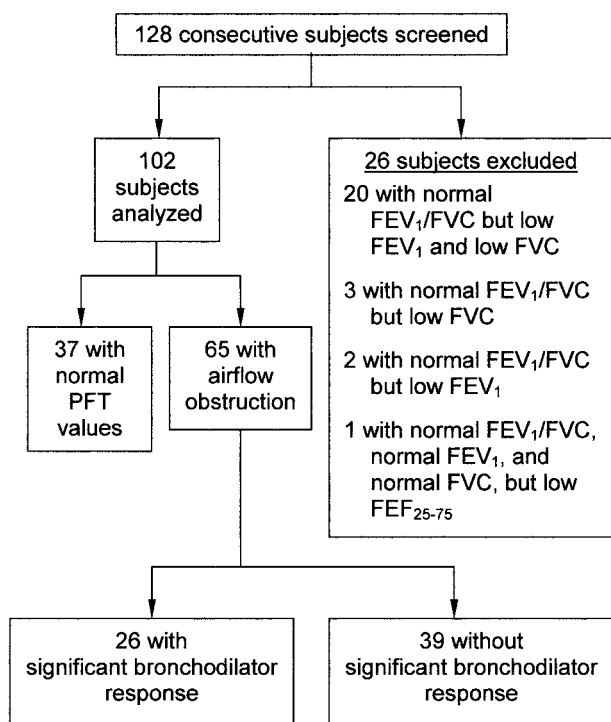
Fig. 1. Patients screened and studied.

Table 1. Patient Demographics

Variable	Normals ($n = 37$)	Patients With Airflow Obstruction ($n = 65$)
Age (mean $\pm$ SD y)	53 ± 13	64 ± 12*
Male (%)	92	97
White/black (%/%)	51/49	63/37
Naïve/experienced (%/%)	78/22	51/49*
Ever-smokers (%)	68	86*
Pack-years (mean $\pm$ SD)	25 ± 33	45 ± 42*
FVC (mean $\pm$ SD % of predicted)	95 ± 12	76 ± 19*
FEV$_1$ (mean $\pm$ SD % of predicted)	96 ± 13	53 ± 19*
FEV$_1$/FVC (mean $\pm$ SD)	80 ± 5	53 ± 12*

*Significant difference ($p < 0.05$) compared with normals
FVC = forced vital capacity
FEV$_1$ = forced expiratory volume in the first second

statistics software. The mixed linear model employed was a generalized least-squares random mixed effects model, in which both the subject and the attempt number (1 through 3) are treated as random effects. This is a conservative way of estimating changes with repeated measures, and was chosen to account for the correlation between successive FETs for a patient performing successive pre-bronchodilator spirograms. We used linear regression to correlate change in FET with change in spirometric performance. In cases where data were skewed, we used the sign rank or the rank sum test. To further characterize the reproducibility of FET, we calculated the coefficient of variation (defined as $100 \times$ standard deviation/mean) for FET as well as for FEV$_1$ and FVC.

Results

Patient Characteristics

Patients with airflow obstruction were significantly older, smoked more, and had impaired FEV$_1$ and FVC, compared to normals. Sixty-two patients (61%) were PFT-naïve, and 40 patients (39%) were PFT-experienced (Table 1).

Pre-bronchodilator FET

The median baseline FET from the best spirogram was 9.15 seconds (25th percentile 8.1, 75th percentile 10.7) for the 37 normals, and 11.3 seconds (25th percentile 9.7, 75th percentile 13.2) for the 65 patients with airflow obstruction ($p = 0.001$ for difference). The majority of pre-bronchodilator loops showed some increment in FET, when comparing a loop with the previous loop, both for normals (70%) and for patients with airflow obstruction (60%). Table 2 shows the changes in FET over the course of successive pre-bronchodilator loops. Using the mixed linear model to assess loops 1 through 3 as a group, we found a significant FET increase in both normals and patients with airflow obstruction ($p < 0.001$ for both groups). The FET increase was seen among both PFT-naïve and PFT-experienced patients ($p < 0.001$ for both). The coefficients of variation for all patients were 14.8% for FET, 4.7% for FEV$_1$, and 4.7% for FVC.

Spirometric Performance and FET

Spirometric performance (FEV$_1$ + FVC) also showed improvement with successive loops (see Table 2). Using the mixed linear model to assess loops 1 through 3 as a group, we found significant increases among normals and among patients with airflow obstruction ($p < 0.001$ for both groups). Significant increases also were seen in PFT-naïve and PFT-experienced patients ($p < 0.001$ for both groups). Using linear regression, FET increase was associated with improvement in spirometric performance among normals ($p < 0.001$, $r = 0.10$); patients with airflow obstruction ($p = 0.005$, $r = 0.09$); PFT-naïve patients ($p = 0.003$, $r = 0.07$); and PFT-experienced patients ($p < 0.001$, $r = 0.18$).

Post-Bronchodilator FET

Sixty-four of the 65 patients with airflow obstruction underwent bronchodilator testing, of whom 26 (41%) had

Table 2. Change in Forced Expiratory Time, FEV$_1$, and FVC

Patient Type	Forced Expiratory Time (seconds)								
	Loop 1			Loop 2			Loop 3		
	Median	25th Percentile	75th Percentile	Median	25th Percentile	75th Percentile	Median	25th Percentile	75th Percentile
Normal*	7.8	7.2	8.4	8.1	7.0	9.8	9.0	7.8	10.6
Airflow obstruction*	10.1	8.6	12.1	10.7	9.2	12.3	11.1	9.3	13.1
PFT-naïve*	8.3	7.2	9.6	9.5	7.7	10.7	9.9	8.3	11.7
PFT-experienced*	10.3	9.0	12.3	11.0	8.7	12.3	10.9	8.6	12.3
	Loop 1			Loop 2			Loop 3		
	FEV$_1$ (L)		FVC (L)	FEV$_1$ (L)		FVC (L)	FEV$_1$ (L)		FVC (L)
Normals (mean ± SD)*	7.0		1.4	7.1		1.4	7.3		1.5
Airflow obstruction (mean ± SD)*	4.5		1.5	4.7		1.5	4.8		1.6
PFT-naïve (mean ± SD)*	5.8		1.9	5.9		1.8	6.1		1.9
PFT-experienced (mean ± SD)*	4.9		1.8	5.0		1.9	5.1		1.9

*p < 0.001, using the mixed linear model to assess overall change from Loop 1 through Loop 3.
FEV$_1$ = forced expiratory volume in the first second
FVC = forced vital capacity
PFT = pulmonary function test

a substantial response. Among the 64 patients who received bronchodilators, the median FET from the best spirogram rose from 11.3 seconds before bronchodilator (25th percentile 9.7, 75th percentile 13.2) to 12.4 seconds after bronchodilator (25th percentile 10.9, 75th percentile 14.4) (p = 0.009 for difference). Comparing pre-bronchodilator to post-bronchodilator values, among bronchodilator responders the FET increase was 1.0 seconds (25th percentile −0.9, 75th percentile 3.0), and among nonresponders the FET increase was 0.5 seconds (25th percentile −0.7, 75th percentile 2.2), but these increments did not reach statistical significance (p = 0.071 and p = 0.083, respectively). The post-bronchodilator FET increment did not differ significantly between responders and nonresponders (p = 0.483). Finally, post-bronchodilator FET increases were generally not related to post-bronchodilator changes in FEV$_1$ and FVC. There was one exception: post-bronchodilator FEV$_1$ increases were associated with FET *decreases* among bronchodilator nonresponders.

Discussion

Our main aims were to describe the change in FET during pre-bronchodilator spirometry, assess the relationship of FET to spirometric performance (FEV$_1$ + FVC), and test the effect of bronchodilator administration on FET. We found significant FET increases during the first 3 pre-bronchodilator spirometric loops among all patients, including both normals and those with airflow obstruction. This pattern pertained to both PFT-naïve and PFT-experienced individuals. The pre-bronchodilator increment in FET was associated with improvement in spirometric performance, defined as the sum of FEV$_1$ and FVC. We also confirmed the previously reported finding of higher variability in FET than in FEV$_1$ or FVC.[21] Finally, though FET increased further after bronchodilator administration, change in FET did not differentiate between responders and nonresponders.

The mechanism of these patterns is unclear. Perhaps the trend toward more sustained and successful efforts in part reflects a learning response, at least through the first 3 loops. As the patient becomes familiar with the laboratory apparatus, the forced expiratory maneuver itself, and the technician, a lengthier effort is made, one that more often than not results in improved spirometric performance. Alternatively, one could speculate that either progressive alveolar recruitment or a subtle change in patient positioning leads to more efficient respiratory muscle functioning and thus to improved FET and spirometric performance.

Our data are compatible with the findings of Hansen et al,[22] who found that patients with airflow obstruction achieved the highest FEV$_1$ values more often on the second, third, or fourth attempt than on the first or fifth. (Those authors did not analyze FET or study patients who had normal PFT values, however.) Though other work based on multiple spirometry sessions found little evidence of a learning effect,[23,24] Larsson et al found (as we did) that the first effort within a single session was significantly less often the best curve (vs the second or third). This phenomenon was referred to as "adaptation to the test."[23]

Our work also confirms Girard and Light's finding that post-bronchodilator FET tends to exceed pre-bronchodilator FET.[17] This could simply represent a continuation of the pre-bronchodilator FET increase. It is also possible that in some patients with airflow obstruction, bronchodilation might allow for opening of closed airways, resulting in a longer expiratory effort, which might lower residual volume and increase FVC.[17] However, we found that post-bronchodilator FET increases did not help distinguish between bronchodilator responders and bronchodilator non-responders. Also, post-bronchodilator FET increases were not associated with further increases in FEV_1 or FVC.

Our distinction between PFT-naïve and PFT-experienced subjects requires comment. Most of our patients lack health insurance that would allow access to private-sector healthcare organizations, and they therefore must use the Philadelphia Veterans Affairs Medical Center exclusively for their health care (based on Veterans Affairs regional eligibility rules). Thus, we believe it is unlikely that many subjects previously had pulmonary function testing at other sites. However, we have no data to specifically test this assumption. Moreover, since the pattern of increments in FET and spirometric performance proved to be similar among the subjects we classified as PFT-naïve and PFT-experienced, the distinction seems less important than originally anticipated.

Several limitations pertain to our study. Most importantly, it was not designed to assess the relationship between change in FET and changes in clinical indices such as dyspnea or walk distance. As a small, retrospective study performed in a single center with a relatively homogeneous cohort of older male veterans, the results may or may not be applicable to other settings and patient populations. In addition, though we recorded and analyzed the *duration* of expiratory effort, we did not gauge the *intensity* of that effort, as would be reflected by transdiaphragmatic or maximum expiratory pressures. We also did not perform body plethysmography, which often can better define true bronchodilation, via measurement of airway resistance and other variables. Most of our patients performed no more than 3 loops, so we cannot comment on subsequent trends in FET or spirometric performance. We also did not investigate various inspiratory indices that have been proposed as potentially useful in defining bronchodilator response,[9–14] though these are seldom used in usual clinical practice. Finally, our inferences are limited by the small sample size, and definitive conclusions must await the completion of larger studies.

Nevertheless, ours is among the first attempts to analyze FET and spirometric performance within a single testing session. Our data apply to individuals with normal PFT values and to a population of broad clinical interest, including a high frequency of cigarette smokers and patients with airflow obstruction. Furthermore, the techniques and bronchodilator criteria we used reflect American Thoracic Society standards and are familiar to most practicing pulmonary physicians and PFT laboratory technicians.

Conclusions

Our data suggest that FET tends to increase during pre-bronchodilator testing among all patients, including both normals and those with airflow obstruction, as well as PFT-naïve and PFT-experienced subjects. FET increases during the first 3 loops are associated with improvements in spirometric performance. Bronchodilator administration further increased FET, but this increase did not help identify bronchodilator responders. Therefore, though our analysis of FET provides insight into spirometric performance during successive maneuvers in a single testing session, a clinical role for FET was not identified. Future larger studies might find a role for FET in characterizing bronchodilator response, with the ultimate goal of correlating spirometric change with clinical outcomes.

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