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Partial versus maximal forced exhalations in COPD: Enhanced signal detection for novel therapies

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ABSTRACT

Background: Evaluation of novel compounds for COPD often relies on FEV1 for signal detection. Partial forced exhalations from end-tidal inspiration (PEFV) might complement FEV1 in identifying such a signal. We examined the prevalence of bronchodilator response (BDR) using PEFV and FEV1 in patients with COPD.

Methods: 110 consecutive COPD patients were tested prospectively with PEFV and maximal expiratory flow before and after inhalation of a short-acting β2 agonist (salbutamol, 400 μg). Partial flow at 800 ml above residual volume was derived from the PEFV (PF800). Significant changes in PF800 and/or FEV1 were set at the upper 95% confidence interval after placebo ($n = 28$).

Results: Four groups were identified by the presence (+) or absence (−) of a BDR: Group 1 [PF800 (−) FEV1(−)] when no change was observed ($n = 31$), Group 2 [PF800(+)FEV1(−)] when PF800 alone improved ($n = 31$), Group 3 [PF800(−)FEV1(+)] when FEV1 alone improved ($n = 26$), and Group 4 [PF800(+)FEV1(+)] when both variables improved ($n = 18$). There were 35 non-responders in any parameter, and 75/110 subjects who showed a response in at least one parameter. The changes in PF800 and FEV1 were not correlated suggesting these assess different airway generations.

Conclusions: The use of PF800 increased detection of a BDR in COPD compared to FEV1 alone and may reflect small airway responses. The PEFV maneuver is simple, repeatable and may avoid some of the theoretical disadvantages of FEV1. The role of PF800 for evaluating novel anti-inflammatory agents remains to be determined.

1. Background

The search for novel therapeutic agents to address the substantial unmet need in COPD is a major challenge confronting this field of research [1]. Once safety has been demonstrated for a novel compound in phase 1, efficacy signals are usually sought in a small study and FEV1 is the most-utilized parameter. Most therapeutics in COPD were first approved for FEV1 e.g. steroids-long-acting bronchodilator combinations [2].

The reliance on FEV1 in a proof of concept pharmaceutical study could result in a falsely negative assessment of response and lead to discontinuation of development despite benefiting other parameters, e.g. COPD exacerbations. For instance, the oral phosphodiesterase-4 inhibitor roflumilast produced a modest reduction for COPD exacerbations (~20%) and non-clinically-meaningful improvement in FEV1 (~40-60 mLs) [3].

FEV1 is derived from maximal expiratory flow volume maneuvers (MEFV) from total lung capacity (TLC) [4]. The advantages of FEV1 include standardization and acceptability by regulatory authorities. However, maximum flows from MEFV maneuvers are predominantly determined by the caliber of central airways and are less sensitive to changes in the distal lung [5], the location of airflow obstruction in COPD [6]. Furthermore, MEFV maneuvers compress intrathoracic airways exaggerating flow limitation [7].

Accordingly, a practical readily-available supplementary measurement for lung function that will complement FEV1 and also assess small airways is begging. We herein report on the prevalence of a bronchodilator response to inhaled salbutamol assessed with

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Abbreviations

6-MWT	6 min walk test
BDR	bronchodilator response
BODE index	multifactorial index of COPD severity (see text)
TLCO	Transfer factor for carbon monoxide
ERV	expiratory reserve volume
FEV1	forced expiratory volume in 1 s
FEV1/FVC	FEV1 to FVC ratio
FVC	forced vital capacity
IC	inspiratory capacity
MEFV	maximal expiratory flow volume
MMFR	mid maximum flow rate
MEF25	maximal expiratory flow at 25% vital capacity
MEF50	maximal expiratory flow at 50% vital capacity
MEF75	maximal expiratory flow at 75% vital capacity
PEF	peak expiratory flow
PF	forced partial expiratory flow
PF800	forced partial expiratory flow at 800 ml above RV
PEFV	partial expiratory flow volume
RV	residual volume
TGV	thoracic gas volume
TLC	total lung capacity
BODE index	multifactorial index of COPD severity (see text)
VC	vital capacity

partial expiratory flow volume (PEFV) maneuvers from end-tidal inspiration and/or MEFV maneuvers (FEV1) in a cohort of subjects with COPD. PEFV maneuvers are less effort-dependent, may reflect to a greater extent pathological changes in the distal lung relevant to COPD as suggested by Bouhuys et al. [8], and are less impacted by compression of the airways due to the forced maneuver than MEFV [9].

2. Material and methods

2.1. Population

122 consecutive COPD patients attending routine consultation were recruited. COPD diagnosis was established according to the COPD GOLD guidelines. Exclusion criteria included BMI >30 kg/m2, a history of asthma, COPD exacerbation during the prior two months, and inability to perform study maneuvers. A >10 pack year history of cigarette use was required and active smokers were included. Other significant respiratory conditions e.g. bronchiectasis, old tuberculosis and interstitial lung disease were not permitted.

2.2. PEFV maneuvers

These were performed before MEFV maneuvers to reduce volume history effects. The patient breathed quietly for 10–15 breaths with tidal breath profiles displayed. When breathing was steady and reproducible, the patient expired forcibly to RV from end tidal inspiration for at least 6 s. The end of test criteria was carefully followed in the same way for PEFV as is required for MEFV maneuvers [10]. As for the maximal flow-volume loop, the partial flow-volume loop can be separated in an effort-dependent part and an independent part [8]. The parameter selected from the PEFV maneuver was partial flow 800 ml above the maximal expiratory point (PF800), so that this flow would fall in the effort-independent part of the partial curve. The choice of 800 ml above RV was considered a good compromise between the flow value, which is accurately measurable even in severe obstruction, and the proximity of RV. Patients with very low expired reserve volume (ERV) were asked to make a small inspiration before the forced expiration in order to obtain (tidal volume + ERV) > 0.8L. Maneuvers that did not start above RV + 0.8L were rejected. In order to avoid variation in the level of measurement of PF 800, patients were asked to expire for at least 6 s but less than 15 s; in most cases they expired for at least 10 s which would have ensured attainment of true RV in the vast majority of efforts. Once defined, this expiratory time was kept constant for the other maneuvers and thereby permitted standardization of the lung volume at which the measure of partial flow was done. Up to five maneuvers were performed to obtain at least 3 measurements within 15%.

Fig. 1 displays a typical PEFV maneuver (Fig. 1a) and a PEFV loop (Fig. 1b); PF800 is indicated on the PEFV loop.

2.3. MEFV maneuvers

After completion of PEFV maneuvers, subjects made three repeatable MEFV maneuvers from TLC to obtain FEV1 (3 measures within 150 ml).

2.4. Order of procedures

Prebronchodilator assessments were in sequence: the Saint George's Respiratory Questionnaire (SGRQ), PEFV followed by MEFV maneuvers, a 6 min walk test (6-MWT) and Borg dyspnea scale [11]. All procedures except SGRQ were repeated 30 min after the administration of 400 μg salbutamol via spacer.

2.5. Determination of thresholds for significant bronchodilator response

To establish thresholds for clinically-meaningful changes, the response of PF800 and FEV1 to placebo was measured at an additional study visit in a single-blind fashion in a subset of the patients in the study. Clinically meaningful responses for FEV1 and PF800 were defined as the 95% upper confidence limits for the placebo response, similarly to previous studies [12].

2.6. Other tests

Measurements of plethysmographic lung volumes and single breath carbon monoxide diffusion (DLCO) were performed to characterize patients. Patients were grouped by severity of COPD [13] and the BODE index was calculated [14].

2.7. Equipment

All lung function variables were acquired with Medisoft equipment (Bodybox, Hyp'Air Compact, Dinant, Belgium). Predicted values for spirometry were obtained from Stanojevic et al. [15] and for DLCO from the ATS/ERS Task Force recommendations [10].

2.8. Statistical analysis

Data were processed with the IBM SPSS version 20.0 (Chicago USA). Mean, standard deviation (SD) and confidence interval at 95% (CI) were used to describe the results. Results post-