The Confounding Effects of Thoracic Gas Compression on Measurement of Acute Bronchodilator Response

Amir Sharafkhaneh^{1,2}, Tony G. Babb³, Todd M. Officer¹, Nicholas A. Hanania¹, Hossein Sharafkhaneh¹, and Aladin M. Boriek¹

¹Baylor College of Medicine, Houston, Texas; ²Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; and ³UT Southwestern Medical Center, Dallas, Texas

Rationale: Improvement in FEV₁ is a main endpoint in clinical trials assessing the efficacy of bronchodilators. However, the effect of bronchodilators on maximal expiratory flow may be confounded by thoracic gas compression (TGC).

Objective: To determine whether TGC confounds effect of albuterol on FEV₁.

Methods: We evaluated the response to albuterol inhalation in 10 healthy subjects, 9 subjects with asthma, and 15 subjects with chronic obstructive pulmonary disease (COPD) with mean (SD) age in years of 38 (SD, 11), 45 (SD, 11), and 64 (SD, 8), respectively. Lung mechanics were measured at baseline and 20 minutes after inhalation of 180 µg of albuterol. We then applied a novel method to calculate FEV₁ corrected for the effect of TGC (NFEV₁).

Results: Prior to albuterol administration, NFEV₁ was significantly higher than FEV₁. However, post-albuterol inhalation, FEV₁ increased more than NFEV₁ because of reduced TGC. In multiple regression analysis, the changes in TGC, inspiratory lung resistance, and ratio of residual volume to total lung capacity postalbuterol predicted more than 75% of FEV₁ improvement in patients with COPD.

Conclusion: Improvements in FEV₁ after albuterol in patients with COPD are due to reduction of lung resistance, hyperinflation, and TGC. The latter is negligible during tidal breathing. Thus, although reduction of lung resistance and hyperinflation may result in improved dyspnea with a bronchodilator, the contribution of TGC reduction to improvement of FEV₁ may not exert any meaningful clinical effect during tidal breathing. This fact has to be taken into consideration when assessing the efficacy of new bronchodilators.

Keywords: FEV₁; chronic obstructive pulmonary disease; asthma; lung mechanics; albuterol

Expiratory airflow limitation is the hallmark of physiologic abnormality in asthma and chronic obstructive pulmonary disease (COPD) (1–3). Bronchodilators improve expiratory airflow, thus improving exercise capacity and relieving symptoms in patients suffering from these diseases. Clinical trials assessing the effect of bronchodilators use the improvement in FEV₁ as the main efficacy endpoint. However, FEV₁ improvement does not correlate very well with improvement in symptoms and exercise capacity (4).

(Received in original form February 20, 2006; accepted in final form November 16, 2006)

Supported in part by NIH HL-072839 (A.M.B.).

Correspondence and requests for reprints should be addressed to Amir Sharafkhaneh, M.D., Assistant Professor of Medicine, Baylor College of Medicine, M.E.D. VAMC, Bldg. 100 (111i), 2002 Holcombe Blvd., Houston, TX 77030. E-mail: amirs@bcm.tmc.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 175, pp 330–335, 2007

Originally Published in Press as DOI: 10.1164/rccm.200602-255OC on November 16, 2006
Internet address: www.atsjournals.org

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung function is used to evaluate response to therapy. However, confounding factors, including thoracic gas compression, may affect change in lung function with therapy.

What This Study Adds to the Field

Thoracic gas compression may confound effect of bronchodilators on lung function. Improvements in FEV₁ after inhaled β-adrenergic agents in COPD are due to reduction in lung resistance, hyperinflation, and thoracic gas compression.

Maximal expiratory airflow results from a unique flow–pressure–volume relationship, which reflects the mechanical properties of lungs and airways (5–7). It is determined by the lung elastic recoil pressure, the upstream frictional pressure loss, and the relationship between cross-sectional area and transmural pressure at the choke point (7, 8). Lung elastic recoil pressure depends on the absolute lung volume (9, 10).

During a forced expiratory maneuver in a subject with expiratory airflow limitation, the expired volume at the mouth (measured by a pneumotachograph) may differ considerably from the change in lung volume measured with a body plethysmograph. This difference in volume is primarily due to thoracic gas compression (TGC). TGC occurs at high and mid-lung volume (3, 11, 12) and is primarily affected by airway resistance, effort, and absolute lung volume (5, 13). TGC is high in subjects with large lung volume, strong expiratory muscles, and expiratory airflow limitation (14).

Bronchodilators improve expiratory airflow limitation by reducing lung resistance. This change in resistance can alter the amount of gas compression and thus results in altered flow–volume–pressure relationship and maximal expiratory airflow. Therefore, the reduction in TGC after inhalation of a bronchodilator may reduce the negative effect of TGC on forced expiratory airflow. Although both diminished lung resistance and TGC with a bronchodilator improve maximal expiratory airflow, only the diminished lung resistance affects expiratory airflow during tidal breathing. Thus, the presence of TGC may confound the effect of a bronchodilator on maximal expiratory airflow.

In this study, we investigated the mechanisms of improved maximal expiratory airflow subsequent to inhalation of albuterol to explore any confounding effects of TGC. We hypothesized that the improvement in FEV₁ postalbuterol is due to the combined effect of reduced airway resistance and reduced gas compression.

METHODS

Study Subjects

We measured lung mechanics at baseline and 20 minutes after inhalation of albuterol (180 µg from a metered dose inhaler) in healthy subjects,

subjects with asthma, and subjects with chronic obstructive pulmonary disease (COPD). The diagnoses of asthma and COPD were based on the American Thoracic Society criteria (15). All subjects had to be in stable clinical condition with no change in respiratory medications within the last 4 weeks of testing. Subjects with asthma and COPD were asked to withhold their short- and long-acting bronchodilators for 8 and 24 hours before the test, respectively. The study was approved by the local institutional review board, and each subject signed a written, informed consent form prior to participation in the study.

Measurements

Lung mechanics were measured with the subject seated in a custom-made volume-displacement plethysmograph (16). During each session, we obtained at least three reproducible forced expiratory maneuvers. Quality control measures, as outlined by the American Thoracic Society, were used to select appropriate maneuvers (17). Inspiratory and expiratory lung resistances were measured during quiet breathing using the model reported before (18). Total lung capacity (TLC) and residual volume (RV) were also measured at baseline and 20 minutes after bronchodilator administration. We recorded esophageal pressure as an indicator of effort. Details of the measurements are provided in the online supplement.

We used a novel computational program in MATLAB environment to calculate the FEV_1 corrected for the effect of TGC ($NFEV_1$). First, the software generates a plot of the expiratory flow signal versus the box volume signal in an x-y graph (Figure 1A). This plot represents the forced expiratory flow volume loop with units of liters/second (L/s) on the y axis and liters (L) on the x axis. Subsequently, the software inverts the expiratory flow signal between TLC and RV, plots box volume signal (L) on the x axis and inverted expiratory flow signal (s/L) on the y axis, and generates a graph (Figure 1B). This new graph contains a very steep negative slope at the beginning of the maneuver that reverses to a positive shallow slope during the effort independent portion (<80% of TLC) of the FVC maneuver. Subsequently, the software uses the following algorithm to calculate the computed time (Z).

$$Z(n) = \sum_{n=1}^{\infty} \frac{1}{V(t_n + t_{n-1})} * V_{box}(t_n + t_{n-1})$$

This computed time (Z), a time based on volume and flow, is the mouth transit time for increments of box volume. By summing each computed time point, the software reconstructs a timeline that represents volume changes based on expiratory mouth flow and body plethysmograph volume.

After generating the computed time, the software calculates the subject's $NFEV_1$ (Figure 1C displayed as a *solid line*). The backward extrapolation technique is used to determine the start time for the $NFEV_1$ calculation. The software uses the computed time for this determination instead of the standard linear time. The start time is determined by assuming that peak flow had begun since the expiration began at TLC. Volume-time curves are shown in Figure 1D. These curves are recorded at the mouth and are based on mouth-flow and box-volume measurements as described. To estimate the magnitude of gas compression, we used the following equation:

$$AFEV_1 = NFEV_1 - FEV_1$$

$$\% \text{Compression} = (NFEV_1 - FEV_1) / NFEV_1$$

Where AFEV and %Compression are absolute and percentage differences between FEV_1 and $NFEV_1$, and $NFEV_1$ and FEV_1 , are absolute values of forced expired volume (L) in the first second as measured by the no compression method (NCM) and standard method (19). In brief, NCM is the novel computation for measuring the effects of gas compression on maximal expiratory flow described above (19). $AFEV_1$ differs from the true compressed volume because the former represents an estimate of cumulative compressed volume in the first second of a forced maneuver whereas the latter is the difference between plethysmographic volume and the expired volume in each instant of the maneuver. The instantaneous volume difference can be used to back-calculate the volume of gas (close to TLC at the beginning of the maneuver) that would have to be compressed with an assumed esophageal pressure. In contrast, $AFEV_1$ cannot be used to back-calculate the volume under compression.

Data Analysis

We used Stata version 9 (StataCorp, College Station, TX) for data analysis. Demographic and baseline lung function data were analyzed by descriptive statistics and are presented as means $\pm$ SD. We used analysis of variance to compare the values among normal subjects and patients with asthma and COPD. We used paired *t* test to compare lung parameters pre- and post-albuterol administration. The relationships between FEV_1 improvement and other lung mechanics parameters were evaluated by stepwise multiple regression analysis. A *p* value of less than 0.05 was considered significant.

RESULTS

We enrolled 10 healthy subjects, 9 patients with asthma, and 15 patients with COPD. All patients with COPD were male,

Figure 1. The steps taken to obtain FEV_1 using no compression method ($NFEV_1$). (A) A flow-volume loop and associated gas compression in a patient with expiratory flow limitation (chronic obstructive pulmonary disease) measured using a plethysmograph. (B) A curve generated by plotting inverse flow (s/L) against volume. The crowding of the data points at the end of this curve is due to compression of the time scale, related to the very low flows. Integrating the area under the curve in B produces the computed time. (C) The volume change measured with plethysmograph versus this computed time. (D) Regular volume versus time (*thin line*) and $NFEV_1$ (*thick line*). Reprinted by permission from Reference 19.

whereas five of the normal subjects were females and five of the patients with asthma were female. Mean (SD) age in years for normal subjects and subjects with asthma or were 38 (SD, 11), 45 (SD, 11), and 64 (SD, 8) years, respectively. Mean heights in centimeters for normal subjects and patients with asthma or COPD were 170 (SD, 11), 172 (SD, 8), and 179 (SD, 6) cm, respectively. Only one of the normal subjects was a smoker, whereas none of the subjects with asthma had a smoking history of more than 10 pack-years. Five subjects with asthma were using short-acting bronchodilator on an as-needed basis, whereas the other four were receiving inhaled corticosteroid and/or long-acting β -agonist. All but five of the patients with COPD had stopped smoking more than a year before the study. All the patients with COPD were receiving inhaled bronchodilators and/or inhaled corticosteroid. Baseline and post-bronchodilator pulmonary function data are shown in Table 1. Mean FEV₁ in subjects with asthma did not reverse to normal range; however, the reversibility was higher than in subjects with COPD who had severe disease with evidence of significant hyperinflation.

Baseline mean FEV₁ and NFEV₁ as well as baseline FVC, TLC, RV/TLC ratio, expiratory lung resistance (R_{Le}), inspiratory lung resistance (R_{Li}), PEF, and maximal esophageal pressure during forced maneuver (EP_{peak}) differed significantly among the three study groups ($p < 0.05$). FEV₁ as well as peak expiratory airflow significantly increased with albuterol inhalation. Furthermore, in patients with asthma and COPD, FVC increased, whereas R_{Le}, R_{Li}, RV, and RV/TLC decreased significantly (for p values, see Table 1).

%Compression was defined as (NFEV₁ – FEV₁)/NFEV₁. We used %Compression as an index of TGC. %Compression was significantly larger in patients with COPD compared with normal subjects ($p < 0.0001$). In univariate regression analysis, prealbuterol %Compression was significantly predicted by R_{Le}, R_{Li}, TLC, RV/TLC ratio, and PEF (all p values < 0.05). In a stepwise multiple regression analysis, %Compression correlated significantly only with R_{Li}, RV/TLC ratio, and EP_{peak} (R_{Li}, $p < 0.05$; RV/TLC ratio, $p < 0.01$; EP_{peak}, $p < 0.0001$; adjusted $R^2 = 0.75$).

We defined the absolute and percent difference between FEV₁ and NFEV₁ as AFEV₁ and %Compression, respectively

(see METHODS). AFEV₁ and %Compression diminished significantly in subjects with COPD post-albuterol inhalation ($p < 0.03$ and $p < 0.005$, respectively) but did not reach statistical significance in subjects with asthma or in normal subjects.

In univariate analyses, absolute and percent FEV₁ improvement postalbuterol significantly correlated with the reduction of %Compression, RV/TLC ratio, and R_{Li} (%Compression: $p < 0.001$, adjusted $R^2 = 0.75$; RV/TLC: $p < 0.0001$, adjusted $R^2 = 0.71$; R_{Li}: $p < 0.01$, adjusted $R^2 = 0.39$) in subjects with asthma and COPD. In multiple regression analysis, FEV₁ improvement correlated significantly with change in R_{Li} and RV/TLC ratio (R_{Li}, $p < 0.004$; RV/TLC ratio, $p < 0.05$; adjusted $R^2 = 0.56$). Addition of change in %Compression improved the regression (p for %compression change < 0.0001 , adjusted $R^2 = 0.79$). This predicts that 23% of FEV₁ improvement was predicted by reduction of gas compression.

In subjects with COPD, FEV₁ increased 190 ml (SD, 150) and 19% (SD, 15) from baseline, whereas NFEV₁ increased only 120 ml (SD, 110) and 7% (SD, 7) from baseline. Both absolute and percentage changes from baseline were significantly different between FEV₁ and NFEV₁ ($p < 0.05$). In subjects with asthma, FEV₁ increased 260 ml (SD, 270) and 15% (SD, 16) from baseline, whereas NFEV₁ increased 240 ml (SD, 216) and 11% (SD, 11) from baseline.

FVC also improved significantly after albuterol inhalation. Reduction in %Compression and RV/TLC ratio significantly predicted FVC improvement in subjects with asthma and COPD ($p < 0.0001$ and $p < 0.0001$, respectively; adjusted $R^2 = 0.93$).

A representative set of data from a subject with COPD before and after albuterol inhalation is presented in Figure 2. Figures 2A and 2B show the flow volume loop before and after inhalation of albuterol. The volume measured with the plethysmograph was appreciably different from the volume measured from integration of mouth flow at baseline and after albuterol. However, after albuterol inhalation, the flow difference at each volume point of FVC between the loops diminished (TGC). The volume at PEF obtained from mouth airflow diminished from 170 to 100 ml with albuterol inhalation. The volume at PEF obtained from plethysmograph flow diminished from 340 to 240 ml with

TABLE 1. LUNG FUNCTION DATA FOR NORMAL SUBJECTS, SUBJECTS WITH ASTHMA, AND SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE BEFORE AND AFTER INHALATION OF ALBUTEROL

Parameters	Normal		Asthma		COPD	
	Pre	Post	Pre	Post	Pre	Post
FEV ₁ , %	94 (3)	100 (4)*	57 (3)	65 (4) [†]	33 (2)	38 (3) [‡]
FEV ₁ , L	3.26 (0.60)	3.43 (0.67)*	1.97 (0.68)	2.23 (0.74) [†]	1.17 (0.49)	1.36 (0.51) [‡]
NFEV ₁ , L	3.61 (0.69)	3.80 (0.76)*	2.52 (0.65)	2.76 (0.64) [†]	1.74 (0.50)	1.86 (0.52) [‡]
AFEV ₁	0.35 (0.06)	0.37 (0.08)	0.39 (0.07)	0.35 (0.09)	0.57 (0.08)	0.50 (0.07) [†]
%Compression	10% (4%)	10% (5%)	15% (10%)	12% (10)	32% (14%)	27% (13) [‡]
FVC, L	4.16 (0.7)	4.23 (0.8)	3.04 (0.9)	3.34 (0.9) [‡]	2.98 (0.9)	3.40 (0.9) [‡]
FEV ₁ /FVC, %	78 (5)	81 (6)	65 (8)	69 (9)	39 (7)	39 (7)
TLC, L	6.5 (0.44)	6.8 (0.47) [†]	7.7 (0.52)	7.6 (1.3)	8.9 (1.32)	9.0 (1.4)
RV/TLC, %	31 (6)	32 (6)	37 (14)	38 (4)	60 (7)	58 (6) [‡]
R _{Le} , cm H ₂ O/L/s	3.2 (0.7)	3.5 (1.7)	15.0 (12.5)	10.9 (9.8) [†]	17.1 (8.7)	12 (7.1) [‡]
R _{Li} , cm H ₂ O/L/s	1.6 (0.5)	1.2 (0.4) [†]	7.8 (5.6)	5.3 (3.5) [†]	4.8 (1.8)	3.4 (1.4)*
PEF, L/s	7.4 (1.9)	8.3 (2.4)*	5.2 (1.4)	5.9 (1.5) [‡]	3.4 (1.1)	3.7 (1.1) [†]
EP _{peak} , cm H ₂ O	80 (21)	86 (19)	129 (44)	132 (53)	133 (62)	132 (55)

Definition of abbreviations: AFEV₁ = NFEV₁ – FEV₁; %Compression = (NFEV₁ – FEV₁)/NFEV₁; EP_{peak} = maximal esophageal pressure during a forced expiratory maneuver; FVC = forced expired volume during a forced maneuver; NFEV₁ = FEV₁ obtained using no compression method; R_{Le} = expiratory lung resistance; R_{Li} = inspiratory lung resistance.

All data are presented as mean and SD.

* p value for comparison of pre- and post-bronchodilator using paired t test, $p < 0.01$.

[†] p value for comparison of pre- and post-bronchodilator using paired t test, $p < 0.05$.

[‡] p value for comparison of pre- and post-bronchodilator using paired t test, $p < 0.005$.

Figure 2. Effect of bronchodilator administration on FEV₁ (dashed line) and NFEV₁ (solid line) in a subject with chronic obstructive pulmonary disease. A and B show the flow-volume loop at (A) baseline (prebronchodilator) and (B) after bronchodilator inhalation. A shows that the volume measured with plethysmograph is appreciably different from the volume measured from exhaled volume. B demonstrates that the difference between the two volumes is smaller after inhalation of albuterol. The difference between volume for PEF from expired flow and volume for PEF from plethysmograph flow diminished with bronchodilator. Similarly, the difference between volumes at RV between mouth-expired volume and plethysmograph volume change diminished with inhalation of albuterol.

albuterol inhalation. The difference in PEF volume for mouth and plethysmograph flow diminished from 170 to 140 ml. Figures 2A and 2B also show similar reduction in volume difference at residual volume between mouth airflow and plethysmograph airflow with inhalation of albuterol.

Data in Figure 3 represent lost volume due to gas compression against time in three study subjects before (*thin line*) and after (*thick line*) inhalation of albuterol. AFEV₁ was appreciably higher in patients with COPD compared with patients with asthma and normal subjects. Furthermore, in all three examples, AFEV₁ was larger before inhalation of albuterol. Figure 3A is from a normal subject. As expected, in this normal subject, lost volume was not appreciably different before and after albuterol. Figure 3B is from a subject with asthma. In this subject, lost volume did not change significantly with albuterol. In contrast, the lost volume in a patient with COPD (Figure 3C) was significantly diminished with albuterol inhalation. In all three subjects (before and after inhalation of albuterol), the lost volume was more at the beginning of the forced maneuver compared with the end of the maneuver.

DISCUSSION

In this study, we explored the mechanisms of maximal expiratory airflow improvement after bronchodilator administration by studying the effect of albuterol inhalation on lung mechanics. Our data show that inhalation of albuterol improves maximal expiratory airflow by reducing lung resistance (R_{Li} and R_{Le}), hyperinflation (RV/TLC ratio), and TGC (AFEV₁ and %Compression). This phenomenon was more pronounced in subjects with more severe airflow obstruction, such as those with COPD. Our finding suggests that, in subjects with COPD, improvement in FEV₁ after a bronchodilator inhalation is confounded by reduction in TGC. Reduction of lung resistance and hyperinflation improve expiratory airflow during both forced and nonforced exhalation and thus may correlate with improvement in symptoms and exercise capacity. However, TGC is negligible during nonforced expiration and occurs mainly with forced expiration and thus its reduction may not have any meaningful clinical

effect during nonforced expiration. Our data suggest that more than 20% of FEV₁ improvement is in fact due to TGC reduction.

Theoretically, gas compression could occur in (1) gas trapped with no access to an open airway (which will include abdominal gas) and (2) gas with open access to an airway but with an axial expiratory velocity greater than 0.3 of the wave speed in that airway at that time so that the air upstream can now act as a compressible fluid. This velocity may be achieved at high lung volume when the flow is high. As is shown in Figures 3A–3C, the lost volume is larger earlier in the forced maneuver than close to the end of the maneuver especially in the patients with COPD. This finding indicates that the gas compression is in part due to the second (2) mechanism mentioned previously because the lost volume is more at the beginning of the breathing maneuver.

Clinical trials use FEV₁ to assess response to bronchodilators. This is despite its insensitivity and inability to predict improvement in symptoms or exercise tolerance (4, 20, 21). Several studies show that improvement in other lung mechanic parameters may correlate better with improvement in symptoms and exercise capacity (4, 21, 22). Available data in the literature show that FEV₁ response to a bronchodilator may underestimate the effect of the bronchodilator (20, 22). In contrast, our data for the first time show that the improvement of FEV₁ may overestimate effect of a bronchodilator on expiratory flow limitation.

In patients with expiratory airflow obstruction, FEV₁ can be negatively affected with effort due to gas compression (23, 24). TGC negatively affects the flow-pressure-volume relationship and maximal expiratory flow by reducing lung volume (24). The data in Figure 1 are similar to those reported by Pedersen and colleagues on the effect of addition of external resistance on maximal expiratory airflow (24). TGC is affected by several factors, including expiratory airflow limitation, lung volume, and strong expiratory muscles (13, 14). Our data, consistent with previous studies, showed that TGC increased with rise in lung resistance, effort, absolute lung volume, and hyperinflation. In normal subjects at baseline, the FEV₁ was less than NFEV₁. However, the percentage difference between FEV₁ and NFEV₁ in normal subjects was appreciably less than patients with COPD.

Figure 3. Plot of lost volume (L) against time (s) before (*thin line*) and after (*thick line*) inhalation of albuterol. A and B show that the lost volume difference before and after albuterol inhalation is not appreciably different in (A) a normal subject and (B) a subject with asthma. In contrast, C shows that the lost volume was significantly less after inhalation of albuterol in a subject with chronic obstructive pulmonary disease (COPD).

This finding was expected because airflow limitation and hyperinflation are required to cause appreciable gas compression (13). Normal individuals can generate significant gas compression despite normal lung resistance if both effort and the flow speed

that is generated are large. However, we did not observe this condition in our normal subjects.

In subjects with COPD, expiratory and inspiratory lung resistances were significantly higher than in normal subjects. All our subjects with COPD with expiratory airflow limitation generated a significant amount of positive intrathoracic pressure during forced expiratory maneuvers. Furthermore, TLC and RV/TLC were considerably higher in subjects with COPD compared with normal subjects. In the patients with COPD, high lung resistance, large lung volume, and large intrathoracic pressure appear to explain the relatively high values of TGC at baseline measurement. On average, our subjects with COPD had 70 ml less gas compression with inhalation of albuterol. This reduction mostly stemmed from reduced resistance and lung hyperinflation. In contrast to forced expiration, due to its dependence on effort, TGC is negligible during nonforced expiration.

The effects of increasing resistance on maximal expiratory flow and TGC were studied by Pedersen and colleagues (24). They showed that addition of various external resistances increased the amount of compressed gas and reduced peak expiratory airflow in proportion to the amount of added resistance (24). TGC reduced the absolute lung volume, and thus negatively influenced the maximal expiratory airflow. This concept is also supported by data reported by Krowka and colleagues demonstrating that the highest values for FEV₁ were associated with forced expiratory maneuvers performed with submaximal effort (14). Consistent with Pedersen and colleagues' study, our data showed that reduction of airway resistance and hyperinflation results in less TGC.

In summary, we demonstrate that the effect of albuterol on maximal expiratory flow is confounded by TGC reduction. Improvement in FEV₁ after albuterol administration is partly explained by the reduction in airway resistance and hyperinflation but also by the reduction in TGC. Although TGC is large during forced maneuver, it is small during tidal breathing. TGC reduction during a forced expiration may not necessarily result in improvement in expiratory flow and thus symptoms and exercise capacity during nonforced breathing. This may in part explain the fact that, in subjects with severe airway obstruction such as COPD, FEV₁ improvement measured using the traditional methods may not always correlate with improvement in symptoms and exercise. A more accurate way of determining a bronchodilator response during forced expiration has to take into account the change in TGC.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Hyatt RE. Expiratory flow limitation. *J Appl Physiol* 1983;55:1–7.
2. Rodarte JR. Physiology of airflow limitation in emphysema. In: Fessler HE, Reilly JJ, Sugarebaker DJ, editors. Lung volume reduction surgery for emphysema. New York: Marcel Dekker, Inc.; 2004. pp. 43–64.
3. Pride NB, Macklem PT. Lung mechanics in disease. In: Fishman AP, editor. Handbook of physiology. Bethesda, MD: Oxford University Press; 1986. pp. 659–692.
4. Newton MF, O'Donnell DE, Forkert L. Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. *Chest* 2002;121:1042–1050.
5. Ingram RH Jr, Schilder DP. Effect of gas compression on pulmonary pressure, flow, and volume relationship. *J Appl Physiol* 1966;21:1821–1826.
6. Hyatt RE, Flath RE. Relationship of air flow to pressure during maximal respiratory effort in man. *J Appl Physiol* 1966;21:477–482.
7. Hyatt RE. Forced expiration. In: Fishman AP, editor. Handbook of physiology. Bethesda, MD: Oxford University Press; 1986. pp. 295–314.
8. Wilson TA, Hyatt RE, Rodarte JR. The mechanisms that limit expiratory flow. *Lung* 1980;158:193–200.

9. Fry DL. Pulmonary mechanics: a unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseases human subjects. *Am J Med* 1960;29:672-689.
10. Pedersen OF, Lyager S, Ingram RH Jr. Airway dynamics in transition between peak and maximal expiratory flow. *J Appl Physiol* 1985;59:1733-1746.
11. Dawson SV, Elliott EA. Wave-speed limitation on expiratory flow: a unifying concept. *J Appl Physiol* 1977;43:498-515.
12. Lambert RK, Wilson TA, Hyatt RE, Rodarte JR. A computational model for expiratory flow. *J Appl Physiol* 1982;52:44-56.
13. Jaeger MJ, Otis AB. Effects of compressibility of alveolar gas on dynamics and work of breathing. *J Appl Physiol* 1964;19:83-91.
14. Krowka MJ, Enright PL, Rodarte JR, Hyatt RE. Effect of effort on measurement of forced expiratory volume in one second. *Am Rev Respir Dis* 1987;136:829-833.
15. American Thoracic Society. Chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1962;84:762-768.
16. Mead J. Volume displacement body plethysmograph for respiratory measurements in human subjects. *J Appl Physiol* 1960;15:736-740.
17. American Thoracic Society. ATS statement: Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis* 1979;119:831-838.
18. Officer TM, Pellegrino R, Brusasco V, Rodarte JR. Measurement of pulmonary resistance and dynamic compliance with airway obstruction. *J Appl Physiol* 1998;85:1982-1988.
19. Sharafkhaneh A, Officer TM, Goodnight-White S, Rodarte JR, Boriek AM. Novel method for measuring effects of gas compression on expiratory flow. *Am J Physiol Regul Integr Comp Physiol* 2004;287:R479-R484.
20. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. *Chest* 1998;114:1607-1612.
21. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557-1565.
22. O'Donnell DE, Forkert L, Webb KA. Evaluation of bronchodilator responses in patients with "irreversible" emphysema. *Eur Respir J* 2001;18:914-920.
23. Ingram RH Jr, Schilder DP. Effect of thoracic gas compression on the flow-volume curve of the forced vital capacity. *Am Rev Respir Dis* 1966;94:56-63.
24. Pedersen OF, Pedersen TF, Miller MR. Gas compression in lungs decreases peak expiratory flow depending on resistance of peak flow-meter. *J Appl Physiol* 1997;83:1517-1521.